Coupling–Isomerization–Enamine Addition–Cyclocondensation Sequences: A Multicomponent Approach to Substituted and Annelated Pyridines

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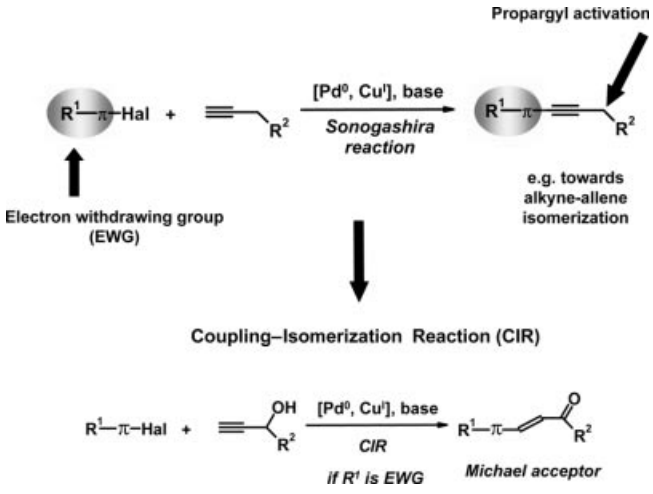
Annelated (dihydropyridines, tetrahydroquinolines, naphthyridines) and substituted pyridines can be synthesized in moderate to good yields in a consecutive one-pot, four-component process by a coupling–isomerization–enamine addition–cyclocondensation sequence of an electron poor (hetero)aryl halide, a terminal propargyl alcohol, an enamine, and ammonium chloride. After the coupling–isomerization sequence a Diels–Alder reaction with inverse electron demand of the intermediate chalcone and the enamine furnishes a cycloadduct **6** that was unambiguously characterized by X-ray structure analysis as well as the 1,5-diketones **4b** and **4g** – the corresponding hydrolysis products – and the pyridine derivatives **11e** (dihydropyridine), **11i** (tetrahydroquinoline), **11o** (naphthyridine), and **14b** and **14c** (ethyl nicotinoates). Additionally, quantum chemical calculations support the stepwise nature of the enamine cycloaddition.

Introduction

In recent years palladium-catalyzed cross-coupling methodology has considerably revolutionized synthetic methodology and the syntheses of complex natural and non-natural target molecules. In particular, the bimetallic, catalytic Sonogashira coupling has turned out to be a versatile and mild alkyne-to-alkyne transformation, i.e. a powerful tool for transforming a terminal alkyne into an internal one as a consequence of an sp-sp^2 C–C bond forming reaction.[1] Besides mild reaction conditions, an excellent compatibility with fragile functional groups dispenses with tedious protection-deprotection operations, and since hydrogen halide (scavenged by weak bases such as amines) is formed as the sole by-product, the Sonogashira coupling displays a high degree of atom economy. As part of our program designed to develop new multicomponent methodologies initiated by transition-metal-catalyzed C–C bond formation, we have recently discovered and developed an unusual mode of alkyne activation by modifying the Sonogashira coupling to give a coupling–isomerization reaction (CIR).[2] Conceptually, the cross-coupling reaction of an electron-deficient halide with a terminal alkyne not only activates the newly formed internal triple bond towards Michael-type additions but also the propargyl position, e.g. towards an alkyne–allene isomerization (Scheme 1).



Scheme 1. The coupling–isomerization reaction (CIR) as a peculiar mode of alkyne activation by cross-coupling.

In particular, the Sonogashira coupling of electron-poor halides with 1-(hetero)aryl propargyl alcohols furnishes chalcones in good to excellent yields. With this new enone synthesis in hand, and based upon the inherent bifunctional electrophilicity of the in situ generated Michael acceptor, we have disclosed novel three- and four-component syntheses of pyrazolines,[2] pyrimidines,[3] dihydrobenzo[*b*][1,4]thiazepines and -diazepines,[4] pyrrols and furans,[5] and pre-

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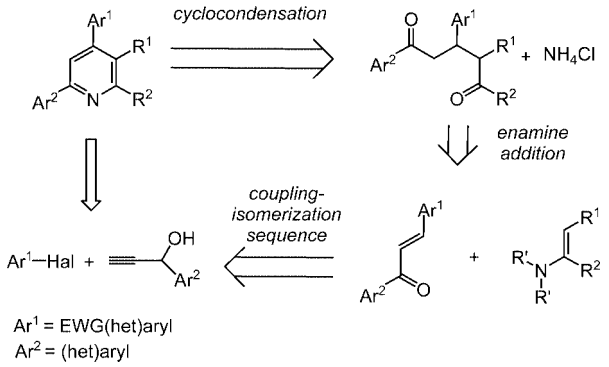
[‡] X-ray structure analyses of **6**, **11e**, **11i**, **11o**, **14b**, **14c** (T. O.), and **4b**, **4g** (K. P.).

liminary studies towards the synthesis of pyridines and tetrahydroquinolines[6] in the sense of sequential one-pot reactions. Here, we report the extension of the facile four-component, one-pot synthesis of substituted and annelated pyridines based upon a CIR followed by a consecutive enamine cycloaddition and a concluding cyclocondensation with ammonium chloride.

Results and Discussion

Among six-membered aromatic heterocycles the pyridyl core[7] adopts a central role. In nature, pyridine is the constituent structural unit in the coenzyme vitamin B_6 family (pyridoxal, pyridoxol, pyridoxamine) and an important subunit in numerous alkaloids.[8] Pyridine derivatives also find broad applications as versatile building blocks in the synthesis of natural products and as ligands in supramolecular coordination chemistry. In pharmaceutical chemistry, highly substituted[9] and annelated[10] pyridines, like 6,7-dihydro-5*H*-[1]pyrindines and 5,6,7,8-tetrahydroquinolines, have recently received considerable interest as antiarteriosclerotics since they efficiently inhibit HMG-CoA reductase and cholesterol transport proteins. Besides the class of pyridines, tetrahydroquinoline and naphthyridine derivatives also display antimycobacterial,[11] fungicidal and bactericidal,[12] antiulcer,[13] antivertigo,[14] antiviral,[15] and anti-inflammatory activities.[16]

There are numerous synthetic approaches to highly substituted pyridines, although novel multicomponent strategies comparable to the powerful, classical Hantzsch dihydropyridine synthesis,[17] remain particularly challenging. The facile access to unsymmetrical pyridines by the cocondensation of Michael acceptors with enols, enamines, or stabilized ylides and ammonia[18] represents an intriguing starting point for the development of a novel multi-component reaction, in particular with respect to the generation of combinatorial libraries. Hence, our retrosynthetic analysis based upon the CI approach (Scheme 2) suggests 1,5-diketones as key intermediates[19] on the way to highly substituted pyridines. As a consequence, we first tested the Stork enamine alkylation[20] with the in situ formed chalcones. Thus, we submitted *p*-bromobenzonitrile (**1a**) or 2-bromo thiazole (**1b**), aryl propynols **2**,[17] and, after some reaction

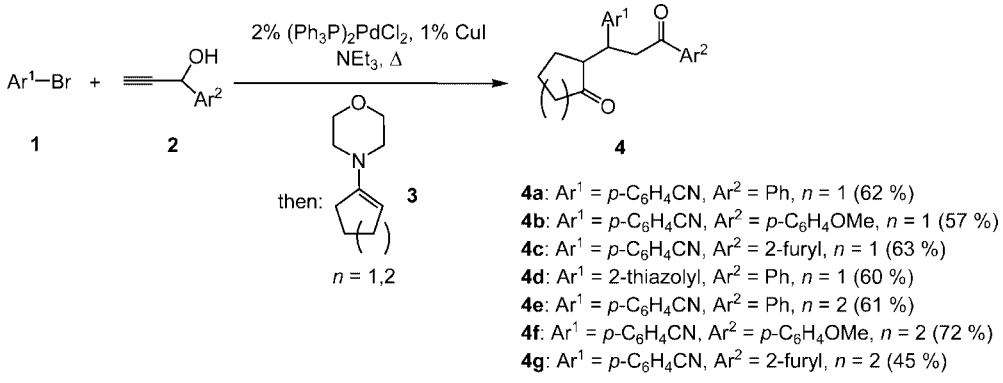


Scheme 2. Retrosynthetic concept of a consecutive one-pot, four-component pyridine synthesis.

time, cyclic enamines **3**, such as 1-morpholinocyclopentene or -hexene, to the reaction conditions of the Sonogashira coupling in boiling triethylamine. After aqueous workup of the crude reaction mixtures, the light-yellow 1,5-diketones **4** were obtained in 45–72% yield as crystalline solids in all cases (Scheme 3).

The structures of the 1,5-diketones **4** were unambiguously assigned by ^{1}H, ^{13}C, COSY, and NOESY NMR experiments. The NMR spectroscopic data support the formation of the 1,5-diketones, in particular, in the ^{13}C NMR spectra of **4** by the indicative appearance of the two significant carbonyl resonances at δ = 196–198 ppm for the arylalkyl ketone or at δ = 187 ppm for the furylalkyl ketone (**4c** and **4g**), and at δ = 219 ppm for the cyclopentanone (**4a**–**4d**) or δ = 212 ppm for the cyclohexanone (**4e**–**4g**). Likewise, in the IR spectra the carbonyl stretching vibrations can be found at 1730 cm^{-1} for cyclopentanones and at 1700 cm^{-1} for cyclohexanones, whereas the (hetero)aryl ketone vibrations appear at 1660–1680 cm^{-1}. Furthermore, the structure of **4** was unambiguously supported by X-ray crystal structure analyses of compounds **4b** and **4g** (Figure 1, Table 2).[21]

Interestingly, only in the case of the cyclopentanone derivatives **4a**–**d** can the formation of diastereomeric 1,5-diketones with a diastereomeric ratio in the range from 2:1 to 4:1 be observed; the cyclohexanone derivatives were formed with excellent diastereoselectivity as a result of a formal *syn* or *like* (*Si*,*Si*) simple diastereofacial enone alkylation of the



Scheme 3. CI–enamine addition three-component sequence to 1,5-diketones **4**.

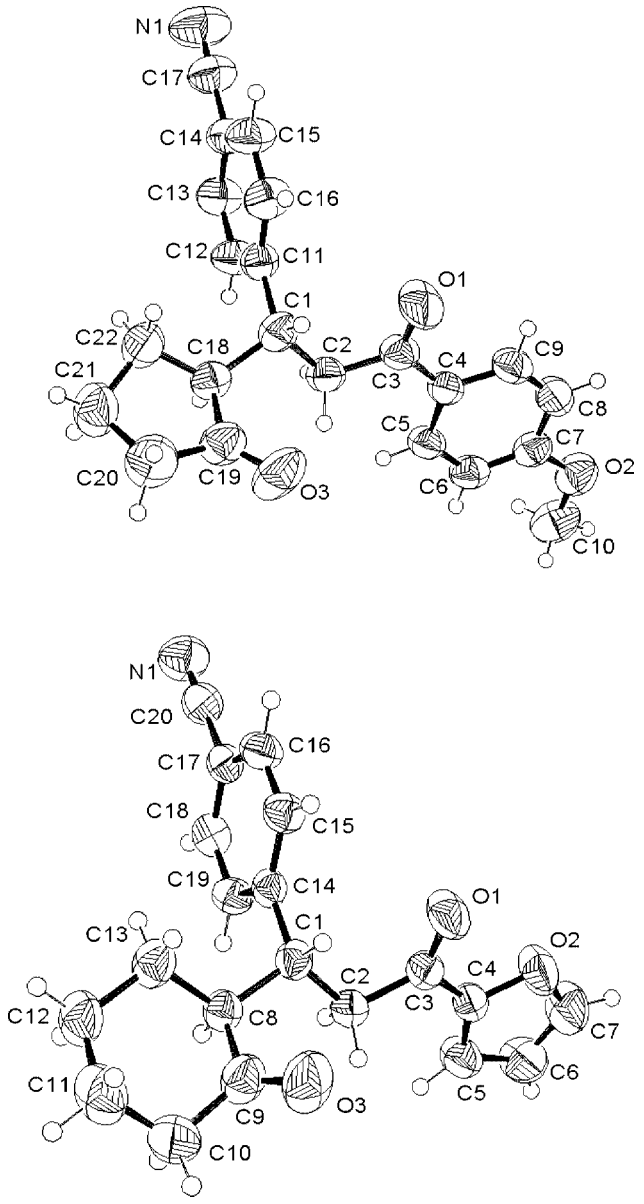


Figure 1. ORTEP plots of compounds **4b** and **4g**.

enamine. However, this remarkable diastereoselection clearly calls for mechanistic rationalization. In deed, several mechanistic pathways can explain the Stork enamine alkylation with enones. Product analysis suggests that the intermediate prior to hydrolysis is either a keto enamine or a cycloadduct, as a consequence of a Diels–Alder reaction with inverse electron demand[22] of an enamine and a chalcone. Therefore, according to Katritzky,[19b] after the CIR of **1a** and **2a** furnishes the chalcone **5**, and after subsequent addition of enamine **3b** followed by reaction at reflux temperature for 16 h, we were able to isolate suitable single crystals of the cycloadduct **6** by careful crystallization of the crude product from petroleum ether (Scheme 4, Figure 2, Table 2).[21]

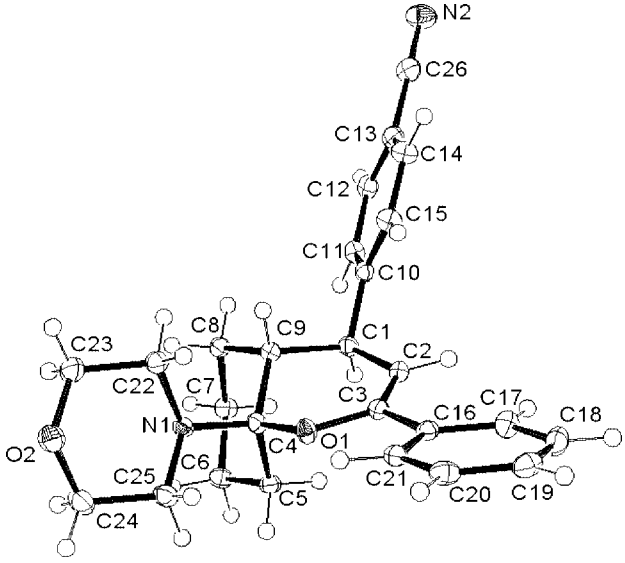
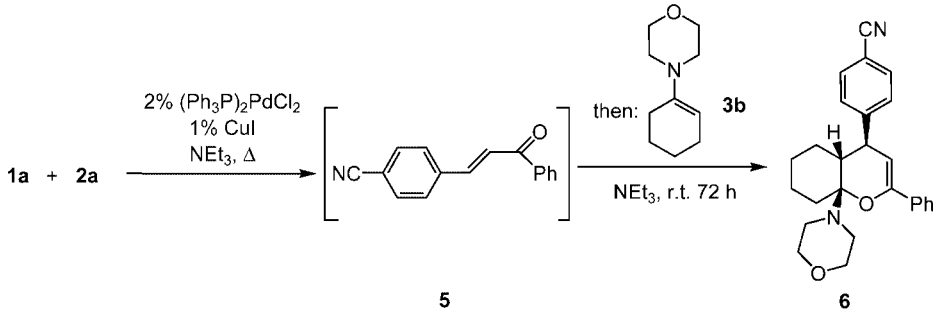


Figure 2. ORTEP plot of cycloadduct **6**.

The ^{1}H NMR assignment of the cycloadduct was rather difficult, since the purified compound was found to be extremely sensitive towards solvolysis under slightly acidic conditions and it also underwent a retro-Diels–Alder upon heating to higher temperatures (>80 °C). Nevertheless, in the ^{1}H NMR spectrum of the isolated product the appearance of a signal at δ = 5.25 ppm unambiguously indicates the formation of a vinyl ether that can be attributed to a cycloadduct. The mass spectrum of the crude mixture indicates the presence of two diastereomers of the cycloadduct **6** with a similar fragmentation pattern. Formally, the formation of the *endo* product **6** is the result of a concerted or stepwise [4+2] cycloaddition. The intermediacy of **6** in the CI–enamine addition reaction is also in full agreement with



Scheme 4. CI–cycloaddition sequence.

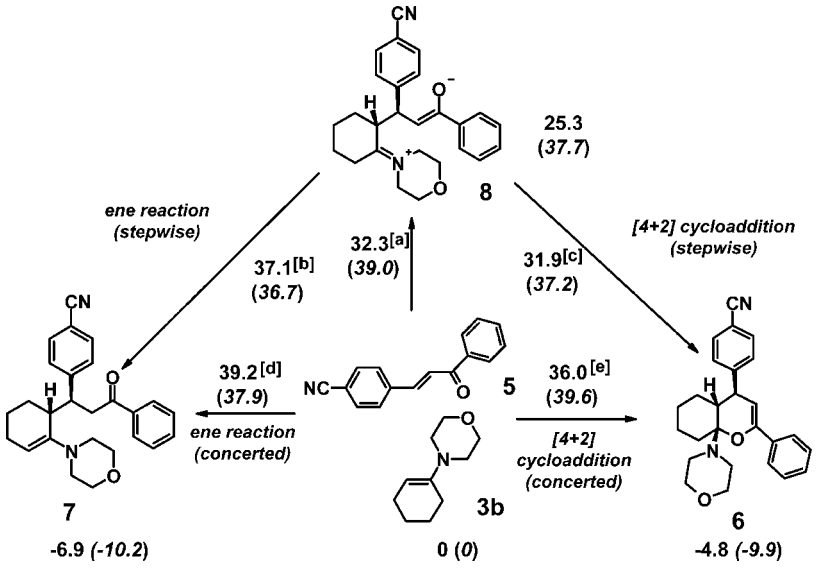


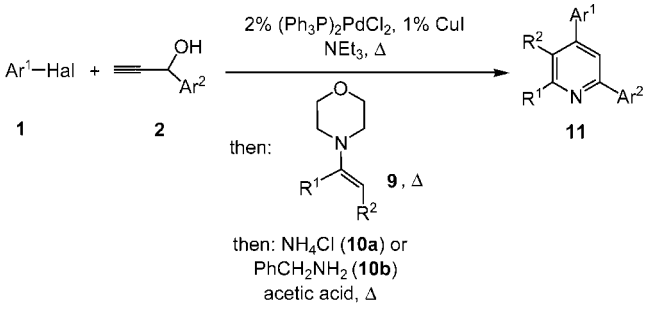
Figure 3. Calculated PM3 energies (kcal mol^{-1}) of the addition of an enamine to a chalcone in solution and in the gas phase (in parentheses). Imaginary frequencies that verify transition states: [a] i473.2 cm^{-1}, [b] i735.1 cm^{-1}, [c] i100.9 cm^{-1}, [d] i947.2 cm^{-1}, [e] i487.4 cm^{-1}.

the observed stereochemistry in the diketone **4e**, which can be considered to be the hydrolysis product of the cyclic aminal **6**.

Molecular modeling of alternative reaction pathways (Figure 3), i.e. concerted and stepwise [4+2] cycloaddition and an ene reaction, was performed at the PM3 level of theory,[23] both in the gas phase and water.[24] The results of the computations reveal that, although the heat of formation of the ene product, i.e. the 5-morpholino δ-enone **7**, is thermodynamically slightly favored over the cycloadduct **6**, under kinetic control a stepwise [4+2] cycloaddition is more likely. In particular, in polar solvents the formation of the dipolar iminium enolate **8** as an intermediate in the rate-determining step most likely concludes by the 1,6-dipolar cyclization of the zwitterion **8** to give the experimentally observed reaction product **6**.

With this efficient three-component, one-pot CI-enamine cycloaddition reaction in hand, the stage was set for the design of a novel four-component pyridine synthesis in the sense of a consecutive CI–enamine cycloaddition–amine cyclocondensation sequence. Therefore, applying electron-poor (hetero)aryl halides **1** and aryl propynols **2** to the conditions of the CIR, and after complete conversion to the corresponding chalcones, adding (hetero)cyclic and a cyclic morpholino enamines **9** to the reaction mixture and, finally, adding ammonium chloride (**10a**) or benzylamine (**10b**) in the presence of acetic acid pyridines **11a**–**f**, tetrahydroquinolines **11g**–**j**, tri(hetero)aryl pyridines **11k**–**n**, and naphthyridines **11o**–**r** were formed in moderate to good yields as colorless crystals (Scheme 5, Table 1).[18,21]

The structure of the pyridine derivatives **11** was unambiguously supported by the expected appearance of the characteristic proton and carbon resonances and multiplicities. In particular, in the ^{1}H NMR spectra of **11** the diagnostic singlets for the pyridine methine signals, which appear between δ = 7.5 and 8.5 ppm, can be used for the



Scheme 5. Four-component synthesis of annelated and substituted pyridines **11** based upon a CI–enamine addition–cyclocondensation sequence.

assignments of the *ortho*-phenyl or phenylene doublets by 2D-NOESY spectra as they give clear cross-peaks as a consequence of spatial proximity. Likewise, the structure of naphthyridines **11o**–**r** can be established by thorough inspection of 2D-NOESY correlations between the methylene groups in the saturated ring, which appear as singlets at δ = 4.5–4.9 ppm, and the proximal methine resonances stemming from the electron-poor (hetero)aryl substituent. Additionally, the mass spectrometric, IR spectroscopic, and combustion analytical data are in full agreement with the suggested molecular structure of the pyridines **11**. Furthermore, the structures of pyridines, tetrahydroquinolines, and naphthyridines **11** were corroborated by X-ray crystal structure analyses of compounds **11e**, **11i**, and **11o** (Figure 4, Table 3).[21]

After the coupling–isomerization reaction and the subsequent enamine cycloaddition, the final step of this new one-pot, four-component reaction begins with the protonation of the cycloadduct with acetic acid to give a reactive electrophilic iminium ion that now initiates the concluding cyclocondensation step with ammonium chloride or benzylamine (Table 1, entry 6). Conformationally fixed enamines

Table 1. One-pot synthesis of annelated and substituted pyridines **11**.

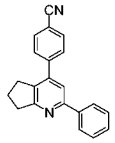
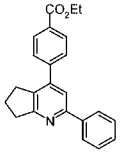
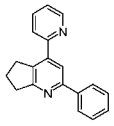
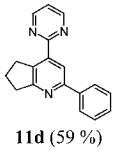
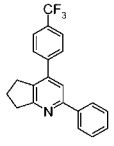
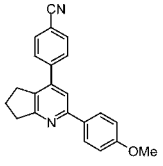
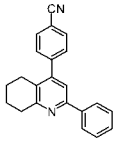
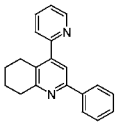
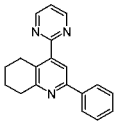
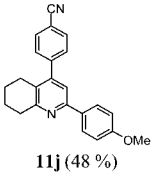
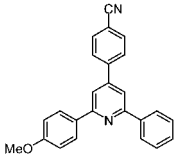
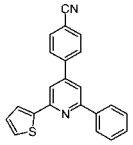
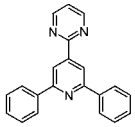
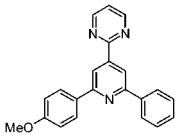
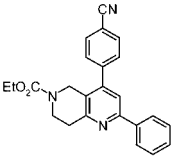
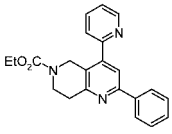
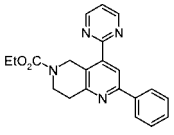
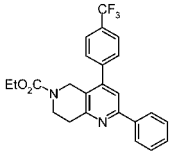
Entry	Aryl halide **1**	Propargyl alcohol **2**	Enamine **9**	Amine **10**	Pyridines **11** (Yield)
1[a]	Ar^1 = *p*-C_6H_4CN (**1a**)	Ar^2 = Ph (**2a**)	R^1,R^2 = –$(CH_2)_3$– (**9a** = **3a**)	NH_4Cl (**10a**)	 **11a** (48 %)
2[b,c]	Ar^1 = *p*-$C_6H_4CO_2Et$ (**1c**)	**2a**	**9a**	**10a**	 **11b** (42 %)
3[b,c]	Ar^1 = 2-pyridyl (**1d**)	**2a**	**9a**	**10a**	 **11c** (62 %)
4[b,c]	Ar^1 = 2-pyrimidyl (**1e**)	**2a**	**9a**	**10a**	 **11d** (59 %)
5[c,d]	Ar^1 = *p*-$C_6H_4CF_3$ (**1f**)	**2a**	**9a**	**10a**	 **11e** (54 %)
6[a]	**1a**	Ar^2 = *p*-C_6H_4OMe (**2b**)	**9a**	benzyl-amine (**10b**)	 **11f** (31 %)
7[a]	**1a**	**2a**	R^1,R^2 = –$(CH_2)_4$– (**9b** = **3b**)	**10a**	 **11g** (70 %)
8[c,d]	**1d**	**2a**	**9b**	**10a**	 **11h** (64 %)
9[b,c]	**1e**	**2a**	**9b**	**10a**	 **11i** (50 %)
10[a]	**1a**	**2b**	**9b**	**10a**	 **11j** (48 %)

Table 1. *(continued)*.

Entry	Aryl halide **1**	Propargyl alcohol **2**	Enamine **9**	Amine **10**	Pyridines **11** (Yield)
11[a,b]	**1a**	**2a**	R^1 = *p*-C_6H_4OMe, R^2 = H (**9c**)	**10a**	 **11k** (54 %)
12[a,b]	**1a**	**2a**	R^1 = 2-thienyl, R^2 = H (**9d**)	**10a**	 **11l** (46 %)
13[b,c]	**1e**	**2a**	R^1 = Ph, R^2 = H (**9e**)	**10a**	 **11m** (68 %)
14[a,b]	**1e**	**2a**	**9c**	**10a**	 **11n** (39 %)
15[a,b]	**1a**	**2a**	R^1, R^2 = –$(CH_2)_2$-N(CO_2Et)-CH_2–, (**9f**)	**10a**	 **11o** (61 %)
16[a,b]	**1c**	**2a**	**9f**	**10a**	 **11p** (41 %)
17[a,b]	**1e**	**2a**	**9f**	**10a**	 **11q** (57 %)
18[a,b]	**1f**	**2a**	**9f**	**10a**	 **11r** (58 %)

[a] Reaction time of the CIR 16 h. [b] In NEt_3. [c] Reaction time of the CIR 12 h. [d] In $HNEt_2$.

like *N*-morpholinocyclopentene, -cyclohexene, or tetrahydropyridine, or enamines of acetophenone derivatives react smoothly in the enamine addition step, and finally lead to the formation of annelated or substituted pyridines, whereas acyclic disubstituted enamines give a mixture of products and were, therefore, not considered for further investigation.

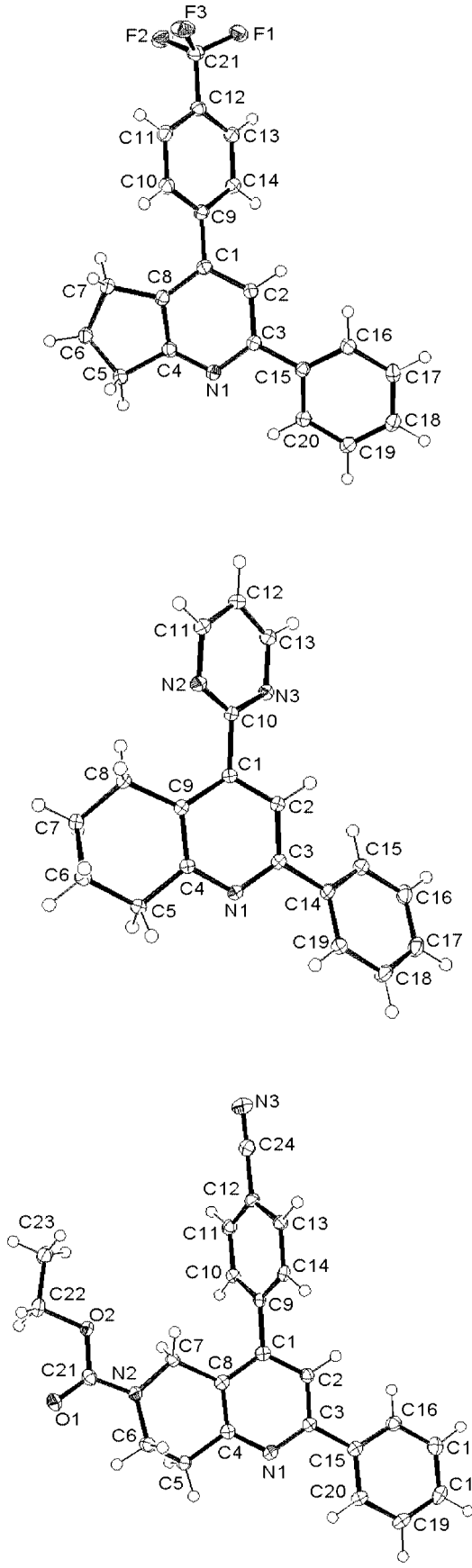


Figure 4. ORTEP plots of pyridine **11e** (top), tetrahydroquinoline **11i** (center), and naphthyridine **11o** (bottom).

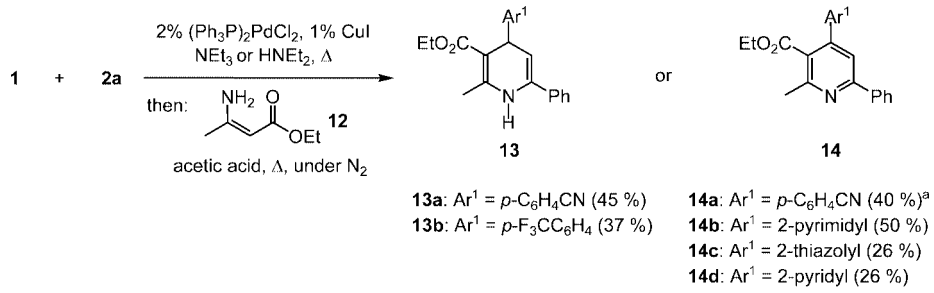
With the exception of benzylamine (Table 1, entry 6), all attempts to apply aliphatic and aromatic primary amines in the final cyclocondensation step met with failure. However, it is still remarkable that the formation of the pyridine **11f** upon application of benzylamine as a source of nitrogen leads to a debenzylation with concomitant aromatization rather than to the formation of the dihydropyridines under these reaction conditions. It is very likely that the palladium and copper species present in the reaction mixture also catalyze the dehydrogenation of the initially formed dihydropyridines (vide infra).

Finally, the implementation of the amino group in the enamine functionality could give rise to a one-pot, three-component pyridine synthesis. Therefore, upon performing the CIR with the aryl halides **1** and the propargyl alcohol **2a**, followed by the addition of ethyl 3-amino crotonate (**12**) as a suitable enamine in the presence of acetic acid and under nitrogen, the expected dihydropyridines **13** could be isolated in a few cases (Scheme 6). However, either under aerobic (compound **14a**) or anaerobic conditions, in most cases the aromatization readily furnishes the ethyl nicotinoate derivatives **14** in moderate yields.

The formation of the dihydropyridines **13** and pyridines **14** is unequivocally supported by the appearance of the characteristic methine proton resonances in the ^{1}H NMR spectra, as multiplets at δ = 5.0 ppm for dihydropyridines **13** and as singlets between δ = 7.5 and 8.5 ppm for ethyl nicotinoate derivatives **14**. Besides, the mass spectrometric, IR spectroscopic, and combustion analytical data are in agreement with the suggested molecular structures of the dihydropyridines **13** and ethyl nicotinoate derivatives **14**. Additionally, the structures of the nicotinoates **14** were corroborated by X-ray crystal structure analyses of compounds **14b** and **14c** (Figure 5, Table 4).

Again, in this three-component pyridine synthesis, as in the four-component sequence, the oxidative aromatization of the actual dihydropyridine intermediate readily occurs under these reaction conditions assisted by the presence of palladium and copper species that obviously catalyze this final step in the sequence. A moderate substituent effect in this dehydrogenating aromatization can be attributed to the fact that only slightly weaker acceptors such as cyano and trifluoromethyl groups give rise to the isolation of the dihydropyridine intermediate. Although the three-component pyridine synthesis opens an entry to further functionalized pyridines, such as ethyl nicotinoate derivatives **14**, the yields of the four-component sequence are consistently higher.

In conclusion, the mild reaction conditions of the CI sequence of electron-poor (hetero)aryl halides with 1-aryl propargyl alcohols, which gives rise to chalcones, can be extended to a one-pot, three-component synthesis of 1,5-diketones by applying an enamine cycloaddition with morpholino enamines and, even further, to a one-pot, four-component synthesis of the pharmaceutically important classes of pyridines, tetrahydroquinolines, pyridines, and naphthyridines. This methodology combines modern catalytic cross-coupling processes with pericyclic reactions and classical cyclocondensations, and, therefore, opens up new



Scheme 6 Three-component synthesis of functionalized dihydropyridines **13** and pyridines **14** based upon a CI–enamine addition–cyclocondensation sequence.

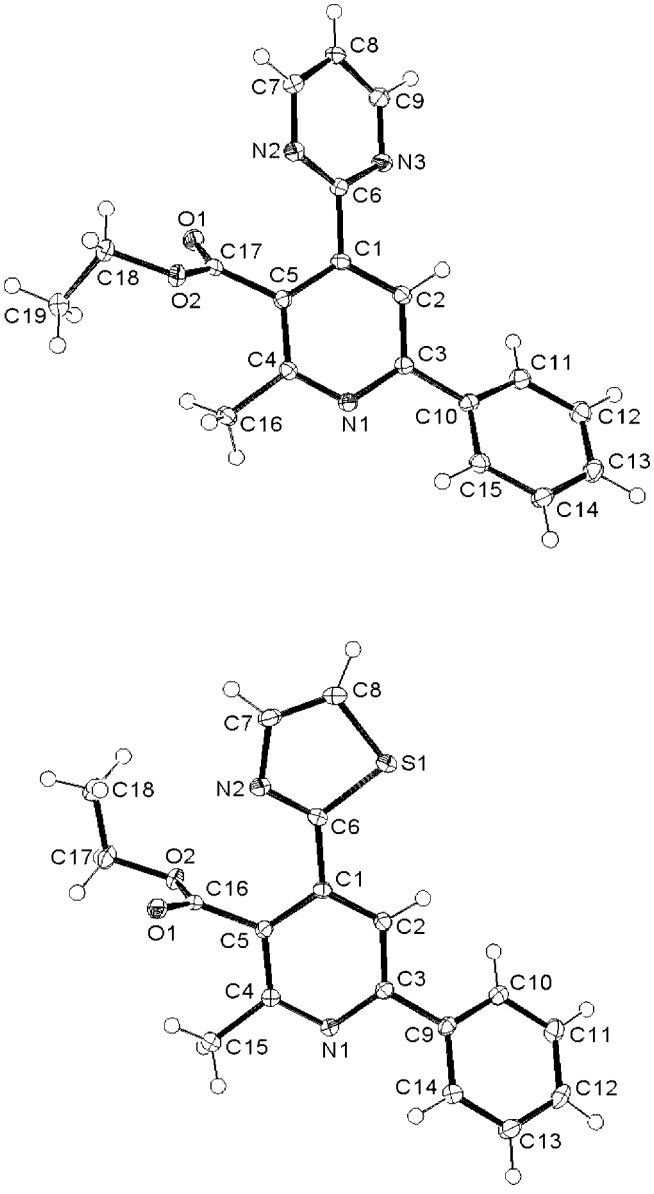


Figure 5. ORTEP plots of nicotinoate derivatives **14b** (left) and **14c** (right).

one-pot synthetic strategies as a consequence of mild reaction conditions and functional group compatibility. Further studies will be directed towards the syntheses and properties of more sophisticated pyridines with pharmaceutical potential and as an entry to supramolecular covalent and noncovalent self-assembly.

Experimental Section

General Considerations: All reactions involving palladium-copper catalysis were performed in degassed, oxygen-free solvents under a nitrogen atmosphere using Schlenk and syringe techniques. Halogen compounds **1**, amines, *N*-morpholinocyclopentene (**9a**), *N*-morpholinocyclohexene (**9b**), ethynylmagnesium bromide (1 M in THF), $[PdCl_2(PPh_3)_2]$, and CuI were purchased as reagent grade from ACROS, Aldrich, Fluka, or Merck and used without further purification. Triethylamine and THF were dried and distilled according to standard procedures.[25] Propargyl alcohols **2** were prepared in analogy to literature procedures[26] by the addition of ethynylmagnesium bromide or lithium trimethylsilylacetylide (and subsequent desilylation) to aromatic aldehydes. The enamines **9c**, **9d**, **9e**, **9f**,[27] and **12**[28] were synthesized in analogy to literature procedures. Column chromatography: silica gel 60 (Merck, Darmstadt), mesh 70–230. TLC: silica gel plates (60 F_{254} Merck, Darmstadt). Melting points (uncorrected values): Büchi Melting Point B-540. ^1H and ^{13}C NMR spectra: Bruker ARX 300, Varian VXR 400S $CDCl_3$ and $[D_6]$DMSO. The assignments of quaternary C, CH, CH_2, and CH_3 signals was possible by using DEPT techniques. IR: Perkin–Elmer Lambda 3. UV/Vis: Perkin–Elmer Models Lambda 16. MS: Finnigan MAT 90 and MAT 95 Q. Elemental analysis was carried out in the Microanalytical Laboratories of the Department Chemie, Ludwig-Maximilians-Universität München, and of the Organisch-Chemisches Institute, Ruprecht-Karls-Universität Heidelberg.

X-ray Structure Determination of Compounds 4b, 4g, 6, 11e, 11i, 11o, 14b, and 14c: Diffraction data were measured on a Bruker Smart APEX apparatus and solved with SHELXL-93. Suitable crystals were mounted on a capillary and transferred to an Enraf–Nonius CAD4 (Munich) or a Bruker Smart APEX (Heidelberg) diffractometer. The structures were solved by direct methods and refined anisotropically on F^2 (program SHELXS-86, SHELXL-93, SHELXTL V6.12, and SADABS V2.03 for absorption correction, G. M. Sheldrick, University of Göttingen and Bruker Analytical X-ray-Division, Madison, Wisconsin 2000 and 2001). Hydrogen atoms were found from differential Fourier synthesis and refined. The data of the X-ray structure analyses are summarized in Tables 2, 3, and 4.

General Procedure for the Coupling–Isomerization–Enamine Addition Sequence to 1,5-Diketones 4: A magnetically stirred solution of 1.00 equiv. of halogen compound **1**, 1.05 equiv. of propargyl alcohol **2**, 0.02 equiv. of $[PdCl_2(PPh_3)_2]$, and 0.01 equiv. of CuI in degassed triethylamine/THF (3:1; 0.5 M) or degassed triethylamine

Table 2. Crystal data and structure refinements for **4b**, **4g**, and **6**.

Compound	**4b**	**4g**	**6**
Empirical formula	$C_{22}H_{21}NO_3$	$C_{20}H_{19}NO_3$	$C_{26}H_{28}N_2O_2$
Formula mass	347.40	321.36	400.50
Temperature, K	293(2)	293(2)	100(2)
Wavelength [Å]	0.71073	0.71073	0.71073
Crystal system	monoclinic	triclinic	monoclinic
Space group	$P2_1/c$	$P\bar{1}$	$P2_1/c$
Z	4	2	4
Unit cell dimensions	a = 19.798(8) Å	a = 5.7041(10) Å	a = 10.080(1) Å
	b = 5.655(2) Å	b = 12.395(3) Å	b = 11.664(1) Å
	c = 16.740(6) Å	c = 12.333(2) Å	c = 18.265(2) Å
	α = 90°	α = 82.39(2)°	α = 90°
	β = 98.35(3)°	β = 89.39(2)°	β = 103.976(2)°
	γ = 90°	γ = 86.14(2)°	γ = 90°
Volume [Å^3]	1854.4(11)	862.4(3)	2083.9(4)
Density (calculated) [g cm^{-3}]	1.24	1.24	1.28
Absorption coefficient [mm^{-1}]	0.083	0.083	0.081
Crystal size [mm^3]	0.47 × 0.33 × 0.13	0.53 × 0.43 × 0.27	0.30 × 0.26 × 0.20
Theta range for data collection [°]	2.46 to 23.97	2.50 to 23.96	2.7 to 28.3
Index ranges	$0 \le h \le 22$	$0 \le h \le 6$	$-13 \le h \le 13$
	$-6 \le k \le 0$	$-14 \le k \le 14$	$-15 \le k \le 15$
	$-19 \le l \le 18$	$-14 \le l \le 14$	$-24 \le l \le 24$
Reflections collected	3006	3011	20 678
Independent reflections	2911 [R(int) = 0.022]	2702 [R(int) = 0.011]	5103 [R(int) = 0.032]
Observed reflections	2911 [$I > 2\sigma(I)$]	2702 [$I > 2\sigma(I)$]	4310 [$I > 2\sigma(I)$]
Absorption correction	semi-empirical from equivalents	semi-empirical from equivalents	semi-empirical from equivalents
Max. and min. transmission	0.989 and 0.980	0.999 and 0.982	0.984 and 0.976
Refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2	full-matrix least-squares on F^2
Data/restraints/parameters	2911/10/292	2702/0/217	5103/0/383
Goodness-of-fit on F^2	1.124	1.043	1.05
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.052, $wR2$ = 0.115	$R1$ = 0.042, $wR2$ = 0.103	$R1$ = 0.049, $wR2$ = 0.114
Largest diff. peak and hole [e Å^{-3}]	0.12 and –0.11	0.29 and –0.14	0.44 and –0.20

Table 3. Crystal data and structure refinements for **11e**, **11i**, and **11o**.

Compound	**11e**	**11i**	**11o**
Empirical formula	$C_{21}H_{16}F_3N$	$C_{19}H_{17}N_3$	$C_{24}H_{21}N_3O_2$
Formula mass	339.4	287.4	383.44
Temperature, K	100(2)	100(2)	100(2)
Wavelength [Å]	0.71073	0.71073	0.71073
Crystal system	triclinic	triclinic	Monoclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1/c$
Z	2	2	4
Unit cell dimensions	a = 9.3792(9) Å	a = 7.2677(8) Å	a = 12.194(2) Å
	b = 9.6624(9) Å	b = 9.4524(10) Å	b = 8.973(2) Å
	c = 9.7227(9) Å	c = 10.9201(12) Å	c = 17.515(3) Å
	α = 112.508(2)°	α = 82.238(2)°	α = 90°
	β = 92.435(2)°	β = 82.509(2)°	β = 96.684(4)°
	γ = 102.162(2)°	γ = 75.802(2)°	γ = 90°
Volume [Å^3]	788.3(1)	716.9(1)	1903.5(6)
Density (calculated) [g cm^{-3}]	1.43	1.33	1.34
Absorption coefficient [mm^{-1}]	0.11	0.08	0.09
Crystal size [mm^3]	0.30 × 0.26 × 0.19	0.37 × 0.30 × 0.20	0.26 × 0.23 × 0.12
Theta range for data collection [°]	2.2 to 28.3	2.8 to 28.3	2.5 to 24.7
Index ranges	$-11 \le h \le 12$	$-9 \le h \le 8$	$-14 \le h \le 14$
	$-12 \le k \le 12$	$-12 \le k \le 11$	$-10 \le k \le 10$
	$-12 \le l \le 12$	$-14 \le l \le 13$	$-20 \le l \le 20$
Reflections collected	5866	5359	13721
Independent reflections	3857 [R(int) = 0.018]	3537 [R(int) = 0.036]	3236 [R(int) = 0.061]
Observed reflections	3587 [$I > 2\sigma(I)$]	3149 [$I > 2\sigma(I)$]	2516 [$I > 2\sigma(I)$]
Absorption correction	semi-empirical from equivalents	none	semi-empirical from equivalents
Max. and min. transmission	0.980 and 0.968	0.984 and 0.971	0.990 and 0.980
Refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2	full-matrix least-squares on F^2
Data/restraints/parameters	3857/0/290	3537/0/267	3236/0/346
Goodness-of-fit on F^2	1.07	1.06	1.04
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.041, $wR2$ = 0.110	$R1$ = 0.041, $wR2$ = 0.119	$R1$ = 0.043, $wR2$ = 0.086
Largest diff. peak and hole [e Å^{-3}]	0.37 and –0.32	0.43 and –0.27	0.20 and –0.18

Table 4. Crystal data and structure refinements for **14b** and **14c**.

Compound	**14b**	**14c**
Empirical formula	$C_{19}H_{17}N_3O_2$	$C_{18}H_{16}N_2O_2S$
Formula mass	319.4	324.39
Temperature, K	100(2)	100(2)
Wavelength [Å]	0.71073	0.71073
Crystal system	orthorhombic	monoclinic
Space group	*Pca*2(1)	$P2_1/c$
Z	4	4
Unit cell dimensions	*a* = 10.4549(8) Å *b* = 19.132(1) Å *c* = 7.6580(6) Å *α* = 90° *β* = 90° *γ* = 90°	*a* = 10.776(3) Å *b* = 7.141(2) Å *c* = 20.236(5) Å *α* = 90° *β* = 92.832(5)° *γ* = 90°
Volume [Å^3]	1531.8(2)	1555.4(6)
Density (calculated) [g cm^{-3}]	1.38	1.38
Absorption coefficient [mm^{-1}]	0.09	0.219
Crystal size [mm^3]	0.37 × 0.37 × 0.23	0.33 × 0.15 × 0.07
Theta range for data collection [°]	2.1 to 28.3	2.7 to 28.3
Index ranges	$-13 \le h \le 13$ $-25 \le k \le 22$ $-9 \le l \le 10$	$-11 \le h \le 14$ $-9 \le k \le 9$ $-26 \le l \le 19$
Reflections collected	10986	11156
Independent reflections	3725 [*R*(int) = 0.030]	3863 [*R*(int) = 0.028]
Observed reflections	3677 [$I > 2\sigma(I)$]	3258 [$I > 2\sigma(I)$]
Absorption correction	none	numerical
Max. and min. transmission	0.9791 and 0.9667	0.985 and 0.931
Refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2
Data/restraints/parameters	3725/1/285	3863/0/272
Goodness-of-fit on F^2	1.06	0.99
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.032	*R*1 = 0.033,
	*wR*2 = 0.085	*wR*2 = 0.087
Largest diff. peak and hole [e Å^{-3}]	0.36 and –0.26	0.37 and –0.25

(0.5 M) under nitrogen was heated to reflux temperature for 12 h. After cooling to room temperature, 1.15 equiv. of enamine **3** in triethylamine (0.5 M) was added and the reaction mixture was heated to reflux temp. for the time indicated. After cooling, either 40 mL of ethyl acetate or 40 mL of diethyl ether and 40 mL of water was added and stirring was continued for 5 to 10 min. The aqueous layer was extracted with diethyl ether or ethyl acetate (4 × 15 mL) and the combined organic phases were dried with anhydrous magnesium sulfate. After filtration the solvents were removed in vacuo and the residue was chromatographed on silica gel (cyclohexane/ethyl acetate or *n*-heptane/ethyl acetate, 2:1) and recrystallized from ethanol to give the analytically pure 1,5-diketones **4** (see Table 5 for experimental details).

4-[3-Oxo-1-(2-oxocyclopentyl)-3-phenylpropyl]benzonitrile (4a): According to the GP, after chromatography on silica gel (cyclohexane/ethyl acetate, 2:1) and recrystallization from ethanol, **4a** (391 mg, 62%) was isolated as a mixture of diastereomers (*dr* = 2:1) and as light-yellow crystals. M.p. 110–112 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* = 1.38–1.51 (m, 1 H), 1.62–1.79 (m, 1 H), 1.85–2.00 (m, 2 H), 2.02–2.17 (m, 1 H), 2.26–2.35 (m, 1 H), 2.43–2.57 (m, 1 H), 3.40 (dd, *J* = 8.6, 8.6 Hz, 0.66 H), 3.58 (m, 0.33 H), 3.68–3.86 (m, 1 H), 3.94 (dd, *J* = 5.1, 17.2 Hz, 1 H), 7.36 (dd, *J* = 8.3, *J* = 2.6 Hz, 2 H), 7.40–7.47 (m, 2 H), 7.52–7.57 (m. 3 H), 7.88–795 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* = 20.1 (CH_2), 28.0 (CH_2), 38.6 (CH_2), 40.8 (CH), 42.2 (CH_2), 52.4 (CH), 110.5 ($C_{quat.}$), 118.7 ($C_{quat.}$), 127.9 (CH), 128.5 (CH), 129.1 (CH), 132.1 (CH), 133.1 (CH), 136.6 ($C_{quat.}$), 148.0 ($C_{quat.}$), 197.7 ($C_{quat.}$), 218.8 ($C_{quat.}$) ppm; additional signals for the minor diastereomer: *δ* = 20.3 (CH_2), 27.0 (CH_2), 39.2 (CH_2), 40.3 (CH), 40.7 (CH), 53.2 (CH), 110.5 ($C_{quat.}$), 118.7 ($C_{quat.}$), 128.0 (CH), 128.6 (CH), 129.2 (CH), 132.2 (CH), 133.3 (CH), 136.6 ($C_{quat.}$), 148.1 ($C_{quat.}$), 197.9 ($C_{quat.}$), 219.2 ($C_{quat.}$) ppm. MS (70 eV, EI): *m*/*z* (%) = 317 (4) [M^+], 234 (17) [$M^+ - C_5H_7O$], 198 (27) [$M^+ - C_8H_7O$], 120 (100) [$C_8H_7O^+$], 105 (93) [$C_7H_5O^+$], 77 (40) [$C_6H_5^+$]. IR (KBr): $\tilde{\nu}$ = 3064 cm^{-1}, 2967, 2228 (C≡N), 1728 (C=O, cyclopentanone), 1682 (C=O, aryl ketone), 1606, 1505, 1448, 1417, 1317, 1300, 1236, 1179, 1154, 1002, 846, 758, 690, 583. $C_{21}H_{19}NO_2$ (317.4): calcd. C 79.47, H 6.03, N 4.41; found C 79.14, H 5.90, N 4.35.

4-[3-(4-Methoxyphenyl)-3-oxo-1-(2-oxocyclopentyl)propyl]benzonitrile (4b): According to the GP, after chromatography on silica gel (cyclohexane/ethyl acetate, 2:1) and recrystallization from ethanol 399 mg (57%) of **4b** was isolated as light-yellow crystals. M.p. 110–111 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* = 1.39–1.49 (m, 1 H), 1.68–1.76 (m, 2 H), 1.86–1.97 (m, 2 H), 2.02–2.13 (m, 1 H), 2.27–2.33 (m, 1 H), 2.44–2.51 (m, 1 H), 3.34 (dd, *J* = 8.4 Hz, 1 H), 3.70–3.85 (m, 4 H), 6.91 (dd, *J* = 5.5, 8.2 Hz, 2 H), 7.36 (dd, *J* = 5.2, 7.6 Hz, 2 H), 7.55 (d, *J* = 7.8 Hz, 2 H), 7.90 (dd, *J* = 8.2, 8.4 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* = 20.1 (CH_2), 27.0 (CH_2), 38.6 (CH_2), 41.0 (CH), 41.8 (CH_2), 52.5 (CH), 55.4 (OCH_3), 110.4 ($C_{quat.}$), 113.7 (CH), 118.7 ($C_{quat.}$), 129.2 (CH), 129.7 ($C_{quat.}$), 130.2 (CH), 148.3 ($C_{quat.}$), 163.7 ($C_{quat.}$), 196.5 ($C_{quat.}$), 219.0 ($C_{quat.}$) ppm; additional signals for the other diastereomer: *δ* = 20.3 (CH_2), 28.0 (CH_2), 39.2 (CH_2), 40.0 (CH_2), 53.2 (CH), 110.5 ($C_{quat.}$), 113.8 (CH), 118.7 ($C_{quat.}$), 129.2 (CH), 129.7 ($C_{quat.}$), 130.3 (CH), 148.4 ($C_{quat.}$), 163.8 ($C_{quat.}$), 196.6 ($C_{quat.}$), 219.4 ($C_{quat.}$) ppm. MS (70 eV, EI): *m*/*z* (%) = 347 (1) [M^+], 263 (6) [$M^+ - C_5H_7O$], 198 (35) [$M^+ - C_9H_9O_2$], 150 (50) [$C_9H_{10}O_2^+$], 135 (100) [$C_8H_7O_2^+$], 77 (15) [$C_6H_5^+$]. IR (KBr): $\tilde{\nu}$ = 3066 cm^{-1}, 2970, 2228 (C≡N), 1731 (C=O, cyclopentanone), 1673 (C=O, aryl ketone), 1603, 1509, 1421, 1261, 1242, 1176, 1027, 982, 841, 580. $C_{22}H_{21}NO_3$ (347.4): calcd. C 76.06, H 6.09, N 4.03; found C 75.80, H 6.03, N 4.08.

Table 5. Experimental details of the one-pot synthesis of 1,5-diketones **4**.

Aryl halide **1** [mg (mmol)]	Propargyl alcohol **2** [mg (mmol)]	Enamine **3** [mg (mmol)]	Time [h]	Yield [mg (% yield)]
364 (2.00) **1a**	280 (2.10) **2a**	368 (2.40) **3a**	24	391 (62) **4a**
364 (2.00) **1a**	340 (2.10) **2b**	337 (2.20) **3a**	24	399 (57) **4b**
364 (2.00) **1a**	269 (2.20) **2c**	368 (2.40) **3a**	20	385 (63) **4c**
328 (2.00) **1b**	280 (2.10) **2a**	368 (2.40) **3a**	20	359 (60) **4d**
364 (2.00) **1a**	280 (2.10) **2a**	586 (3.50) **3b**	18	404 (61) **4e**
364 (2.00) **1a**	340 (2.10) **2b**	380 (2.30) **3b**	46	519 (72) **4f**
364 (2.00) **1a**	269 (2.20) **2c**	401 (2.40) **3b**	20	289 (45) **4g**

4-[3-(Furan-2-yl)-3-oxo-1-(2-oxocyclopentyl)propyl]benzonitrile (4c): According to the GP, after chromatography on silica gel (cyclohexane/ethyl acetate, 2:1) and crystallization from ethyl acetate/cyclohexane 385 mg (63%) of **4c** was isolated as light-yellow crystals. M.p. 104–106 °C (ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.38–1.50 (m, 1 H), 1.64–2.12 (m, 4 H), 2.31 (dd, J = 7.5, 7.5 Hz, 1 H), 2.43–2.52 (m, 1 H), 3.25–3.44 (m, 1 H), 3.67–3.85 (m, 2 H), 6.50 (dd, J = 1.7, 3.5 Hz, 1 H), 7.15 (d, J = 3.2 Hz, 1 H), 7.36 (d, J = 8.3 Hz, 2 H), 7.56 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.1 (CH_2), 27.7 (CH_2), 38.6 (CH_2), 40.5 (CH), 41.9 (CH_2), 52.4 (CH), 110.5 ($C_{quat.}$), 112.3 (CH), 117.1 (CH), 118.7 ($C_{quat.}$), 129.2 (CH), 132.1 (CH), 146.3 (CH), 147.7 ($C_{quat.}$), 152.5 ($C_{quat.}$), 186.8 ($C_{quat.}$), 218.6 ($C_{quat.}$) ppm. MS (70 eV, EI): m/z (%) = 307 (1) [M^+], 223 (23) [$M^+ - C_5H_7O$], 197 (35) [$M^+ - C_6H_6O_2$], 110 (100) [$C_6H_{16}O_2^+$]. IR (KBr): $\tilde{\nu}$ = 3122 cm^{-1}, 2967, 2226 (C≡N), 1728 (C=O cyclopentanone), 1659 (C=O, aryl ketone), 1468, 1397, 1273, 1155, 1021, 844, 782, 595, 555.

2-[3-Oxo-3-phenyl-1-(thiazol-2-yl)propyl]cyclopentanone (4d): According to the GP, after chromatography on silica gel (cyclohexane/ethyl acetate, 2:1) and recrystallization from ethanol 359 mg (60%) of **4d** was isolated as a mixture of diastereomers (dr = 4:1) and as light-yellow crystals. M.p. 110–112 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.66–2.34 (m, 6 H), 2.58–2.70 (m, 1 H), 3.46–3.83 (m, 2 H), 4.29–4.37 (m, 1 H), 7.17 (t, J = 4.0 Hz, 1 H), 7.42 (dt, J = 1.5, 8.0 Hz, 2 H), 7.50 (dd, J = 1.3, 7.2 Hz, 1 H), 7.62 (t, J = 3.2 Hz, 1 H), 7.96 (dd, J = 1.3, 7.2 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.0 (CH_2), 26.2 (CH_2), 37.7 (CH), 40.6 (CH_2), 52.5 (CH), 118.3 (CH), 127.8 (CH), 128.3 (CH), 132.9 (CH), 136.4 ($C_{quat.}$), 141.7 (CH), 170.3 ($C_{quat.}$), 171.3 ($C_{quat.}$), 197.4 ($C_{quat.}$), 218.4 ($C_{quat.}$) ppm; additional signals for the minor diastereomer: δ = 20.3 (CH_2), 26.6 (CH_2), 38.1 (CH), 41.7 (CH_2), 118.3 (CH), 127.9 (CH), 128.3 (CH), 132.9 (CH), 141.7 (CH), 197.4 ($C_{quat.}$), 218.5 ($C_{quat.}$) ppm. MS (70 eV, EI): m/z (%) = 299 (2) [M^+], 216 (1) [$M^+ - C_5H_7O$], 194 (100) [$M^+ - C_7H_5O$], 180 (10) [$M^+ - C_8H_7O$]. IR (KBr): $\tilde{\nu}$ = 3078 cm^{-1}, 2959, 1731 (C=O, cyclopentanone), 1679 (C=O, aryl ketone), 1594, 1496, 1450, 1399, 1353, 1258, 1217, 1154, 1045, 998, 776, 740, 694, 584. $C_{17}H_{17}NO_2S$ (299.4): calcd. C 68.20, H 5.72, N 4.68, S 10.71; found C 68.04, H 5.77, N 4.62, S 10.74.

4-[3-Oxo-1-(2-oxocyclohexyl)-3-phenylpropyl]benzonitrile (4e): According to the GP, after chromatography on silica gel (cyclohexane/ethyl acetate, 2:1) and recrystallization from ethanol 404 mg (61%) of **4e** was isolated as colorless crystals. M.p. 160–162 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.19–1.29 (m, 1 H), 1.55–1.83 (m, 4 H), 2.00–2.11 (m, 1 H), 2.36–2.54 (m, 2 H), 2.66–2.81 (m,1 H), 3.26 (dd, J = 9.8, 1 H), 3.55 (dd, J = 3.9, 12.8 Hz, 1 H), 3.76–3.84 (m, 1 H), 7.34 (d, J = 8.3 Hz, 2 H), 7.39–7.44 (m, 2 H), 7.50–7.56 (m, 3 H), 7.91 (d, J = 9.0 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.5 (CH_2), 28.4 (CH_2), 32.6 (CH_2), 41.1 (CH), 42.5 (CH_2), 43.3 (CH_2), 55.1 (CH), 110.4 ($C_{quat.}$), 118.8 ($C_{quat.}$), 128.0 (CH), 128.6 (CH), 129.3 (CH), 132.2 (CH), 133.1 (CH), 136.6 ($C_{quat.}$), 148.0 ($C_{quat.}$), 197.9 ($C_{quat.}$), 212.3 ($C_{quat.}$) ppm. MS (70 eV, EI): m/z (%) = 331 (3) [M^+], 332 (2) [M^+ – H], 234 (84) [$M^+ - C_6H_9O$], 212 (79) [$M^+ - C_{14}H_{14}NO$], 120 (100) [$C_8H_8O^+$], 105 (92) [$C_7H_5O^+$], 77 (36) [$C_7H_5^+$]. IR (KBr): $\tilde{\nu}$ = 3065 cm^{-1}, 2928, 2235 (C≡N), 1705 (C=O, cyclohexanone), 1678 (C=O, aryl ketone), 1607, 1597, 1508, 1448, 1419, 1368, 1309, 1247, 1233, 1179, 1128, 982, 830, 756, 682, 584, 564. $C_{22}H_{21}NO_2$ (331.4): calcd. C 79.73, H 6.39, N 4.23; found C 78.10, H 6.33, N 4.14.

4-[3-(4-Methoxyphenyl)-3-oxo-1-(2-oxocyclohexyl)propyl]benzonitrile (4f): According to the GP, after chromatography on silica gel (cyclohexane/ethyl acetate, 2:1) and recrystallization from ethanol 519 mg (72%) of **4f** was isolated as light-yellow crystals. M.p. 154–155 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.16–1.28 (m, 1 H), 1.56–1.82 (m, 4 H), 2.02 (d, J = 7.4 Hz, 1 H), 2.24–2.51 (m, 2 H), 2.74 (td, J = 4.9, 9.8 Hz, 1 H), 3.21 (dd, J = 9.8 Hz, 1 H), 3.50 (dd, J = 4.0, 4.0 Hz, 1 H), 3.75–3.84 (m, 1 H), 3.84 (s, OCH_3, 3 H), 6.89 (d, J = 8.7 Hz, 2 H), 7.33 (d, J = 8.2 Hz, 2 H), 7.54 (d, J = 8.0 Hz, 2 H), 7.89 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.4 (CH_2), 28.3 (CH_2), 32.5 (CH_2), 41.2 (CH), 42.4 (CH_2), 42.9 (CH_2), 55.1 (CH), 55.3 (OCH_3), 110.2 ($C_{quat.}$), 113.6 (CH), 118.7 ($C_{quat.}$), 129.3 (CH), 129.6 ($C_{quat.}$), 130.3 (CH), 132.1 (CH), 148.0 ($C_{quat.}$), 163.4 ($C_{quat.}$), 196.4 ($C_{quat.}$), 212.3 ($C_{quat.}$) ppm. MS (70 eV, EI): m/z (%) = 361 (1) [M^+], 263 (37) [$M^+ - C_6H_8O$], 211 (20) [$M^+ - C_9H_{10}O_2$], 150 (59) [$C_9H_{10}O_2^+$], 135 (100) [$C_8H_7O_2^+$], 77 (19) [$C_6H_5^+$]. IR (KBr): $\tilde{\nu}$ = 2937 cm^{-1}, 2229 (C≡N), 1701 (C=O, cyclohexanone), 1672 (C=O, aryl ketone), 1601, 1575, 1509, 1420, 1310, 1259, 1172, 1028, 838, 581. $C_{23}H_{23}NO_3$ (361.4): calcd. C 76.43, H 6.41, N 3.88; found C 76.10, H 6.37, N 3.86.

4-[3-(Furan-2-yl)-3-oxo-1-(2-oxocyclohexyl)propyl]benzonitrile (4g): According to the GP, after chromatography on silica gel (cyclohexane/ethyl acetate, 2:1) and recrystallization from ethanol 289 mg (45%) of **4g** was isolated as light-yellow crystals. M.p. 126–128 °C (ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.19–1.29 (m, 1 H), 1.55–1.83 (m, 4 H), 2.00–2.10 (m, 1 H), 2.33–2.53 (m, 2 H), 2.66–2.81 (m, 1 H), 3.19 (dd, J = 9.8 Hz, 1 H), 3.33 (dd, J = 15.0, 4.2 Hz, 1 H), 3.74–3.88 (m, 1 H), 6.48–6.50 (m, 1 H), 7.17 (d, J = 3.5 Hz, 1 H), 7.35 (d, J = 8.9 Hz, 2 H), 7.53 (d, J = 4.6 Hz, 1 H), 7.55 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.47 (CH_2), 28.30 (CH_2), 32.42 (CH_2), 40.71 (CH), 42.43 (CH_2), 42.83 (CH_2), 54.89 (CH), 110.48 ($C_{quat.}$), 112.24 (CH), 117.21 (CH), 118.75 ($C_{quat.}$), 129.34 (CH), 132.18 (CH), 146.31 (CH), 147.74 ($C_{quat.}$), 152.45 ($C_{quat.}$), 186.89 ($C_{quat.}$), 212.10 ($C_{quat.}$). IR (KBr): $\tilde{\nu}$ = 3060 cm^{-1}, 2935, 2227 (C≡N), 1673 (C=O, aryl ketone), 1601, 1512, 1305, 1255, 1159, 1096, 1028, 906, 835, 816, 668, 558.

4-(8a-Morpholino-2-phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-chromen-4-yl)benzonitrile (6): According to the GP, after the cycloaddition of enamine to the chalcone, column chromatography of the crude reaction mixture through a short pad of basic aluminum oxide (hexane/acetone, 5:1), and recrystallization from petroleum ether, 100 mg (25%) of **6** (mixture of two diastereomers, 4:1) was isolated as colorless crystals. MS (70 eV, EI): m/z (%) = 400.2 (8) [M^+], 313.2 (6) [$M^+ - C_4H_9NO$], 233.1 (24) [$M^+ - C_{10}H_{17}NO$]. HRMS ($C_{26}H_{28}N_2O_2$): calcd. 400.2151; found 400.2185.

General Procedure for the Coupling–Isomerization–Enamine Addition–Aminocyclization Sequence to Pyridines 11: A magnetically stirred solution of 364 mg (2.00 mmol) of **1a**, 2.1–2.8 mmol of propargyl alcohol **2**, 28 mg (0.04 mmol) of [$PdCl_2(PPh_3)_2$], and 4 mg (0.02 mmol) of CuI in 4 mL of a degassed mixture of triethylamine and THF (3:1) or in 4 mL of triethylamine or diethylamine under nitrogen was heated to reflux temperature for 12–16 h. After cooling to room temperature 2.5–3.5 mmol of enamine **9** in 1 mL of triethylamine was added and the reaction mixture was heated to reflux temp. for 16 h. After cooling to room temperature 8 mmol of ammonium chloride (**10a**) or 4 mmol of benzylamine (**10b**) and 5 mL of acetic acid were added and the mixture was heated to reflux temperature for the time indicated. After cooling to room temp., 40 mL of an aqueous solution of K_2CO_3 and 40 mL of ethyl acetate were added. The aqueous layer was extracted several times with ethyl acetate (4 × 20 mL). The combined organic phases were dried with magnesium sulfate, the solvents were removed in vacuo, and the residue was chromatographed on silica gel (cyclohexane/ethyl acetate or *n*-heptane/ethyl acetate, 2:1) and/or recrystallized from ethanol to give the analytically pure dihydropyridines and tetrahydroquinolines **5** (see Table 6 for experimental details).

Table 6. Experimental details of the one-pot synthesis of pyridine derivatives **11**.

Entry	Aryl halide **1** [mg (mmol)]	Propargyl alcohol **2** [mg (mmol)]	Enamine **9** [mg (mmol)]	Amine **10** [mg (mmol)]	*t* [h]	Pyridines **11** [mg (% yield)]
1[a]	364 (2.00) **1a**	280 (2.10) **2a**	378 (2.47) **9a**	428 (8.00) **10a**	5	287 (4) **11a**
2[b,c]	465 (2.03) **1c**	278 (2.10) **2a**	404 (2.64) **9a**	428 (8.00) **10a**	36	296 (42) **11b**
3[b,c]	320 (2.03) **1d**	278 (2.10) **2a**	404 (2.64) **9a**	428 (8.00) **10a**	36	344 (62) **11c**
4[b,c]	322 (2.03) **1e**	278 (2.10) **2a**	404 (2.64) **9a**	428 (8.00) **10a**	48	330 (59) **11d**
5[c,d]	455 (2.02) **1f**	278 (2.10) **2a**	404 (2.64) **9a**	428 (8.00) **10a**	48	368 (54) **11e**
6[a]	364 (2.00) **1a**	340 (2.10) **2b**	378 (2.47) **9a**	429 (4.00) **10b**	48	300 (31) **11f**
7[a]	364 (2.00) **1a**	280 (2.10) **2a**	460 (2.84) **9b**	428 (8.00) **10a**	14	432 (70) **11g**
8[c,d]	320 (2.03) **1d**	278 (2.10) **2a**	427 (2.55) **9b**	428 (8.00) **10a**	48	372 (64) **11h**
9[b,c]	322 (2.03) **1e**	278 (2.10) **2a**	427 (2.55) **9b**	428 (8.00) **10a**	48	290 (50) **11i**
10[a]	364 (2.00) **1a**	340 (2.10) **2b**	401 (2.47) **9b**	428 (8.00) **10a**	14	329 (48) **11j**
11[a,b]	182 (1.00) **1a**	139 (1.05) **2a**	275 (1.25) **9c**	214 (4.00) **10a**	24	177 (54) **11k**
12[a,b]	159 (0.87) **1a**	139 (1.05) **2a**	245 (1.25) **9d**	214 (4.00) **10a**	24	136 (46) **11l**
13[b,c]	161 (1.01) **1e**	139 (1.05) **2a**	427 (2.26) **9e**	214 (4.00) **10a**	48	211 (68) **11m**
14[a,b]	160 (1.00) **1e**	139 (1.05) **2a**	275 (1.25) **9c**	214 (4.00) **10a**	24	132 (39) **11n**
15[a,b]	182 (1.00) **1a**	139 (1.05) **2a**	300 (1.25) **9f**	214 (4.00) **10a**	24	234 (61) **11o**
16[a,b]	159 (1.00) **1c**	139 (1.05) **2a**	300 (1.25) **9f**	214 (4.00) **10a**	24	148 (41) **11p**
17[a,b]	160 (1.00) **1e**	139 (1.05) **2a**	300 (1.25) **9f**	214 (4.00) **10a**	24	206 (57) **11q**
18[a,b]	225 (1.00) **1f**	139 (1.05) **2a**	300 (1.25) **9f**	214 (4.00) **10a**	24	248 (58) **11r**

[a] Reaction time of the CIR 16 h. [b] In NEt_3. [c] Reaction time of the CIR 12 h. [d] In $HNEt_2$.

4-(2-Phenyl-6,7-dihydro-5*H*-[1]pyrindin-4-yl)benzonitrile (11a): According to the GP, after chromatography on silica gel (cyclohexane/ethyl acetate, 2:1) and recrystallization from ethanol 287 mg (48%) of analytically pure **11a** was isolated as colorless crystals. M.p. 154–156 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.16 (m, J = 7.6 Hz, 2 H, CH_2), 3.00 (t, J = 7.3 Hz, 2 H, CH_2), 3.16 (t, J = 7.6 Hz, 2 H, CH_2), 7.38–7.47 (m, 4 H), 7.61 (d, J = 8.4 Hz, 2 H), 7.75 (d, J = 8.4 Hz, 2 H), 7.98 (dd, J = 7.1, 1.1 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.3 (CH_2), 30.3 (CH_2), 34.6 (CH_2), 111.9 ($C_{quat.}$), 118.4 ($C_{quat.}$), 119.5 ($C_{quat.}$), 126.8 (CH), 128.8 (CH), 128.9 (CH), 128.8 (CH), 132.3 (CH), 132.8 (CH), 139.3 ($C_{quat.}$), 143.5 ($C_{quat.}$), 143.8 ($C_{quat.}$), 156.7 ($C_{quat.}$), 167.1 ($C_{quat.}$) ppm. MS (70 eV, EI): *m*/*z* (%) = 296 (89) [M^+]. IR (KBr): $\tilde{\nu}$ = 3056 cm^{-1}, 2953, 2227 (C≡N), 1590, 1576, 1497, 1422, 1372, 840, 776, 696, 570, 538. $C_{21}H_{16}N_2$ (296.4): calcd. C 85.11, H 5.44, N 9.45; found C 85.13, H 5.49, N 9.35.

Ethyl 4-(2-Phenyl-6,7-dihydro-5*H*-[1]pyrindin-4-yl)benzoate (11b): According to the GP, after chromatography on silica gel (hexane/ethyl acetate, 4:1) and recrystallization from ethanol 296 mg (42%) of **11b** was isolated as light-yellow crystals. M.p. 95–96 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.42 (t, J = 7.1 Hz, 3 H), 2.15 (m, 2 H), 3.03 (t, J = 7.3 Hz, 2 H), 3.16 (t, J = 7.6 Hz, 2 H) 4.4 (q, J = 7.1 Hz, 2 H), 7.32–7.48 (m, 3 H), 7.51 (s, 1 H), 7.56 (dt, J = 1.8, 8.6 Hz, 2 H), 7.96–7.98 (m, 2 H), 8.13 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.3 (CH_3), 23.5 (CH_2), 30.5 (CH_2), 34.7 (CH_2), 61.1 (CH_2), 117.9 (CH), 127.0 (CH), 128.1 (CH), 128.6 (CH), 128.7 (CH), 129.8 (CH), 130.2 ($C_{quat.}$), 133.1 ($C_{quat.}$), 139.5 ($C_{quat.}$), 143.3 ($C_{quat.}$), 144.9 ($C_{quat.}$), 156.5 ($C_{quat.}$), 166.2 ($C_{quat.}$), 166.8 ($C_{quat.}$) ppm. MS (70 eV, EI): *m*/*z* (%) = 343 (100) [M^+], 342 (70) [M^+ – H], 314 (38) [M^+ – C_2H_5]. IR (KBr): $\tilde{\nu}$ = 2975 cm^{-1}, 1715, 1610, 1591, 1577, 1554, 1458, 1440, 1424, 1367, 1311, 1274, 1182, 1106, 1021, 859, 776, 708, 698. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 262 nm (34 700), 308 (7800). $C_{23}H_{21}NO_2$ (343.4): calcd. C 80.44, H 6.16, N 4.08; found C 80.11, H 6.19, N 4.08.

2-Phenyl-4-(pyridin-2-yl)-6,7-dihydro-5*H*-[1]pyrindine (11c): According to the GP, after chromatography on silica gel (hexane/ethyl acetate, 4:1) and recrystallization from ethanol 344 mg (62%) of **11c** was isolated as light-brown crystals. M.p. 93 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.06–2.17 (m, 2 H), 3.10–3.17 (m, 4 H), 7.22–7.44 (m, 4 H), 7.45–7.69 (m, 1 H), 7.70 (dt, J = 1.8, 7.7 Hz, 1 H), 7.87 (s, 1 H), 8.00–8.03 (m, 2 H), 8.70–8.72 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.2 (CH_2), 30.9 (CH_2), 34.3 (CH_2), 117.3(CH), 122.7 (CH), 122.8 (CH), 126.8 (CH), 128.3 (CH), 128.4 (CH), 133.2 (C_{quat}), 136.3 (CH), 139.6 (C_{quat}), 143.8 (C_{quat}), 149.5 (CH), 156.24 (C_{quat}), 156.28 (C_{quat}), 167.0 ($C_{quat.}$) ppm. MS (70 eV, EI): *m*/*z* (%) = 272.1 (100) [M^+], 217.1 (10) [M^+ – C_3H_6N], 167.1 (12) [M^+ – C_5H_6N]. IR (KBr): $\tilde{\nu}$ = 3060 cm^{-1}, 2957, 2927, 1587, 1577, 1556, 1476, 1458, 1434, 1423, 1376, 1231, 992, 879, 793, 778, 748, 733, 696. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 248 nm (24 000), 266 (21 900), 310 (8300). $C_{19}H_{16}N_2$ (272.4): calcd. C 83.79, H 5.90, N 10.29; found C 83.31, H 6.10, N 10.06.

2-Phenyl-4-(pyrimidin-2-yl)-6,7-dihydro-5*H*-[1]pyrindine (11d): According to the GP, after chromatography on silica gel (hexane/ethyl acetate, 4:1) and recrystallization from ethanol 330 mg (59%) of **11d** was isolated as light-brown crystals. M.p. 120 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.09–2.20 (m, 2 H), 3.11 (t, J = 7.8 Hz, 2 H), 3.38 (t, J = 7.5 Hz, 2 H), 7.16 (t, J = 4.8 Hz, 1 H), 7.25–7.47 (m, 3 H), 8.02–8.06 (m, 2 H), 8.37 (s, 1 H), 8.79 (d, J = 4.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.9 (CH_2), 32.0 (CH_2), 34.1 (CH_2), 117.6 (CH), 119.3 (CH), 126.9 (CH), 127.1 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 133.9 ($C_{quat.}$), 139.5 ($C_{quat.}$), 141.5 ($C_{quat.}$), 156.1 ($C_{quat.}$), 156.7 (CH), 156.8 (CH), 164.4 ($C_{quat.}$), 167.6 ($C_{quat.}$) ppm. MS (70 eV, EI): *m*/*z* (%) = 273 (100) [M^+], 245 (5) [M^+ – C_2H_4], 194 (8) [M^+ – C_5H_5N]. IR (KBr): $\tilde{\nu}$ = 3063 cm^{-1}, 3040, 2961, 1592, 1569, 1548, 1457, 1424, 1375, 1261, 1232, 1186, 1176, 1075, 818, 773, 696, 628. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 250 nm (30 900), 290 (5100), 342 (6600). $C_{18}H_{15}N_3$ (273.3): calcd. C 79.10, H 5.53, N 15.37; found C 78.66, H 5.53, N 14.55.

2-Phenyl-4-[4-(trifluoromethyl)phenyl]-6,7-dihydro-5*H*-[1]pyrindine (11e): According to the GP, after chromatography on silica gel (hexane/ethyl acetate, 4:1) and recrystallization from ethanol, 368 mg (54%) of **11e** was isolated as light-brown crystals. M.p. 115–118 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.12–2.22 (m, 2 H), 3.01 (t, J = 7.3 Hz, 2 H), 3.17 (t, J = 7.6 Hz, 2 H), 7.37–7.5 (m, 3 H), 7.50 (s, 1 H), 7.62–7.76 (m, 4 H), 7.97–7.99 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.5 (CH_2), 30.4 (CH_2), 34.6 (CH_2), 118.0 (CH), 122.2 (CH), 125.6 (CH), 125.5 (CH), 125.6 (CH), 125.8 ($C_{quat.}$), 133.2 ($C_{quat.}$), 139.3 ($C_{quat.}$), 142.5 ($C_{quat.}$), 144.7 ($C_{quat.}$), 156.6 ($C_{quat.}$), 166.9 ($C_{quat.}$) ppm. MS (70eV, EI): *m*/*z* (%) = 339 (65) [M^+], 338 (100) [M^+ – H], 320 (7) [M^+ – F], 270 (7) [M^+ – F –

HF]. IR (KBr): $\tilde{\nu}$ = 3058 cm^{-1}, 2993,2974, 2954, 2885, 2836, 1619, 1592, 1576, 1560, 1438, 1425, 1412, 1373, 1324, 1160, 1134, 1126, 1109, 1065, 1016, 846, 776, 695. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 254 nm (30 900), 306 (8700). $C_{21}H_{16}F_3N$ (339.4): calcd. C 74.33, H 4.75, N 4.13; found C 74.08, H 4.45, N 4.25.

4-[2-(4-Methoxyphenyl)-6,7-dihydro-5*H*-[1]pyrindin-4-yl]benzonitrile (11f): According to the GP, after chromatography on silica gel (cyclohexane/ethyl acetate, 2:1) 300 mg (31%) of analytically pure **11f** was isolated as colorless crystals. M.p. 166–168 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.13 (m, J = 7.3 Hz, 2 H), 2.97 (t, J = 7.3 Hz, 2 H), 3.12 (t, J = 7.5 Hz, 2 H), 3.81 (s, 3 H), 6.95 (d, J = 8.9 Hz, 2 H), 7.40 (s, 1 H), 7.59 (d, J = 8.4 Hz, 2 H), 7.73 (d, J = 8.4 Hz, 2 H), 7.93 (d, J = 8.9 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.2 (CH_2), 30.2 (CH_2), 34.5 (CH_2), 55.1 (OCH_3), 111.7 ($C_{quat.}$), 113.9 (CH), 116.5 (CH), 118.4 ($C_{quat.}$), 127.9 (CH), 128.7 (CH), 131.8 ($C_{quat.}$), 131.9 ($C_{quat.}$), 132.0 ($C_{quat.}$), 132.2 (CH), 143.5, 143.7 ($C_{quat.}$), 156.2 ($C_{quat.}$), 160.1 ($C_{quat.}$), 166.8 ($C_{quat.}$) ppm. MS (70 eV, LC-ESI): m/z = 413 [M^+ + Na], 327 [M^+ + H]. IR (KBr): $\tilde{\nu}$ = 2966 cm^{-1}, 2227 (C≡N), 1606, 1572, 1545, 1438, 1412, 1361, 1301, 1242, 1179, 1109, 1031, 832, 792, 665, 605, 565. $C_{22}H_{18}N_2O$ (326.4): calcd. C 80.96, H 5.56, N 8.58; found C 80.84, H 5.29, N 8.54.

4-(2-Phenyl-5,6,7,8-tetrahydroquinolin-4-yl)benzonitrile (11g): According to the GP, after chromatography on silica gel (cyclohexane/ethyl acetate, 1:1), and recrystallization from ethanol 432 mg (70%) of analytically pure **11g** was isolated as colorless crystals. M.p. 194–195 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.77 (m, J = 7.0 Hz, 2 H), 1.95 (m, J = 6.0 Hz, 2 H), 2.59 (t, J = 6.4 Hz, 2 H), 3.10 (t, J = 6.6 Hz, 2 H), 7.26 (s, 1 H), 7.34–7.50 (m, 5 H), 7.75 (dd, J = 8.6, J = 2.0 Hz, 2 H), 7.96 (dd, J = 8.0, J = 1.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.8 (CH_2), 22.9 (CH_2), 27.1 (CH_2), 33.2 (CH_2), 111.7 ($C_{quat.}$), 118.3 (CH), 118.5 ($C_{quat.}$), 126.8 (CH), 127.8 ($C_{quat.}$), 128.7 (CH), 128.7 (CH), 129.4 (CH), 132.2 (CH), 139.2 ($C_{quat.}$), 144.5 ($C_{quat.}$), 148.2 ($C_{quat.}$), 154.6 ($C_{quat.}$), 158.1 ($C_{quat.}$) ppm. MS (70 eV, EI): m/z (%) = 310 (92) [M^+], 309 (100) [M^+ – H]. IR (KBr): $\tilde{\nu}$ = 2934 cm^{-1}, 2224 (C≡N), 1590, 1537, 1442, 1433, 1381, 901, 843, 774, 691, 590. $C_{22}H_{18}N_2$ (310.4): calcd. C 85.13, H 5.85, N 9.02; found C 84.80, H 5.87, N 8.94.

2-Phenyl-4-(pyridin-2-yl)-5,6,7,8-tetrahydroquinoline (11h): According to the GP, after chromatography on silica gel (hexane/ethyl acetate, 4:1), and recrystallization from ethanol 372 mg (64%) of **11h** was isolated as red-brown crystals. M.p. 95–96 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.73–1.81 (m, 2 H), 1.90–2.03 (m, 2 H), 2.74 (t, J = 6.36 Hz, 2 H), 3.07 (t, J = 6.45 Hz, 2 H), 7.29–7.46 (m, 5 H), 7.52 (s, 1 H), 7.76 (dt, J = 1.8, 7.7 Hz, 1 H), 7.95–7.99 (m, 2 H), 8.71–8.73 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.7 (CH_2), 22.8 (CH_2), 22.6 (CH_2), 33.2 (CH_2), 118.5 (CH), 122.4 (CH), 123.6 (CH), 126.7 (CH), 128.3 (CH), 128.4 (CH), 136.6 (CH), 139.4 ($C_{quat.}$), 148.2 ($C_{quat.}$), 149.2 (CH), 154.3 ($C_{quat.}$), 157.9 ($C_{quat.}$) ppm. MS (70 eV, EI): m/z (%) = 287 (28) [M^+ + 1], 286 (68) [M^+ – C_2H_4], 77 (100) [$C_6H_5^+$]. IR (KBr): $\tilde{\nu}$ = 2936 cm^{-1}, 2858, 1630, 1583, 1567, 1544, 1473, 1455, 1444, 1429, 1383, 793, 776, 753, 695, 657, 602, 584, 549. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 240 nm (19 500), 258 (21 400), 300 (9300). $C_{20}H_{18}N_2$ (286.4): calcd. C 83.88, H 6.34, N 9.78; found C 83.76, H 6.30, N 9.80.

2-Phenyl-4-(pyrimidin-2-yl)-5,6,7,8-tetrahydroquinoline (11i): According to the GP, after chromatography on silica gel (hexane/ethyl acetate, 4:1), and recrystallization from ethanol 290 mg (50%) of **11i** was isolated as light-brown crystals. M.p. 120 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.33–1.82 (m, 2 H), 1.90–2.16 (m, 2 H), 2.94 (t, J = 6.4 Hz, 2 H), 3.11 (t, J = 6.4 Hz, 2 H), 7.26 (t, J = 4.8 Hz, 1 H), 7.32–7.46 (m, 3 H), 7.84 (s, 1 H), 7.98–8.02 (m, 2 H), 8.85 (d, J = 4.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.6 (CH_2), 22.7 (CH_2), 26.7 (CH_2), 33.3 (CH_2), 118.8 (CH), 119.3 (CH), 126.7 (CH), 128.3 (CH), 128.9 (CH), 129.1 ($C_{quat.}$), 139.3 ($C_{quat.}$), 145.8 ($C_{quat.}$), 154.3 ($C_{quat.}$), 156.8 (CH), 158.2 ($C_{quat.}$), 166.1 ($C_{quat.}$) ppm. MS (70 eV, EI): m/z (%) = 287 (100) [M^+], 272 (32) [M^+ – CH_3], 259 (12) [M^+ – C_2H_4]. IR (KBr): $\tilde{\nu}$ = 3050 cm^{-1}, 2939, 2915, 2878, 2857, 1592, 1564, 1543, 1456, 1440, 1419, 1378, 1228, 845, 831, 771, 736, 694, 633. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 250 nm (26 300), 286 (7100), 308 (7600). $C_{19}H_{17}N_3$ (287.4): calcd. C 79.41, H 5.96, N 14.62; found C 79.15, H 5.93, N 14.49.

4-[2-(4-Methoxyphenyl)-5,6,7,8-tetrahydroquinolin-4-yl]benzonitrile (11j): According to the GP, after chromatography on silica gel (cyclohexane/ethyl acetate, 2:1), and recrystallization from ethanol 329 mg (48%) of analytically pure **11j** was isolated as colorless crystals. M.p. 125–127 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.67 (m, 2 H), 1.84 (m, 2 H), 2.48 (m, 2 H), 2.98 (m, 2 H), 3.75 (s, 3 H), 6.88 (d, J = 8.7 Hz, 2 H), 7.20 (s, 1 H), 7.36 (d, J = 8.0 Hz, 2 H), 7.65 (d, J = 7.9 Hz, 2 H), 7.83 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.8 (CH_2), 22.9 (CH_2), 27.0 (CH_2), 33.2 (CH_2), 55.2 (OCH_3), 111.5 ($C_{quat.}$), 114.0 (CH), 117.6 (CH), 118.5 (CH), 127.0 ($C_{quat.}$), 127.9 (CH), 129.3 (CH), 131.7 ($C_{quat.}$), 132.1 (CH), 144.5 ($C_{quat.}$), 148.2 ($C_{quat.}$), 154.1 ($C_{quat.}$), 157.8 ($C_{quat.}$), 160.2 ($C_{quat.}$), 166.8 ($C_{quat.}$) ppm. MS (70 eV, LC-ESI): m/z = 341 [M^+ + H]. IR (KBr): $\tilde{\nu}$ = 2934 cm^{-1}, 2225 (C≡N), 1604, 1509, 1241, 1170, 1029, 834, 605, 565. $C_{23}H_{20}N_2O$·0.33 EtOH (355.7): calcd. C 79.80, H 6.23, N 7.87; found C 79.80, H 5.93, N 7.72.

4-[2-(4-Methoxyphenyl)-6-phenylpyridin-4-yl]benzonitrile (11k): According to the GP, after chromatography on silica gel (hexane/ethyl acetate, 4:1), and recrystallization from ethanol 177 mg (54%) of **11k** was isolated as colorless crystals. M.p. 134–135 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.88 (s, 3 H), 7.02 (d, J = 8.9 Hz, 2 H), 7.45–7.54 (m, 3 H), 7.75–7.79 (m, 6 H), 8.13–8.19 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.4 (OCH_3), 112.5 ($C_{quat.}$), 114.1 (CH), 116.0 (CH), 116.1 (CH), 118.5 ($C_{quat.}$), 127.0 (CH), 127.9 (CH), 128.4 (CH), 128.7 (CH), 129.3 (CH), 131.6 ($C_{quat.}$), 132.8 (CH), 139.1 ($C_{quat.}$), 143.6 ($C_{quat.}$), 148.0 ($C_{quat.}$), 157.4 ($C_{quat.}$), 157.7 ($C_{quat.}$), 160.8 ($C_{quat.}$) ppm. MS (70 eV, EI): m/z (%) = 362 (100) [M^+], 347 (20) [M^+ – CH_3]. IR (KBr): $\tilde{\nu}$ = 2922 cm^{-1}, 2227, 1599, 1580, 1566, 1542, 1513, 1432, 1417, 1391, 1249, 1178, 1209, 831, 776, 694, 586, 547, 516. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 250 nm (36 300), 282 (28 200), 332 (5900). $C_{25}H_{18}N_2O$ (326.4): calcd. C 82.85, H 5.01, N 7.73; found C 82.61, H 5.01, N 7.71.

4-[2-Phenyl-6-(thiophen-2-yl)pyridin-4-yl]benzonitrile (11l): According to the GP, after chromatography on silica gel (hexane/ethyl acetate, 4:1), and recrystallization from ethanol 136 mg (46%) of **11l** was isolated as yellow crystals. M.p. 192 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.14–7.16 (m, 1 H), 7.33–7.54 (m, 4 H), 7.71–7.74 (m, 3 H), 7.80–7.81 (m, 4 H), 8.14–8.17 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 112.6 ($C_{quat.}$), 114.8 (CH), 116.3 (CH), 118.2 ($C_{quat.}$), 126.8 (CH), 127.7 (CH), 127.9 (CH), 127.9 (CH), 128.6 (CH), 129.3 (CH), 132.7 (CH), 138.3 ($C_{quat.}$), 143.1 ($C_{quat.}$), 144.7 ($C_{quat.}$), 148.0 ($C_{quat.}$), 152.9 ($C_{quat.}$), 157.5 ($C_{quat.}$) ppm. MS (70eV, EI): m/z (%) = 338 (100) [M^+], 305 (8) [M^+ – HS]. IR (KBr): $\tilde{\nu}$ = 2227 cm^{-1}, 1597, 1581, 1569, 1544, 1508, 1497, 1437, 1419, 1389, 1236, 832, 775, 732, 695, 634. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 268 nm (55 000), 290 (31 600), 336 (11 000). $C_{22}H_{14}N_2S$ (338.4): calcd. C 78.08, H 4.17, N 8.28; found C 77.66, H 4.23, N 8.28.

2-(2,6-Diphenylpyridin-4-yl)pyrimidine (11m): According to the GP, after chromatography on silica gel (hexane/ethyl acetate, 1:1), and recrystallization from ethanol, 211 mg (68%) of **11m** was isolated as light-brown crystals. M.p. 224 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.32 (t, J = 4.8 Hz, 1 H), 7.42–7.56 (m, 6 H), 8.29–8.32 (m, 4

H), 8.75 (s, 2 H), 8.90 (d, J = 4.89 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 116.9 (CH), 120.3 (CH), 127.0 (CH), 128.5 (CH), 128.9 (CH), 129.1 (CH), 139.2 ($C_{quat.}$), 146.2 ($C_{quat.}$), 157.2 (CH), 157.5 ($C_{quat.}$), 163.0 ($C_{quat.}$) ppm. MS (70eV, EI): m/z (%) = 309 (68) [M^+], 77 (100) [$C_6H_5^+$]. IR (KBr): $\tilde{\nu}$ = 3038 cm^{-1}, 1602, 1580, 1565, 1549, 1462, 1449, 1424, 1399, 1233, 896, 811, 772, 732, 691, 669, 640, 629, 618. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 248 nm (79 400), 270 (38 000), 332 (11 200). $C_{21}H_{15}N_3$ (309.4): calcd. C 81.53, H 4.89, N 13.58; found C 81.30, H 4.84, N 13.23.

2-[2-(4-Methoxyphenyl)-6-phenylpyridin-4-yl]pyrimidine (11n): According to the GP, after work up, chromatography on silica gel (hexane/ethyl acetate, 1:1), and recrystallization from ethanol, 132 mg (39%) of **11n** was isolated as yellow crystals. M.p. 144 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.87 (s, 3 H), 7.02 (dt, J = 1.5, 5.3 Hz, 2 H), 7.29 (t, J = 2.9 Hz, 1 H), 7.43–7.52 (m, 3 H), 8.24–8.28 (m, 4 H), 8.52 (s, 1 H), 8.53 (s, 1 H), 8.87 (d, J = 2.9 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.3 (OCH_3), 114.0 (CH), 116.3 (CH), 116.3 (CH), 120.5 (CH), 127.1 (CH), 128.4 (CH), 128.6 (CH), 129.0 (CH), 132.0 ($C_{quat.}$), 139.5 ($C_{quat.}$), 146.3 ($C_{quat.}$), 157.3 ($C_{quat.}$), 157.4 ($C_{quat.}$), 157.4 ($C_{quat.}$), 160.6 ($C_{quat.}$), 163.2 ($C_{quat.}$) ppm. MS (70 eV, EI): m/z (%) = 339 (100) [M^+], 324 (20) [$M^+ - CH_3$], 296 (18) [M^+]. IR (KBr): $\tilde{\nu}$ = 3043 cm^{-1}, 2831, 1606, 1580, 1566, 1547, 1515, 1457, 1434, 1419, 1400, 1305, 1251, 1232, 1176, 1031, 835, 807, 773, 696, 640. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 252 nm (48 000), 282 (20 900), 344 (8300). $C_{20}H_{17}N_3O$ (339.4): calcd. C 77.88, H 5.01, N 12.39; found C 77.66, H 5.08, N 12.27.

Ethyl 4-(4-Cyanophenyl)-2-phenyl-7,8-dihydro-5*H*-[1,6]naphthyridine-6-carboxylate (11o): According to the GP, after work up, chromatography on silica gel (hexane/ethyl acetate, 4:1), and recrystallization from ethanol, 234 mg (61%) of **1o** was isolated as light-yellow crystals. M.p. 189 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.20–1.31 (m, 3 H), 3.19 (t, J = 6.0 Hz, 2 H), 3.83 (t, J = 6.1 Hz, 2 H), 4.10 (q, J = 7.1 Hz, 2 H), 4.48 (s, 2 H), 7.38–7.49 (m, 6 H), 7.77 (d, J = 8.2 Hz, 2 H), 7.96 (dd, J = 1.5, 8.2 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.7 (CH_3), 32.6 (CH_2), 41.4 (CH_2), 43.6 (CH_2), 61.7 (CH_2), 112.5 ($C_{quat.}$), 118.3 ($C_{quat.}$), 119.0 (CH), 126.9 (CH), 128.8 (CH), 129.2 (CH), 129.2 (CH), 132.6 (CH), 138.6 ($C_{quat.}$), 142.8 ($C_{quat.}$), 155.5 ($C_{quat.}$), 155.7 ($C_{quat.}$) ppm. MS (70 eV, EI): m/z (%) = 383 (18) [M^+], 354 (100) [$M^+ - CH_2CH_3$], 310 (55) [$M^+ - CO_2CH_2CH_3$]. IR (KBr): $\tilde{\nu}$ = 2984 cm^{-1}, 2225, 1698, 1591, 1545, 1482, 1468, 1418, 1386, 1329, 1270, 1240, 1190, 1135, 1103, 1024, 846, 781, 697. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 254 nm (47 900), 300 (12 900). $C_{22}H_{14}N_2S$ (383.44): calcd. C 75.18, H 5.52, N 10.96; found C 74.91, H 5.53, N 10.83.

Ethyl 2-Phenyl-4-(pyridin-2-yl)-7,8-dihydro-5*H*-[1,6]naphthyridine-6-carboxylate (11p): According to the GP, after work up and chromatography on silica gel (hexane/ethyl acetate, 4:1), 148 mg (41%) of **11p** was isolated as yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.20–1.26 (m, 3 H), 3.13 (t, J = 6.0 Hz, 2 H), 3.85 (t, J = 6.1 Hz, 2 H), 4.12 (q, J = 7.0 Hz, 2 H), 4.82 (s, 2 H), 7.42–7.51 (m, 4 H), 7.76 (dd, J = 1.0, 8.0 Hz, 1 H), 7.85 (s, 1 H), 7.97 (dt, J = 1.8, 8.0 Hz, 1 H), 8.16–8.20 (m, 2 H), 8.74–8.76 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.9 (CH_3), 33.4 (CH_2), 42.0 (CH_2), 44.7 (CH_2), 61.7 (CH_2), 119.2 (CH), 124.1 (CH), 124.9 (CH), 127.5 (CH), 129.4 (CH), 129.7 (CH), 138.0 (CH), 139.8 ($C_{quat.}$), 147.5 ($C_{quat.}$), 151.4 (CH), 156.3 ($C_{quat.}$), 157.8 ($C_{quat.}$). IR (KBr): $\tilde{\nu}$ = 2980 cm^{-1}, 1696, 1583, 1547, 1430, 1384, 1332, 1271, 1239, 1203, 1172, 1144, 1107, 1048, 1024, 794, 774, 748, 696. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 254 nm (19 100), 300 (9100), 366 (900). HRMS ($C_{22}H_{21}N_3O_2$): calcd. 359.1634; found 359.1645.

Ethyl 2-Phenyl-4-(pyrimidin-2-yl)-7,8-dihydro-5*H*-[1,6]naphthyridine-6-carboxylate (11q): According to the GP, after work up, chromatography on silica gel (hexane/ethyl acetate, 4:1), and recrystallization from ethanol, 206 mg (57%) of **11q** was isolated as yellow crystals. M.p. 163 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.18–1.23 (m, 3 H), 3.13 (t, J = 6.0 Hz, 2 H), 3.78 (t, J = 6.1 Hz, 2 H), 4.05 (q, J = 7.1 Hz, 2 H), 5.00 (s, 2 H), 7.23 (t, J = 4.9 Hz, 1 H), 7.29–7.41 (m, 3 H), 7.73 (d, J = 8.1 Hz, 2 H), 7.96 (dt, J = 1.5, 6.9 Hz, 2 H), 8.16 (s, 1 H), 8.80 (d, J = 4.9 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.7 (CH_3), 33.0 (CH_2), 41.1 (CH_2), 44.6 (CH_2), 61.4 (CH_2), 119.4 (CH), 119.8 (CH), 125.7 (CH), 126.9 (CH), 128.6 (CH), 128.8 (CH), 138.9 ($C_{quat.}$), 155.5 ($C_{quat.}$), 155.5 ($C_{quat.}$), 157.1 (CH), 164.7 ($C_{quat.}$) ppm. MS (70 eV, EI): m/z (%) = 360 (92) [M^+], 287 (100) [$M^+ - CO_2CH_2CH_3$], 260 (58) [M^+]. IR (KBr): $\tilde{\nu}$ = 2984 cm^{-1}, 2939, 1685, 1589, 1542, 1468, 1437, 1415, 1385, 1306, 1287, 1274, 1169, 1105, 818, 782, 739, 704. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 250 nm (30 900), 288 (6000), 312 (8100). $C_{21}H_{20}N_4O_2$ (360.4): calcd. C 69.98, H 5.59, N 15.55; found C 69.52, H 5.56, N 15.22.

Ethyl 2-Phenyl-4-[4-(trifluoromethyl)phenyl)-7,8-dihydro-5*H*-[1,6]naphthyridine-6-carboxylate (11r): According to the GP, after work up, chromatography on silica gel (hexane/ethyl acetate, 4:1), and recrystallization from ethanol, 248 mg (58%) of **11r** was isolated as yellow crystals. M.p. 126 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.22–1.25 (m, 3 H), 3.19 (t, J = 6.1 Hz, 2 H), 3.84 (t, J = 6.1 Hz, 2 H), 4.11 (q, J = 7.1 Hz, 2 H), 4.51 (s, 2 H), 7.38–7.49 (m, 6 H), 7.73 (d, J = 8.1 Hz, 2 H), 7.96–7.99 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.7 (CH_3), 32.6 (CH_2), 41.4 (CH_2), 43.6 (CH_2), 61.6 (CH_2), 119.3 (CH), 119.0 (CH), 125.7 (CH), 125.8 (CH), 125.8 (CH), 126.9 (CH), 128.7 (CH), 130.4 (CH), 130.9 (CH), 138.8 ($C_{quat.}$), 141.7 ($C_{quat.}$), 155.5 ($C_{quat.}$), 155.5 ($C_{quat.}$), 155.7 ($C_{quat.}$) ppm. MS (70 eV, EI): m/z (%) = 426 (10) [M^+], 397 (100) [$M^+ - CH_2CH_3$], 353 (30) [$M^+ - CO_2CH_2CH_3$]. IR (KBr): $\tilde{\nu}$ = 2984 cm^{-1}, 1698, 1592, 1548, 1469, 1431, 1387, 1326, 1284, 1270, 1243, 1198, 1169, 1129, 1108, 1065, 1019, 847, 778, 696. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 250 nm (22 400), 288 (10 000), 298 (9500). $C_{24}H_{21}N_2O_2$ (426.4): calcd. C 67.60, H 4.96, N 6.57; found C 67.30, H 5.19, N 6.81.

General Procedure for the Coupling–Isomerization–Enamino Ester–Cyclocondensation: A magnetically stirred solution of 1.0 equiv. of halogen compound **1**, 1.05 equiv. of propargyl alcohol **2a**, 0.02 equiv. of [$PdCl_2(PPh_3)$], and 0.01 equiv. of CuI in 4 mL of degassed triethylamine or diethylamine under nitrogen was heated to reflux temperature for 12 h (see Table 7 for experimental details). After cooling to room temperature a solution of 1.0 equiv. of ethyl 3-aminocrotonate (**12**) in 1 mL of triethylamine or diethylamine and 2 mL of acetic acid were added, and the reaction mixture was heated to reflux temperature for 24 h. After cooling to room temperature 40 mL of ethyl acetate and 40 mL of water were added and stirring was continued for 5 to 10 min. The aqueous layer was extracted with ethyl acetate (4 × 15 mL) and the combined organic phase was dried with magnesium sulfate. After filtration the solvents were removed in vacuo and the residue was chromatographed on silica gel (hexane/ethyl acetate, 4:1 or 1:1) and recrystallized from ethanol or pentane/chloroform (1:1) to give the analytically pure dihydropyridine (**13**) and pyridine derivatives (**14**).

Ethyl 4-(4-Cyanophenyl)-2-methyl-6-phenyl-1,4-dihydropyridine-3-carboxylate (13a): According to the GP, after chromatography on silica gel (hexane/ethyl acetate, 4:1) 155 mg (45%) of **13a** was isolated as yellow crystals. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.01 (t, J = 7 Hz, 3 H), 2.34 (s, 3 H), 3.89–3.98 (m, 2 H), 4.66 (d, J = 5.5 Hz, 1 H), 5.00 (dd, J = 2, 5.3 Hz, 1 H), 5.78 (s, 1 H), 7.18–7.35 (m, 7 H), 7.45–7.48 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.5 (CH_3), 19.7 (CH_3), 41.6 (CH), 59.5 (CH_2), 97.5 ($C_{quat.}$),

Table 7. Experimental details of the one-pot, three-component synthesis of dihydropyridines **13** and pyridines **14**.

Entry	Aryl halide **1** [mg (mmol)]	1-Phenylpropargyl alcohol (**2a**) [mg (mmol)]	Ethyl 3-aminocrotonate (**12**) [mg (mmol)]	Pyridines **11** (yield) [mg (% yield)]
1[a]	182 (1.00) **1a**	139 (1.05)	263 (2.00)	155 (45) **13a**
2[b]	561 (2.00) **1f**	278 (2.10)	526 (4.00)	268 (37) **13b**
3[a]	182 (1.00) **1a**	139 (1.05)	263 (2.00)	137 (40) **14a**
4[a]	161 (1.00) **1e**	139 (1.05)	263 (2.00)	154 (50) **14b**
5[c]	140 (1.00) **1b**	139 (1.05)	263 (2.00)	85 (26) **14c**
6[b]	320 (2.00) **1d**	139 (1.05)	263 (2.00)	83 (26) **14d**

[a] In NEt_3. [b] In $HNEt_2$. [c] In NEt_3/THF (1:1).

103.9 (CH), 110.1 ($C_{quat.}$), 119.7 ($C_{quat.}$), 126.3 (CH), 127.1 (CH), 129.2 (CH), 132.9 (CH), 133.2 (CH), 136.2 ($C_{quat.}$), 136.6 ($C_{quat.}$), 150.2 ($C_{quat.}$), 151.3 ($C_{quat.}$), 155.5 ($C_{quat.}$), 168.3 ($C_{quat.}$) ppm. MS (70eV, EI): *m/z* (%) = 344.2 (15) [M^+], 315.1 (36) [$M^+ - C_2H_5$], 271.2 (20) [$M^+ - CO_2C_2H_5$], 242.2 (100) [$M^+ - C_7H_4N$].

Ethyl 2-Methyl-6-phenyl-4-[4-(trifluoromethyl)phenyl]-1,4-dihydropyridine-3-carboxylate (13b): According to the GP, after chromatography on silica gel (hexane/ethyl acetate, 5:1) 268 mg (37%) of **13b** was isolated as yellow crystals. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.01 (t, *J* = 7 Hz, 3 H), 2.30 (s, 3 H), 3.86–3.94 (m, 2 H), 4.64 (d, *J* = 5.25 Hz, 1 H), 5.00 (dd, *J* = 1.75, 5.25 Hz, 1 H), 5.65 (s, 1 H), 7.20–7.33 (m, 7 H), 7.40 (d, *J* = 8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.1 (CH_3), 20.6 (CH_3), 41.0 (CH), 59.3 (CH_2), 98.4 ($C_{quat.}$), 104.1 (CH), 125.1 (CH), 128.3 (CH), 128.7 (CH), 134.9 ($C_{quat.}$), 147.4 ($C_{quat.}$), 152.7 ($C_{quat.}$), 168.0 ($C_{quat.}$) ppm. MS (70eV, EI): *m/z* (%) = 387.1 (15) [M^+], 358.1 (18) [$M^+ - C_2H_5$], 314.1 (25) [$M^+ - CO_2C_2H_5$], 242.1 (100) [$M^+ - C_7H_4F_3$]. HRMS ($C_{22}H_{20}F_3NO_2$): calcd. 387.1446; found 387.1453.

Ethyl 4-(4-Cyanophenyl)-2-methyl-6-phenylnicotinate (14a): According to the GP, after chromatography on silica gel (hexane/ethyl acetate, 4:1) and recrystallization from ethanol, 137 mg (40%) of **14a** was isolated as light-brown crystals. M.p. 131 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.01 (t, *J* = 7.1 Hz, 3 H), 2.73 (s, 1 H), 4.09 (q, *J* = 7.2 Hz, 2 H), 7.43–7.53 (m, 6 H), 7.72–7.75 (m, 2 H), 8.00–8.03 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.7 (CH_3), 23.2 (CH_3), 61.5 (CH_2), 112.4 ($C_{quat.}$), 117.9 (CH), 118.3 ($C_{quat.}$), 126.1 ($C_{quat.}$), 127.1 (CH), 128.7 (CH), 128.8 (CH), 129.6 (CH), 132.1 (CH), 132.2 (CH), 138.2 ($C_{quat.}$), 143.6 ($C_{quat.}$), 147.1 ($C_{quat.}$), 156.3 ($C_{quat.}$), 157.7 ($C_{quat.}$), 168.1 ($C_{quat.}$) ppm. MS (70eV, EI): *m/z* (%) = 342 (100) [M^+], 313 (60) [$M^+ - C_2H_5$], 297 (76) [$M^+ - C_2H_5O$]. IR (KBr): $\tilde{\nu}$ = 3060 cm^{-1}, 2993, 2229, 1722, 1588, 1567, 1540, 1500, 1380, 1361, 1280, 1265, 1243, 1184, 1148, 1097, 1078, 850, 772, 695, 587. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 256 (35 500), 298 (12 000). $C_{22}H_{18}N_2O_2$ (342.4): calcd. C 77.17, H 5.30, N 8.18; found C 76.84, H 5.33, N 8.12.

Ethyl 2-Methyl-6-phenyl-4-pyrimidin-2-ylnicotinate (14b): According to the GP, after chromatography on silica gel (hexane/ethyl acetate, 1:1) and recrystallization from ethanol, 154 mg (50%) of **14b** was isolated as light-brown crystals. M.p. 115–118 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.27–1.35 (m, 3 H), 2.77 (s, 3 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 7.28 (t, *J* = 4.9 Hz, 1 H), 7.44–7.53 (m, 3 H), 8.13–8.15 (m, 2 H), 8.49 (s, 1 H), 8.83 (d, *J* = 4.9 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.9 (CH_3), 22.8 (CH_3), 61.2 (CH_2), 117.3 (CH), 120.2 (CH), 126.5 ($C_{quat.}$), 127.0 (CH), 127.1 (CH), 128.6 (CH), 129.3 (CH), 138.5 ($C_{quat.}$), 143.8 ($C_{quat.}$), 156.1 ($C_{quat.}$), 156.9 (CH), 157.6 ($C_{quat.}$), 162.9($C_{quat.}$), 169.3 ($C_{quat.}$) ppm. MS (70eV, EI): *m/z* (%) = 319 (93) [M^+], 274 (100) [$M^+ - C_2H_5O$], 246 (36) [$M^+ - C_3H_5O_2$]. IR (KBr): $\tilde{\nu}$ = 2975 cm^{-1}, 1715, 1585, 1565, 1550, 1457, 1424, 1386, 1369, 1274, 1175, 1158, 1110, 1075, 1010, 837, 813, 760, 696. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 250 nm (28 200), 314 (10 200). $C_{19}H_{17}N_3O_2$ (319.4): calcd. C 71.46, H 5.37, N 13.16; found C 71.28, H 5.35, N 13.08.

Ethyl 2-Methyl-6-phenyl-4-(thiazol-2-yl)nicotinate (14c): According to the GP, after chromatography on silica gel (hexane/ethyl acetate, 5:1) 268 mg (37%) of **13b** was isolated as yellow crystals. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.30 (t, *J* = 7 Hz, 3 H), 2.90 (s, 3 H), 4.36 (q, *J* = 7 Hz 2 H), 7.4 (d, *J* = 3.25 Hz, 1 H), 7.47–7.51 (m, 3 H), 7.88 (s, 1 H), 7.94 (d, *J* = 3.25 Hz, 1 H), 8.03–8.06 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.1 (CH_3), 22.9 (CH_3), 62.1 (CH_2), 117.2 (CH), 122.6 (CH), 123.1 (CH), 126.1 ($C_{quat.}$), 127.9 (CH), 129.6 (CH), 130.5 (CH), 138.8 ($C_{quat.}$), 139.9 ($C_{quat.}$), 144.9 (CH), 156.8 ($C_{quat.}$), 158.2 ($C_{quat.}$), 164.4 ($C_{quat.}$), 168.7 ($C_{quat.}$) ppm. MS (70eV, EI): *m/z* (%) = 324.0 (38) [M^+], 295.0 (10) [$M^+ - C_2H_5$], 279.1 (36) [$M^+ - C_2H_5O$].

Ethyl 2′-Methyl-6′-phenyl-1′,4′-dihydro-2,4-bipyridinyl-3′-carboxylate (14d): According to the GP, after chromatography on silica gel (hexane/ethyl acetate, 1:1) and recrystallization from ethanol, 83 mg (26%) of **14d** was isolated as a brown oil. ^1H NMR ($CDCl_3$, 3000 MHz): δ = 1.03 (t, *J* = 7 Hz, 3 H), 2.68 (s, 3 H), 4.12 (q, *J* = 7 Hz, 2 H), 7.23–7.28 (m, 1 H), 7.35–7.45 (m, 3 H), 7.57 (d, *J* = 8 Hz, 1 H), 7.70–7.77 (m, 2 H), 7.96–8.00 (m, 2 H), 8.59–8.61 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.7 (CH_3), 23.1 (CH_3), 61.2 (CH_2), 117.3 (CH), 122.3 (CH), 122.3 (CH), 123.3 (CH), 127.4 (C_{quat}), 128.7 (CH), 136.8 (CH), 138.7 (C_{quat}), 147.0 (C_{quat}), 149.3 (CH), 156.0 (C_{quat}), 156.5 (C_{quat}), 157.6 (C_{quat}), 169.0 (C_{quat}). IR (KBr): $\tilde{\nu}$ = 3060 cm^{-1}, 2980, 2930, 2902, 2860, 1952, 1728, 1585, 1549, 1474, 1434, 1383, 1364, 1344, 1269, 1183, 1153, 1106, 1028, 994, 859, 797, 768, 695. UV/Vis (CH_2Cl_2): λ_{max} (ε) = 252 nm (19 500), 304 (9300). HRMS-EI ($C_{20}H_{18}N_2O_2$): calcd. 318.1368; found 318.1367.

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