One-Pot Reactions

DOI: 10.1002/anie.201103296

Catalytic Syntheses of N-Heterocyclic Ynones and Ynediones by In Situ Activation of Carboxylic Acids with Oxalyl Chloride**

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Dedicated to Professor Kenkichi Sonogashira on the occasion of his 80th birthday

Ynones are highly reactive Michael systems and can be smoothly reacted with various mono- and binucleophiles in addition and addition–cyclocondensation processes. Consequently, they have received considerable attention as valuable building blocks in heterocycle[1] and natural-product[2] synthesis. Ynediones contain a 1,2-dione motif and are even more densely functionalized electrophiles, thus enabling a more multifaceted transformation profile towards heterocycles.[3,4] Despite their auspicious synthetic potential, ynediones have remained scarcely explored owing to a lack of a general and practical preparative access.[5] Therefore, a direct, simple, and efficient route to this class of compounds would be highly desirable.

Aryl-substituted ynones can be easily prepared by stoichiometric or catalytic acylation of organometallic reagents, especially by Sonogashira coupling.[6,7] However, an essential limitation of this methodology to date is the lack of an efficient method for the preparation of ynones with N-heterocyclic substituents.[8,9] N-Heteroarenes are pervasive in numerous natural products[10] and in biologically active agents in medicinal chemistry, and the quest for nitrogen-containing building blocks is enormous. However, the often observed low reactivity in cross-coupling reactions resulting from substrate or product inhibition by coordination to transition metals[11] has fostered the necessity to develop a convincing and robust methodology for breaking this bottleneck. For instance, pyridine or quinoline carboxylic acid chlorides, which are highly interesting building blocks in medicinal chemistry, are often not readily available and thus, their transformation to ynones under modified Sonogashira coupling conditions[12] was not considered to be practical. On the other hand, N-heterocyclic carboxylic acids are the immediate precursors of acid chlorides. Therefore, a one-pot access to ynones starting directly from carboxylic acids could overcome the shortcomings of acid chloride preparation and isolation, and a valuable, conceptually new synthetic tool for ynone preparation could evolve.

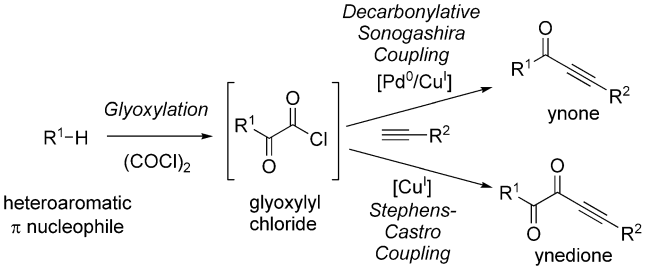
Aromatic carboxylic acids have received considerable attention as aryl-nucleophile precursors in metal-catalyzed cross-couplings,[13] which in most cases proceed under decarboxylation.[14,15] Cross-couplings of carboxylic acids using an excess of anhydrides or carbonates for activation allow for the carbonyl group to be maintained but result in the formation of simple alkyl and aryl ketones.[16]

At the same time, the activation of carboxylic acids with oxalyl chloride is a widespread, mild, and clean method for the preparation of acid chlorides, which produces only gaseous by-products (carbon monoxide, carbon dioxide, and hydrogen chloride).[17] Thus, an in situ conversion of carboxylic acids to acid chlorides using oxalyl chloride followed by alkyne coupling in a one-pot fashion can be considered as an activation–alkynylation sequence to ynones and ynediones. To our knowledge this straightforward alkynylation methodology is unprecedented to date.

Recently, we disclosed conceptually novel approaches to ynones and ynediones initiated by glyoxylation of electron-rich heteroaromatic π nucleophiles with oxalyl chloride and subsequent alkyne coupling. The Pd/Cu-catalyzed decarbonylative Sonogashira coupling gives rise to the formation of ynones,[9] whereas the Cu-catalyzed Stephens–Castro coupling maintains both carbonyl groups and results in the generation of ynediones (Scheme 1).[4]

Inspired by the alkynylation of in situ generated glyoxylyl chlorides, we set out to design one-pot activation–alkynylation sequences that either start from α-keto carboxylic acids **1** and apply Castro conditions for the synthesis of ynediones **3** or from carboxylic acids **4** using Sonogashira conditions for the generation of ynones **5** (Scheme 2), especially addressing notoriously difficult transformations of N-heterocyclic carboxylic acids.

For the optimization of the activation–alkynylation sequence phenylglyoxylic acid (**1a**) and phenylacetylene



Scheme 1. One-pot three-component glyoxylation–alkynylation syntheses of ynones and ynediones.

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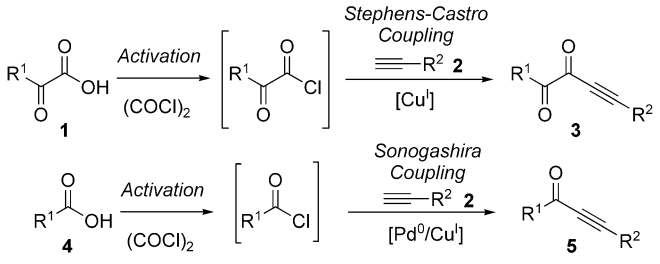
[**] The authors cordially thank Merck Serono, Darmstadt, for the financial support, and the Fonds der Chemischen Industrie.

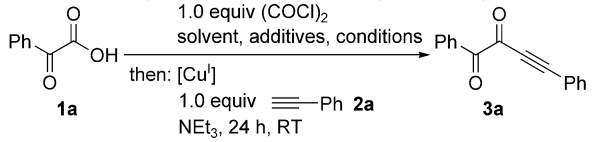
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201103296.



Scheme 2. Conceptual access to ynediones and ynones by sequential activation–alkynylation.

(**2a**) were chosen as model substrates furnishing 1,4-diphenylbut-3-yne-1,2-dione (**3a**; Table 1). Different ethereal solvents were examined and parameters such as temperature, reaction time, order of reagent addition, and amount of CuI were modified (for experimental details and full optimization, see the Supporting Information).

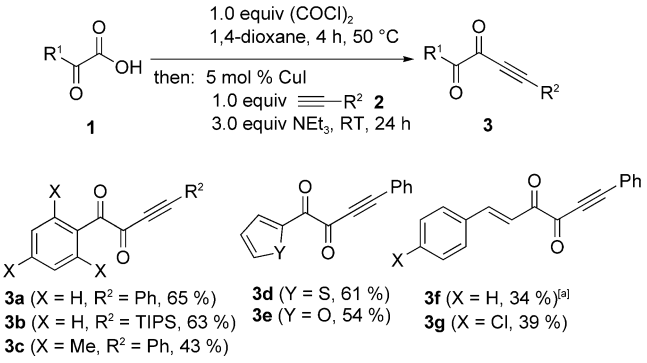
Table 1: Selected optimization trials for the synthesis of ynedione **3a**.



Entry	First reaction step[a]	Second reaction step	Yield [%][b]
1	1.0 equiv NEt_3, THF	5 mol% CuI, 2.0 equiv NEt_3	39
2	THF	5 mol% CuI, 3.0 equiv NEt_3	43
3	**1,4-dioxane**	**5 mol% CuI, 3.0 equiv NEt_3**	**65**
4	1,4-dioxane/DMF[c]	5 mol% CuI, 3.0 equiv NEt_3	51
5	1,4-dioxane	2 mol% CuI, 3.0 equiv NEt_3	47
6	1,4-dioxane	10 mol% CuI, 3.0 equiv NEt_3	64

[a] Reaction temperature: 50°C, reaction time: 4 h. [b] Yield of isolated product on a 2.0 mmol scale. [c] Addition of 2 mol% *N*,*N*-dimethylformamide.

The addition of triethylamine in the first step for deprotonation of the carboxylic acid in the chlorination step or scavenging the generated hydrogen chloride is not necessary (Table 1, entries 1 and 2). The most significant increase of the yield of isolated product from 43 to 65% was observed upon changing the solvent from THF to 1,4-dioxane (entry 3). It is known that 1,4-dioxane and oxalyl chloride form oligomeric complex chains of alternating 1,4-dioxane and oxalyl chloride molecules by coordination of the oxygen atoms of 1,4-dioxane to the chlorine atoms of oxalyl chloride.[18] Presumably, the enhanced reactivity is caused by an activation of the reagent by destabilization of the chlorine–carbon bond of oxalyl chloride. We also attempted to exploit the known catalytic effect of DMF on the chlorination with oxalyl chloride by addition of 2 mol% of DMF; however, the obtained yield was lower (entry 4). The variation of the CuI loading in the alkynylation step from 2 to 10 mol% revealed an optimum with 5 mol% of the catalyst (entries 3, 5, and 6). These optimized conditions were successfully applied to one-pot syntheses of several ynediones **3**, which were obtained in moderate to good yields (Scheme 3).[19]



Scheme 3. One-pot synthesis of ynediones **3** by an activation–Stephens–Castro alkynylation sequence. All reactions were carried out on a 2.00 mmol scale [c(**1**) = 0.2 M] and yields refer to isolated and purified compounds. [a] The potassium carboxylate was used as a substrate. Ph = phenyl, TIPS = triisopropylsilyl, Me = methyl.

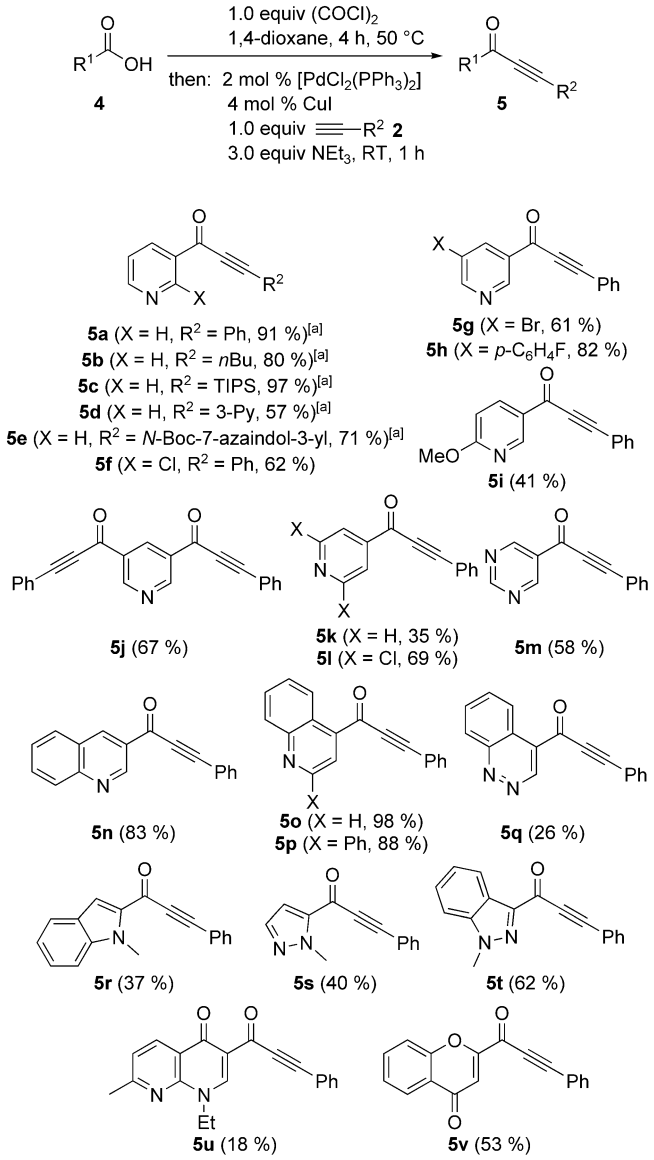
With this new and mild activation–Stephens–Castro alkynylation sequence it was possible to prepare aryl (**3a–c**), heteroaryl (**3d,e**), and alkenyl ynediones (**3f,g**) in moderate to good yields starting directly from α-keto carboxylic acids **1** or their carboxylates. This novel, valuable sequence convincingly complements the glyoxylation–Stephen–Castro coupling sequence,[4] because electron-neutral and even sterically hindered substrates (see formation of **3c**) can be transformed uneventfully.

Likewise, the one-pot in situ activation–alkynylation scenario was transposed to carboxylic acids **4** in the presence of 2 mol% $[PdCl_2(PPh_3)_2]$ and 4 mol% CuI as a catalyst system, leading to the successful formation of ynones **5** in moderate to excellent yields (Scheme 4).[19] Expectedly, the reaction times under Sonogashira conditions are considerably shorter, and complete conversion was achieved after only 1 h at room temperature.

The activation–Sonogashira alkynylation sequence starting from heterocyclic carboxylic acids and carboxylates **4** furnishes a broad variety of the corresponding ynones **5**. Most remarkably, Sonogashira coupling of commercially available pyridine-3-carbonyl chloride hydrochloride (Merck KGaA) to give ynone **5a** under identical reaction conditions failed completely, even if the reason for this strange observation is yet unknown.

For sodium nicotinate (**4a**) it was demonstrated that the variation of the alkyne **2** was feasible. Besides phenylacetylene, 1-hexyne, and TIPS-acetylene, also N-heterocyclic alkynes can be efficiently coupled to yield highly functionalized building blocks (see formation of **5d,e**). The example of the ynone **5e** shows that even the highly labile Boc protective group on the 7-azaindolyl moiety is preserved.

Substituents in 2-, 5-, and 6- as well as in 2,6-positions of the pyridine core are well tolerated (**5f–i** and **5l**). Bromine in 3-position of pyridine (**5g**) remains untouched under these gentle conditions, ready for addressing this ynone in further functionalizations. It could also be shown that dinicotinic acid can be activated and coupled to give a bis(ynone) (**5j**) in a good yield. In addition to pyridine-containing carboxylic acids, this method can be well applied to convert a whole



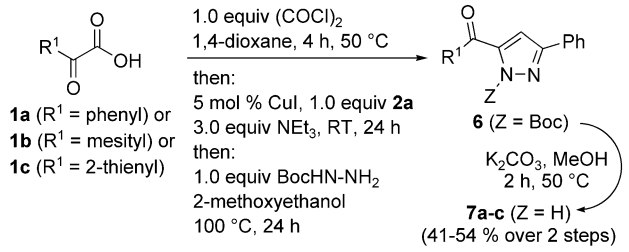
Scheme 4. One-pot synthesis of ynones **5** by an activation–Sonogashira alkynylation sequence. All reactions were carried out on a 2.00 mmol scale [c(**4**) = 0.2 M] and yields refer to isolated and purified compounds. [a] The sodium carboxylate was used as a substrate. *n*Bu = *n*-butyl, Py = pyridyl, Boc = *tert*-butyloxycarbonyl.

variety of 6-membered N-heterocyclic carboxylic acids, such as isonicotine, pyrimidine, quinoline, and cinnoline carboxylic acid (see formation of **5k–q**). Also azoles such as indole, pyrazole, and indazole carboxylic acids can be successfully carried through the sequence (see formation of **5r–t**).

It is noteworthy that the indazole derivative **5t** is accessible neither by the carbonylative Sonogashira coupling[2] nor by the glyoxylation–decarbonylative alkynylation sequence.[9] Therefore, it is quite remarkable that there is no limitation with respect to the electronic nature of the substrates. Electron-poor (**5a–q**) as well as electron-rich (**5r–t**) ynones are accessible. Interestingly, the antimicrobial nalidixic acid[20] (**4p**) can also be functionalized (**5u**) as well as a chromone carboxylic acid (**4q**) to give a chromenyl ynone (**5v**), now opening access to heterocyclic derivatives of flavones.

Both activation–alkynylation sequences for the preparation of ynediones **3** and ynones **5** are preparatively very simple, mild, and straightforward to perform. In particular, they open an entry to derivatives that are not accessible or difficult or expensive to access with known methods. Carboxylic acids are easily available, stable, and generally nontoxic compounds. Moreover, oxalyl chloride is a liquid which can be conveniently handled. Both sequences use simple standard catalyst systems. Neither exotic ligands nor additives are required, and the alkynylation steps proceed smoothly at room temperature. Finally, all reactants and reagents are used in strictly equimolar amounts without the need for excess reagents.

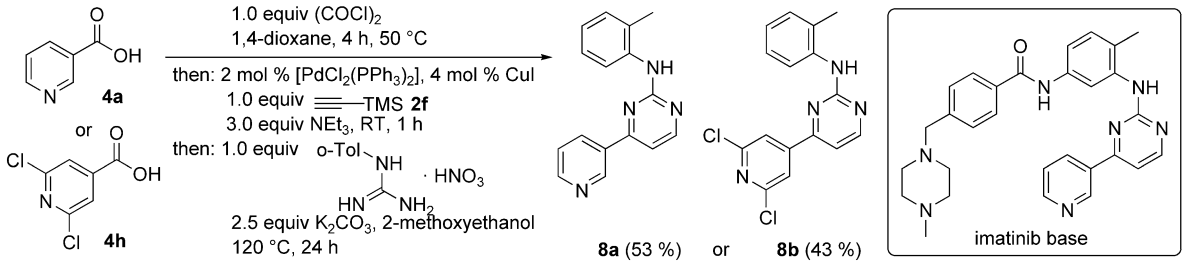
As an illustration of the applicability of ynediones and ynones as intermediates, one-pot three-component heterocycle syntheses of *N*-Boc-5-acylpyrazoles **6** and 2-aminopyrimidines **8** were conceived. In a consecutive three-component fashion the in situ generated ynediones **3** can be selectively transformed to *N*-Boc-protected 5-acylpyrazoles **6** with *N*-Boc-hydrazine. After deprotection, the 5-acylpyrazoles **7a–c** are isolated as analytically pure products (Scheme 5).



Scheme 5. One-pot three-component access to 5-acylpyrazoles **6**.

Likewise, the cyclocondensation of *o*-tolyl guanidinium nitrate with the in situ generated trimethylsilyl (TMS) ynones concludes the one-pot three-component synthesis of 2-*o*-tolylaminopyrimidines **8** (Scheme 6). 4-(3-Pyridyl)-2-*o*-tolylaminopyrimidine (**8a**) is the pharmacophore of the blockbuster drugs imatinib (Gleevec)[21] and nilotinib (Tasigna),[22] both acting as tyrosine kinase inhibitors in cancer chemotherapy. This new sequence allows the rapid assembly of the phenylaminopyrimidine scaffold in a one-pot fashion using simple and cheap starting materials, whereas other known procedures take two or more steps and use more elaborate precursors.[23] Most remarkably, the analogue **8b** possesses two activated chlorine atoms that have remained untouched, again emphasizing the high compatibility with other functionalities and the mild reaction conditions of the presented methodology.

In conclusion, we have developed new one-pot activation–alkynylation sequences starting from α-keto carboxylic acids or carboxylic acids as versatile and efficient approaches to ynediones and N-heterocyclic ynones, respectively. The one-pot three-component syntheses of 5-acylpyrazoles and 2-*o*-tolylaminopyrimidines illustrate the implementation of this



Scheme 6. One-pot three-component synthesis of 4-pyridyl-2-*o*-tolylaminopyrimidines **8**. Tol = tolyl.

highly efficient methodology in multicomponent syntheses of pharmaceutically important heterocycles. Further methodological studies are currently underway.

Experimental Section

3a: Phenylglyoxylic acid (**1a**, 306 mg, 2.00 mmol) in dry 1,4-dioxane (10 mL) was placed under argon atmosphere in a screw-cap Schlenk vessel with septum. Argon was passed through the solution for 5 min. Then, oxalyl chloride (0.18 mL, 2.00 mmol) was added dropwise to the reaction mixture at room temperature (water bath). The mixture was stirred for 4 h at 50 °C in a preheated oil bath and then cooled to room temperature. CuI (20 mg, 0.10 mmol), phenylacetylene (**2a**, 0.23 mL, 2.00 mmol), and dry triethylamine (0.84 mL, 6.00 mmol) were successively added to the mixture, and stirring at room temperature was continued for 24 h. After complete conversion, water (10 mL) was added and the mixture was extracted with dichloromethane. The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuum the residue was adsorbed on Celite and purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 50:1; $R_f = 0.14$) to give the analytically pure 1,4-diphenylbut-3-yne-1,2-dione (**3a**, 302 mg, 65 %) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta =$ 7.39–7.43 (m, 2H), 7.48–7.56 (m, 3H), 7.63–7.70 (m, 3H), 8.07–8.10 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 87.0$ (C_{quat}), 99.1 (C_{quat}), 119.1 (C_{quat}), 128.7 (CH), 128.9 (CH), 130.5 (CH), 131.5 (C_{quat}), 131.7 (CH), 133.6 (CH), 134.9 (CH), 178.5 (C_{quat}), 188.4 ppm (C_{quat}); elemental analysis calcd (%) for $C_{16}H_{10}O_2$ (234.3): C 82.04, H 4.30; found: C 82.13, H 4.31.

5o: Quinoline-4-carboxylic acid (**4k**, 357 mg, 2.00 mmol) in dry 1,4-dioxane (10 mL) was placed under argon atmosphere in a screw-cap Schlenk vessel with septum. Argon was passed through the solution for 5 min. Then, oxalyl chloride (0.18 mL, 2.00 mmol) was added dropwise to the reaction mixture at room temperature (water bath). The mixture was stirred for 4 h at 50 °C in a preheated oil bath and was cooled to room temperature. [$PdCl_2(PPh_3)_2$] (28 mg, 0.04 mmol), CuI (15 mg, 0.08 mmol), phenylacetylene (**2a**, 0.23 mL, 2.00 mmol), and dry triethylamine (0.84 mL, 6.00 mmol) were successively added to the mixture and stirring at room temperature was continued for 1 h. After complete conversion, water (10 mL) was added, and the mixture was extracted with dichloromethane. The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuum the residue was adsorbed on Celite and purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 6:1, $R_f = 0.22$) to give the analytically pure 3-phenyl-1-(quinolin-4-yl)prop-2-yn-1-one (**5o**, 505 mg, 98 %) as a pale brown solid. M.p. 93 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta =$ 7.38–7.56 (m, 3H), 7.65–7.76 (m, 3H), 7.76–7.85 (m, 1H), 8.16–8.28 (m, 2H), 8.93–9.02 (m, 1H), 9.12–9.19 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 88.4$ (C_{quat}), 94.1 (C_{quat}), 119.9 (C_{quat}), 124.3 (C_{quat}), 124.4 (CH), 125.9 (CH), 129.1 (CH), 129.4 (CH), 130.3 (CH), 130.4 (CH), 131.6 (CH), 133.6 (CH), 139.9 (C_{quat}), 149.6 (C_{quat}), 150.3 (CH), 179.3 ppm (C_{quat}); elemental analysis calcd. (%) for $C_{18}H_{11}NO$ (257.3): C 84.03, H 4.31, N 5.44; found: C 83.86, H 4.40, N 5.51.

Received: May 13, 2011
Published online: September 9, 2011

Keywords: alkynylation · carboxylic acids · C—C coupling · heterocycles · one-pot reactions

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