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[3+3] Cyclization reactions of β-nitroenamines and β-enaminonitriles with α,β-unsaturated carboxylic acid chlorides

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ABSTRACT

New indolizidines, quinolizidines, and octahydro-pyrido[1,2-*a*]azepines of lactam type were synthesized from 2-nitromethylene-pyrrolidine, -piperidine, and -hexahydroazepine, respectively, by [3+3] cyclizations with α,β-unsaturated carboxylic acid chlorides. In the case of quinolizidines, a double bond migration was observed, and explained in terms of amidity percentage. Cyanomethylene-pyrrolidine gave indolizidines of lactam type, while transformations of 1-cyanomethylene-tetrahydoisoquinoline resulted in lactams as well as ketones, when simple open-chain acid chlorides or cinnamoyl chloride were used, respectively.

1. Introduction

Piperidine, indolizidine, and quinolizidine are common skeletons in both natural and synthetic products[1,2] that possess a wide range of biological activities. Accordingly, and because of their scarce occurrence in exotic organisms, novel strategies for the synthesis of these *N*-heterocycles have received considerable attention in the past decades.[3] Heterocyclic enamines are versatile building blocks for the synthesis of various bicyclic and tricyclic structures bearing a bridgehead nitrogen atom (Fig. 1). These highly reactive compounds include a unique push–pull bonding structure and readily react with different bis-electrophiles resulting in substituted indolizidines and quinolizidines. The cyclizations of easily accessible β-enaminonitriles and β-enaminoesters are well documented in the literature.[4] Their acylations either with acyl chlorides or esters have been described[5] as well. It can be assumed that replacement of the nitrile group of the enaminonitriles with another strongly electron withdrawing group such as NO_2 will also provide compounds of high reactivity. Although several nitroenamines have been known for a long time, apart from a few reactions[6] they have not been used in organic synthesis. These observations prompted us to investigate the acylation reactions of some β-nitroenamines and β-enaminonitriles.

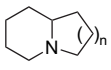

Figure 1.

2. Results and discussion

β-Substituted enamines (**1**, EWG=NO_2, CN, COOEt) and α,β-unsaturated carboxylic acid chlorides can theoretically result in regioisomeric 3,4-dihydro-2-pyridones **2** and 2,3-dihydro-4-pyridones **3** in [3+3] cyclizations (Scheme 1). Reactions of cyclic β-enaminoesters with α,β-unsaturated carboxylic acid chlorides **2a–d** published earlier,[2] lead to 3,4-dihydro-2-pyridones **3** exclusively. These transformations were catalyzed by simple tertiary amines, e.g., pyridine, triethylamine. On the other hand, both regioisomeric benzoquinolizines have been prepared[7] with α,β-unsaturated carbonyls from 1-cyanomethylene-tetrahydoisoquinoline (**13**).

In this paper, we describe the transformations of compounds of general formula **1**, EWG=NO_2, CN with carboxylic acid chlorides. Using the simple amine catalysts mentioned above, very poor conversions were unfortunately observed. To find more efficient catalysts a series of other compounds were tested in model reactions between nitroenamine **5** or enaminonitrile **13** and crotonoyl chloride (**2b**) at room temperature. The conversion of the reactants and the degree of side-reaction (e.g., polymerization) were semi-quantitatively monitored by TLC.

Since the aza-Michael addition can also be catalyzed by Lewis-acids,[8] our attention turned to ionic compounds showing mild-to-moderate Lewis-acidic and moderate-to-strong Brønsted/Lewis-basic properties together. Such catalysts (single or composite), such as $Ca(OH)_2$, $Ba(OH)_2$, LiBr/Et_3N, $MgBr_2$/Et_3N, $Mg(OCH_3)_2$ or Zr(O*i*-Pr)$_4$ are well known in carbonyl chemistry.[9] Considering the conversion, the reaction time, and the work-up procedure, $La(OH)_3$ and some carbonates M_nCO_3 (M=Li, Mg, Ca, Ba) were found to catalyze our reactions most efficiently, although LiF, LiOAc, $Mg(OAc)_2 \cdot 4H_2O$ also worked well for β-nitroenamines. Since these ionic compounds are sparingly soluble in acetonitrile, and the

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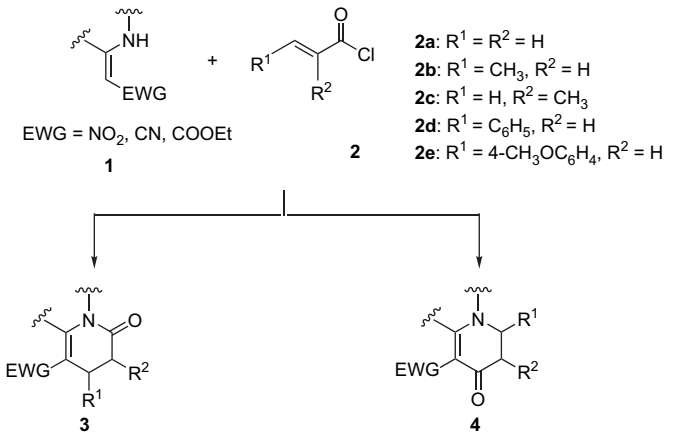
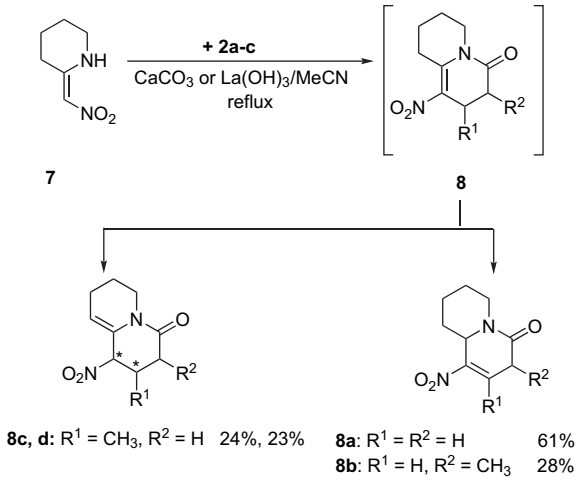


Scheme 1.



Scheme 3.

reactions certainly proceed on the surface of the catalysts, they were employed in 4–6 equimolar amounts. Some other ionic compounds, like $AlF_3 \cdot 3H_2O$, ZrF_4, $Ca(OH)_2$, and $LiOH \cdot H_2O$, and LiBr/Et_3N gave poor yields. It was noteworthy, that neutral, strong oxygen-donor Lewis-bases, such as HMPA or TMU (1,1,3,3-tetramethylurea) efficiently catalyzed the cyclization, providing good-to-excellent conversions, but due to difficulties in the work-up they were disregarded.

2.1. Reactions of nitroenamines with α,β-unsaturated carbonyl chlorides

The reaction of 2-nitromethylene-pyrrolidine[10] (**5**) with different acid chlorides resulted in various indolizidine derivatives **6a–c** (Scheme 2). In the case of acryloyl chloride the reaction took place even at room temperature without any catalyst, giving **6a** in good yield. The reactions with crotonoyl (**2b**) and methacryloyl chlorides (**2c**) proceeded in refluxing acetonitrile, in the presence of $CaCO_3$ or $La(OH)_3$ catalyst. In the transformation with methacryloyl chloride, the non-cyclized by-product **6d** was also isolated (**6c**/**6d**=3:1). Using cinnamoyl chloride (**2d**) no cyclized product was formed, and the amide **6e** was obtained. The acylation was accompanied by the isomerization of the nitromethylene moiety, indicated by the significant downfield shift of H-3 of **5** (from 2.70 to 3.35 ppm).

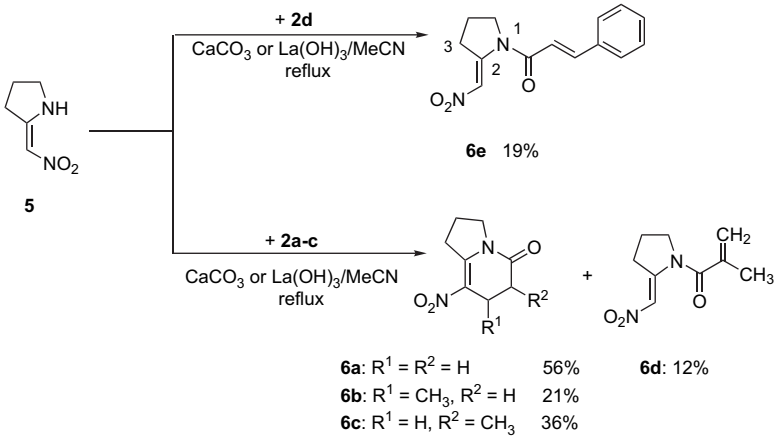
Quinolizidine derivatives were produced when 2-nitromethylene piperidine[11] (**7**) was subjected to reactions with acid chlorides. Acryloyl chloride (**2a**) and methacryloyl chloride (**2c**) gave **8a** and **8b**, respectively (Scheme 3). Using crotonoyl chloride (**2b**) the diastereomers **8c** and **8d** were separated and characterized. It might be assumed that they were formed in an isomerization process from **8**, which could be neither isolated nor detected. The new position of the double bond in products **8a–d** was proven by their NMR spectra.

The unexpected double bond migration can be interpreted in terms of amidity values.[12] In order to measure the amide bond reactivity, a general, quick, and simple protocol was recently quantified for the extent of conjugation, based on the hydrogenation enthalpy. The parameter obtained was labeled 'amidity', analogous to the terms 'aromaticity and antiaromaticity'.[13–15] On this linear scale, *N*,*N*-dimethylacetamide was denoted as having 100% amidity, and a 0% amidity was assigned to azaadamantan-2-one.

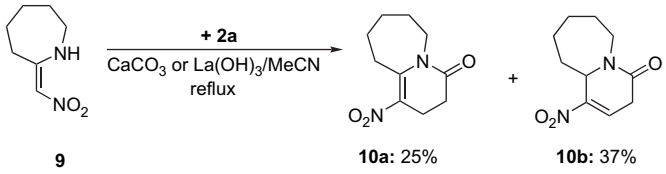
Amidity values for the structures **8**, **8a–d** were obtained from the B3LYP/6-31G(d,p) geometry-optimized structures. While the supposed product **8** possesses only 72% of amidity, due to the strongly conjugated amide bond, for **8a**,**b** and **8c**,**d** 81% and 99% were calculated,[16–18] respectively, showing their favored formation. The lower amidity of **8a**,**b** can be attributed to its twisted, therefore strained conformation, which hinders the delocalization. The high amidity value of **8c**,**d** reflects their very stable, completely planar amide bond.

With cinnamoyl chloride (**2d**) no isolable product was formed.

The reaction of 2-nitromethylene-azepine[4a] (**9**) with acryloyl chloride (**2a**) without catalyst gave the isomeric pyrido[1,2-*a*]azepine derivatives **10a** and **10b** differing in the position of the double bond (Scheme 4). Using other unsaturated acid chlorides (**2b–d**)



Scheme 2.



Scheme 4.

the reactions did not result in cyclized or other identifiable products displaying the moderate reactivity of **9** to α,β-unsaturated carbonyl chlorides.

2.2. Reactions of enaminonitriles with α,β-unsaturated acid chlorides

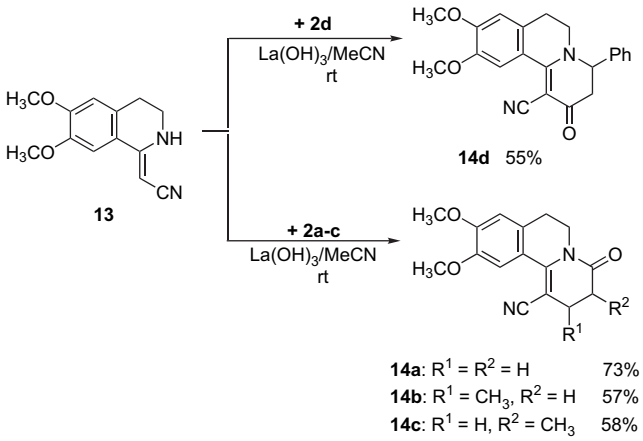
β-Enaminonitriles **11** and **13** were also tested with the acid chlorides used in the above transformations. Reaction of **11** with **2a**–**c** gave the expected cyclic compounds **12a**,**b**,**d** and the open-chain products **12c**,**e** were also isolated (Scheme 5). Using cinnamoyl chloride (**2d**), only the non-cyclized product **12f** was formed.

In the presence of $BaCO_3$ or $La(OH)_3$ catalyst, the reaction of β-enaminonitrile **13** with the non-aromatic α,β-unsaturated carboxylic acid chlorides **2a**–**c** in acetonitrile led to 3,4-dihydro-2-pyridones **14a**–**c**. On the other hand, in the reaction with cinnamoyl chloride (**2d**) the 2,3-dihydro-4-pyridone **14d** was produced predominantly (Scheme 6).

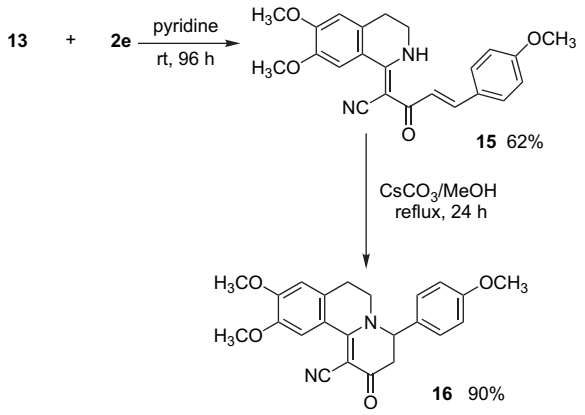
The reaction of β-enaminonitrile **13** with *p*-methoxycinnamoyl chloride (**2e**) in pyridine gave the ketone **15**, which did not undergo ring closure even at reflux temperature. The aza-Michael cyclization of **15** was effected in boiling methanol with Cs_2CO_3 catalyst (Scheme 7) affording **16**.

3. Conclusion

In summary, this work demonstrates the synthetic usefulness of nitroenamines, that are able to undergo regioselective cyclizations with α,β-unsaturated carboxylic acid chlorides. It was established that lanthanum(III) hydroxide and some carbonates catalyze these reactions efficiently. Depending on the ring size of the cyclic nitroenamines, various new indolizines, quinolizines, and octahydro-pyrido[1,2-*a*]azepines have been prepared in acceptable to good yield. The position of the carbon–carbon double bond in these compounds is determined by the ring strain, expressed in the amidity percentage quantitatively.



Scheme 6.

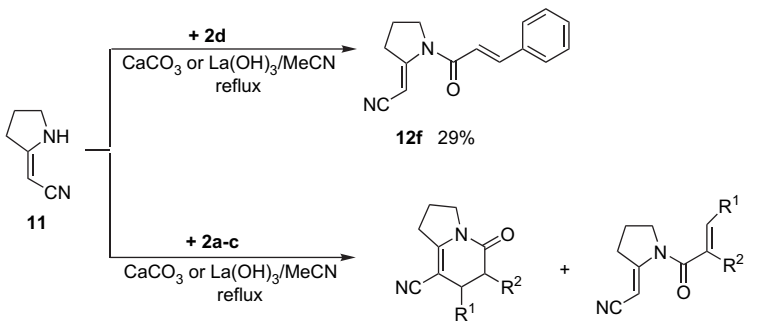


Scheme 7.

4. Experimental

4.1. General

All melting points were measured with a Büchi SMP-20 apparatus and are uncorrected. NMR spectra were recorded with a Bruker Avance 400 DRX spectrometer (^1H: 400 MHz; ^{13}C: 100 MHz). The HRMS analyses were performed with a Waters LCT Premier XE apparatus. IR spectra were recorded with a Perkin–Elmer 1600 FT/IR spectrometer. Column chromatography was conducted with Merck Kieselgel 60 (0.063–0.200 mm). Analytical



Scheme 5.

TLC was carried out on precoated plates (Merck silica gel 60, F254). Solvents were dried and freshly distilled according to the common practice.

4.2. General procedures

*4.2.1. Method A (for the synthesis of the compounds **6a**, **8a**, **10a**, **10b**, **12a**)*

Nitroenamine (**5**, **7**, **9**) or enaminonitrile (**11**) (3 mmol) and acryloyl chloride (CAUTION: Lachrymator!) **2a** (3.6 mmol, 1.2 equiv) were stirred in acetonitrile (50 mL) at ambient temperature. After 12 h the mixture was concentrated and the crude oil was crystallized from EtOAc or purified by column chromatography.

*4.2.2. Method B (for the synthesis of the compounds **6b–e**, **8b–d**, **12b–f**)*

Nitroenamine (**5**, **7**, **9**) or enaminonitrile (**11**) (3 mmol), calcium carbonate or lanthanum(III) hydroxide (12 mmol, 4 equiv), and carboxylic acid chlorides (CAUTION: Lachrymator!) **2b–d** (3.6 mmol, 1.2 equiv) were refluxed in acetonitrile (50 mL) for 3–6 h. The catalyst was filtered, and the solvent was removed in vacuo. The crude oil was purified by column chromatography.

*4.2.3. Method C (for the synthesis of the compounds **14a–d**)*

To the solution of β-enaminonitrile **13** (0.10 g, 0.43 mmol) in acetonitrile (8 mL) $La(OH)_3$ (0.33 g, 1.74 mmol, 4.05 equiv) and carboxylic acid chlorides (**2a–d**) (0.50 mmol, 1.15 equiv) were added. The reaction mixture was stirred for 1–120 h at room temperature and monitored by TLC. The catalyst was filtered off, then the solvent was removed under reduced pressure at 40 °C, and the crude product was purified by column chromatography or recrystallization.

*4.2.3.1. 8-Nitro-2,3,6,7-tetrahydro-1H-indolizin-5-one (**6a**).* Recrystallization of the crude product (EtOAc) gave **6a** (306 mg, 56%) as a white solid, mp 101–102 °C; R_f (EtOAc) 0.67; ν_{max} (KBr) 1688, 1638, 1487, 1364, 1300, 1256, 1204, 1116 cm^{-1}; δ_H (DMSO-d_6) 1.98 (2H, q, J=7.6 Hz), 2.65 (2H, t, J=8.0 Hz), 2.90 (2H, dt, J=8.0 Hz), 3.32 (2H, t, J=7.6 Hz), 3.68 (2H t, J=7.6 Hz); δ_C (DMSO-d_6) 20.7; 21.8, 30.4, 33.8, 42.9, 124.3, 155.4, 169.3; HRMS (ESI-TOF) calcd for $C_8H_{11}N_2O_3$: 183.0770 ($[M+H]^+$), found: 183.0765 ($[M+H]^+$).

*4.2.3.2. 7-Methyl-8-nitro-2,3,6,7-tetrahydro-1H-indolizin-5-one (**6b**).* Purification of the product by column chromatography (EtOAc) gave the title compound **6b** (124 mg, 21%) as a colorless oil; R_f (EtOAc) 0.73; ν_{max} (KBr) 2960, 1700, 1638, 1477, 1385, 1300, 1249, 1196 cm^{-1}; δ_H (DMSO-d_6) 1.05 (3H, t, J=6.8 Hz), 2.00 (2H, q, J=7.6 Hz), 2.43 (1H, t, J=13.4 Hz), 2.96 (1H, dd, J=16.8 Hz), 3.32 (2H, t, J=7.6 Hz), 3.71 (2H, t, J=7.6 Hz); δ_C (DMSO-d_6) 18.0, 20.7, 28.2, 33.8, 38.2, 47.2, 129.2, 154.6, 168.2; HRMS (ESI-TOF) calcd for $C_9H_{13}N_2O_3$: 197.0926 ($[M+H]^+$), found: 197.0923 ($[M+H]^+$).

*4.2.3.3. 6-Methyl-8-nitro-2,3,6,7-tetrahydro-1H-indolizin-5-one (**6c**).* Purification of the product by column chromatography (diethyl ether) gave the title compound **6c** (212 mg, 36%) as a white solid, mp 78–79 °C; R_f (EtOAc) 0.77; ν_{max} (KBr) 2970, 2348, 1685, 1638, 1445, 1320, 1240, 1217, 1166 cm^{-1}; δ_H (DMSO-d_6) 1.18 (3H, t, J=6.6 Hz), 1.99 (2H, q, J=7.6 Hz), 2.60 (1H, dd, J_1=14.8 Hz, J_2=2 Hz), 2.73 (1H, m), 3.11 (1H, dd, J=6.6 Hz), 3.32 (2H, t, J=7.6 Hz), 3.69 (2H, t, J=7.6 Hz); δ_C (DMSO-d_6) 15.5, 20.8, 29.4, 33.7, 35.0, 47.4, 123.8, 155.4, 171.4; HRMS (ESI-TOF) calcd for $C_9H_{13}N_2O_3$: 197.0926 ($[M+H]^+$), found: 197.0923 ($[M+H]^+$).

*4.2.3.4. 2-Methyl-1-(2-nitromethylene-pyrrolidin-1-yl)-propenone (**6d**).* Purification of the product by column chromatography (diethyl ether) gave the title compound **6d** (71 mg, 12%) as a colorless oil; R_f (EtOAc) 0.60; ν_{max} (KBr) 2970, 2348, 1685, 1638, 1445, 1320, 1240, 1217, 1166 cm^{-1}; δ_H (DMSO-d_6) 1.93 (3H, s), 1.95 (2H, q, J=7.6 Hz), 3.32 (2H, t, J=7.6 Hz), 3.88 (2H, t, J=7.6 Hz), 5.38 (2H, d, J=16.6 Hz), 8.41 (1H, s); δ_C (DMSO-d_6) 19.8, 21.9, 33.4, 47.4, 118.9, 123.0, 125.0, 156.5, 166.5; HRMS (ESI-TOF) calcd for $C_9H_{13}N_2O_3$: 197.0926 ($[M+H]^+$), found: 197.0924 ($[M+H]^+$).

*4.2.3.5. 1-(2-Nitromethylene-pyrrolidin-1-yl)-3-phenyl-propenone (**6e**).* Purification of the product by column chromatography (dichloromethane) gave the title compound **6e** (147 mg, 19%) as a white solid, mp 170–172 °C; R_f (dichloromethane) 0.68; ν_{max} (KBr) 1670, 1618, 1484, 1389, 1300, 1285, 1216, 1190 cm^{-1}; δ_H (DMSO-d_6) 2.02 (2H, q, J=7.4 Hz), 3.35 (2H, dt, J=7.4 Hz), 4.15 (2H, t, J=7.4 Hz), 7.15 (1H, d, J=15.4 Hz), 7.44 (2H, m), 7.44 (1H, m), 7.79 (1H, d, J=15.4 Hz), 8.63 (1H, s); δ_C (DMSO-d_6) 21.2, 33.2, 51.3, 119.7, 123.3, 129.1, 129.2, 131.0, 134.6, 145.7, 157.9, 166.6; HRMS (ESI-TOF) calcd for $C_{14}H_{15}N_2O_3$: 259.1083 ($[M+H]^+$), found: 259.1085 ($[M+H]^+$).

*4.2.3.6. 1-Nitro-3,6,7,8,9,9a-hexahydro-quinolizin-4-one (**8a**).* Recrystallization of the crude product (EtOAc) gave **8a** (426 mg, 61%) as a white solid, mp 98–99 °C; R_f (EtOAc) 0.56; ν_{max} (KBr) 2960, 1637, 1548, 1387, 1251, 1206, 1179, 1074, 783 cm^{-1}; δ_H (DMSO-d_6) 1.76 (2H, m), 2.14 (2H, m), 2.25 (1H, m), 2.25 (1H, m), 2.45 (1H, m), 2.45 (1H, m), 3.30 (1H, ddd, J_1=0.6 Hz, J_2=6.0 Hz, J_3=17.4 Hz), 4.0 (1H, ddd, J_1=0.6 Hz, J_2=6.0 Hz, J_3=17.4 Hz), 5.29 (1H, t, J=4.0 Hz), 5.60 (1H, t, J=1.0 Hz); δ_C (DMSO-d_6) 20.8, 22.3, 23.8, 27.7, 39.9, 83.2, 113.13, 130.4, 165.5; HRMS (ESI-TOF) calcd for $C_9H_{13}N_2O_3$: 197.0926 ($[M+H]^+$), found: 197.0924 ($[M+H]^+$).

*4.2.3.7. 3-Methyl-1-nitro-3,6,7,8,9,9a-hexahydro-quinolizin-4-one (**8b**).* Purification of the product by column chromatography (diethyl ether) gave the title compound **8b** (176 mg, 28%) as a white solid, mp 70–71 °C; R_f (EtOAc) 0.77; ν_{max} (KBr) 2959, 1636, 1549, 1388, 1258, 1187, 1124, 995 cm^{-1}; δ_H (DMSO-d_6) 1.13 (3H, d, J=6.6 Hz), 1.75 (2H, m), 2.10 (2H, m), 2.10 (1H, m), 2.25 (1H, m), 2.53 (1H, m), 3.36 (1H, m), 3.93 (1H, m), 5.26 (1H, t, J=6.2 Hz), 5.62 (1H, dd, J_1=3.2 Hz, J_2=6.2 Hz); δ_C (DMSO-d_6) 16.8, 20.9, 22.2, 31.5, 32.0, 40.3, 83.4, 113.1, 130.5, 168.7; HRMS (ESI-TOF) calcd for $C_{10}H_{15}N_2O_3$: 211.1083 ($[M+H]^+$), found: 211.1081 ($[M+H]^+$).

*4.2.3.8. 2-Methyl-1-nitro-1,2,3,6,7,8-hexahydro-quinolizin-4-one (**8c**).* Purification of the product by column chromatography (diethyl ether) gave the title compound **8c** (151 mg, 24%) as a white solid, mp 94–95 °C; R_f (Et_2O) 0.60; ν_{max} (KBr) 2962, 1674, 1649, 1545, 1386, 1353, 1255, 1204, 1111 cm^{-1}; δ_H (DMSO-d_6) 1.12 (3H, d, J=7.0 Hz), 1.76 (2H, m), 2.12 (2H, m), 2.28 (1H, m), 2.43 (1H, m), 2.71 (1H, m), 3.35 (1H, m), 3.98 (1H, m), 5.28 (1H, t, J=1.2 Hz), 5.42 (1H, d, J=2.8 Hz); δ_C (DMSO-d_6) 17.8, 20.9, 22.4, 29.4, 34.7, 39.4, 88.1, 114.4, 128.8, 164.8; HRMS (ESI-TOF) calcd for $C_{10}H_{15}N_2O_3$: 211.1083 ($[M+H]^+$), found: 211.1082 ($[M+H]^+$).

*4.2.3.9. 2-Methyl-1-nitro-1,2,3,6,7,8-hexahydro-quinolizin-4-one (**8d**).* Purification of the product by column chromatography (diethyl ether) gave the title compound **8d** (124 mg, 23%) as a white solid, mp 63–65 °C; R_f (Et_2O) 0.43; ν_{max} (KBr) 2969, 2370, 1638, 1544, 1385, 1259, 1204 cm^{-1}; δ_H (DMSO-d_6) 0.98 (3H, d, J=6.4 Hz), 1.72 (2H, m), 2.11 (2H, m), 2.14 (1H, m), 2.51 (1H, m), 2.51 (1H, m), 3.31 (1H, m), 4.00 (1H, m), 5.29 (1H, t, J=4.0 Hz), 5.54 (1H, d, J=3.4 Hz); δ_C (DMSO-d_6) 17.0, 20.8, 22.3, 29.1, 35.0, 39.5, 88.4, 112.1, 131.0, 165.8; HRMS (ESI-TOF) calcd for $C_{10}H_{15}N_2O_3$: 211.1083 ($[M+H]^+$), found: 211.1081 ($[M+H]^+$).

*4.2.3.10. 1-Nitro-2,6,7,8,9,10-hexahydro-3H-pyrido[1,2-a]azepin-4-one (**10a**).* Purification of the product by column chromatography (diethyl ether) gave the title compound **10a** (158 mg, 25%) as a yellow oil; R_f (EtOAc) 0.80; ν_{max} (KBr) 2931, 2858, 1694, 1621, 1494, 1439, 1298, 1194, 1152 cm^{-1}; δ_H (DMSO-d_6) 1.60 (2H, m), 1.60 (2H,

m), 1.69 (2H, m), 2.61 (1H, t, J=8.1 Hz), 2.61 (1H, t, J=8.1 Hz), 2.90 (1H, t, J=8.1 Hz), 2.90 (1H, t, J=8.1 Hz), 3.10 (2H, m), 3.91 (2H, m); δ_C (DMSO-d_6) 22.2, 26.0, 28.0, 28.0, 28.1, 30.6, 42.1, 130.6, 152.9, 169.3; HRMS (ESI-TOF) calcd for $C_{10}H_{15}N_2O_3$: 211.1083 ([M+H]$^+$), found: 211.1082 ([M+H]$^+$).

*4.2.3.11. 1-Nitro-6,7,8,9,10,10a-hexahydro-3H-pyrido[1,2-a]azepin-4-one (**10b**).* Purification of the product by column chromatography (diethyl ether) gave the title compound **10b** (233 mg, 37%) as a colorless oil; R_f (EtOAc) 0.61; ν_{max} (KBr) 2958, 2360, 1646, 1544, 1396, 1349, 1329, 1220, 1173 cm^{-1}; δ_H (DMSO-d_6) 1.65 (1H, m), 1.65 (1H, m), 1.70 (2H, m), 2.30 (1H, m), 2.30 (1H, m), 2.35 (2H, m), 2.35 (2H, m), 3.02 (1H, dt, J_1=4.0 Hz, J_2=12.8 Hz), 4.30 (1H, dt, J_1=7.0 Hz, J_2=12.8 Hz), 5.46 (1H, dd, J_1=6.0 Hz, J_2=6.4 Hz), 5.58 (1H, t, J=3.2 Hz); δ_C (DMSO-d_6) 24.0, 24.1, 25.8, 26.9, 28.9, 28.1, 45.5, 84.2, 121.1, 135.4, 167.7; HRMS (ESI-TOF) calcd for $C_{10}H_{15}N_2O_3$: 211.1083 ([M+H]$^+$), found: 211.1083 ([M+H]$^+$).

*4.2.3.12. 5-Oxo-1,2,3,5,6,7-hexahydro-indolizine-8-carbonitrile (**12a**).* Purification of the product by column chromatography (*tert*-butyl methyl ether) gave the title compound **12a** (379 mg, 78%) as a white solid, mp 50–52 °C; R_f (EtOAc) 0.60; ν_{max} (KBr) 2902, 2359, 2201, 1685, 1654, 1387, 1317, 1275 cm^{-1}; δ_H (DMSO-d_6) 1.93 (2H, q, J=7.0 Hz), 2.48 (2H, s), 2.48 (2H, s), 2.83 (2H, t, J=7.0 Hz), 3.62 (2H, t, J=7.0 Hz); δ_C (DMSO-d_6) 20.7, 20.9, 30.1, 30.6, 46.9, 78.2, 119.6, 156.7, 167.7; HRMS (ESI-TOF) calcd for $C_9H_{11}N_2O$: 163.0871 ([M+H]$^+$), found: 163.0867 ([M+H]$^+$).

*4.2.3.13. 7-Methyl-5-oxo-1,2,3,5,6,7-hexahydro-indolizine-8-carbonitrile (**12b**).* Purification of the product by column chromatography (diethyl ether) gave the title compound **12b** (106 mg, 20%) as a white solid, mp 118–120 °C; R_f (Et_2O) 0.55; ν_{max} (KBr) 2197, 1686, 1646, 1387, 1351, 1319, 1276, 1194 cm^{-1}; δ_H (DMSO-d_6) 1.09 (3H, t, J=6.6 Hz), 1.94 (2H, q, J=7.2 Hz), 2.48 (1H, dd, J_1=6.6 Hz, J_2=8.6 Hz), 2.65 (1H, dd, J_1=8.6 Hz, J_2=16.2 Hz), 2.73 (1H, m), 2.82 (2H, t, J=7.2 Hz), 3.62 (2H, t, J=7.2 Hz); δ_C (DMSO-d_6) 19.3, 21.0, 28.0, 30.6, 38.2, 46.9, 84.6, 118.9, 156.0, 167.4; HRMS (ESI-TOF) calcd for $C_{10}H_{13}N_2O$: 177.1028 ([M+H]$^+$), found: 177.1025 ([M+H]$^+$).

*4.2.3.14. (1-But-2-enoyl-pyrrolidin-2-ylidene)-acetonitrile (**12c**).* Purification of the product by column chromatography (diethyl ether) gave the title compound **12c** (190 mg, 36%) as a white solid, mp 108–109 °C; R_f (Et_2O); 0.26; ν_{max} (KBr) 2202, 1676, 1633, 1600, 1396, 1340, 1312, 1246 cm^{-1}; δ_H (DMSO-d_6) 1.91 (2H, q, J=7.6 Hz), 1.91 (3H, d, J=3 Hz), 2.84 (2H, t, J=7.6 Hz), 3.90 (2H, t, J=7.6 Hz), 6.26 (1H, s), 6.41 (1H, d, J=14,0 Hz), 6.83 (1H, dq, J_1=3.0 Hz, J_2=14.0 Hz); δ_C (DMSO-d_6) 18.3, 21.0, 32.9, 51.5, 75.4, 119.7, 123.8, 145.4, 161.3, 166.1; HRMS (ESI-TOF) calcd for $C_{10}H_{13}N_2O$: 177.1028 ([M+H]$^+$), found: 177.1025 ([M+H]$^+$).

*4.2.3.15. 6-Methyl-5-oxo-1,2,3,5,6,7-hexahydro-indolizine-8-carbonitrile (**12d**).* Purification of the product by column chromatography (diisopropyl ether/dichloromethane 4:1) gave the title compound **12d** (127 mg, 24%) as a white solid, mp 103–104 °C; R_f (Et_2O) 0.46; ν_{max} (KBr) 2198, 1683, 1656, 1456, 1390, 1328, 1284 cm^{-1}; δ_H (DMSO-d_6) 1.19 (3H,d, J=6.2 Hz), 1.94 (2H, q, J=7 Hz), 2.25 (1H, m), 2.55 (1H, m), 2.55 (1H, m), 2.83 (2H, t, J=7 Hz), 3.62 (2H, t, J=7.0 Hz); δ_C (DMSO-d_6) 15.4, 21.1, 29.5, 30.6, 34.7, 47.1, 77.7, 119.5, 155.7, 170.8; HRMS (ESI-TOF) calcd for $C_{10}H_{13}N_2O$: 177.1028 ([M+H]$^+$), found: 177.1026 ([M+H]$^+$).

*4.2.3.16. [1-(2-Methyl-acryloyl)-pyrrolidin-2-ylidene]-acetonitrile (**12e**).* Purification of the product by column chromatography (diisopropyl ether/dichloromethane 4:1) gave the title compound **12e** (143 mg, 27%) as a white solid, mp 92–94 °C; R_f (Et_2O) 0.67; ν_{max} (KBr) 3108, 2202, 1668, 1610, 1383, 1343, 1232 cm^{-1}; δ_H (DMSO-d_6) 1.90 (3H, d, J=6.2 Hz), 1.94 (2H, q, J=6.8 Hz), 2.87 (2H, dt, J_1=1.8 Hz, J_2=7.0 Hz), 3.85 (2H, t, J=6.8 Hz), 5.27 (1H, s), 5.36 (1H, q, J=0.6 Hz), 6.18 (1H, t, J=1.8 Hz); δ_C (DMSO-d_6) 19.6, 21.7, 33.1, 53.4, 76.1, 118.0, 119.4, 140.8, 171.7; HRMS (ESI-TOF) calcd for $C_{10}H_{13}N_2O$: 177.1028 ([M+H]$^+$), found: 177.1026 ([M+H]$^+$).

*4.2.3.17. [1-(3-Phenyl-acryloyl)-pyrrolidin-2-ylidene]-acetonitrile (**12f**).* Purification of the product by column chromatography (dichloromethane) gave the title compound **12f** (207 mg, 29%) as a white solid, mp 164–165 °C; R_f (dichloromethane) 0.33; ν_{max} (KBr) 3108, 2360, 2197, 1670, 1617, 1396, 1340, 1245 cm^{-1}; δ_H (DMSO-d_6) 1.97 (2H, q, J=7.0 Hz), 2.87 (2H, dt, J_1=1.4 Hz, J_2=7.0 Hz), 4.10 (2H, t, J=7.0 Hz), 6.35 (1H, s), 7.08 (1H, d, J=15 Hz), 7.43 (2H, m), 7.43 (1H, m), 7.64 (1H, d, J=15 Hz), 7.76 (2H, m); δ_C (DMSO-d_6) 21.0, 32.9, 51.7, 75.7, 119.5, 119.7, 128.9, 129.2, 130.8, 134.7, 144.8, 161.4, 166.3; HRMS (ESI-TOF) calcd for $C_{15}H_{15}N_2O$: 239.1184 ([M+H]$^+$), found: 239.1186 ([M+H]$^+$).

*4.2.3.18. 9,10-Dimethoxy-4-oxo-3,4,6,7-tetrahydro-2H-pyrido[2,1-a]isoquinoline-1-carbonitrile (**14a**).* Recrystallization from 2-propanol gave **14a** (89 mg, 73%) as a pale yellow solid, mp 151–152 °C; R_f (EtOAc) 0.57; ν_{max} (KBr) 2946, 2192, 1689, 1515, 1374, 1282, 1131 cm^{-1}; δ_H 2.69 (4H, s), 2.81 (2H, t, J=6.0 Hz), 3.85 (2H, t, J=6.0 Hz), 3.93 (3H, s), 3.96 (3H, s), 6.70 (1H, s), 7.77 (1H, s); δ_C ($CDCl_3$) 23.1, 28.4, 30.4, 39.2, 55.9, 56.2, 83.0, 110.1, 110.7, 119, 9, 120.8, 130.5, 147.6, 147.9, 151.0, 169.1; HRMS (ESI-TOF) calcd for $C_{16}H_{17}N_2O_3$: 285.1239 ([M+H]$^+$), found: 285.1242 ([M+H]$^+$).

*4.2.3.19. 9,10-Dimethoxy-2-methyl-4-oxo-3,4,6,7-tetrahydro-2H-pyrido[2,1-a]isoquinoline-1-carbonitrile (**14b**).* Purification of the product by column chromatography (isobutyl acetate) gave the title compound **14b** (73 mg, 57%) as a pale yellow solid, mp 176–177 °C; R_f (isobutyl acetate) 0.43; ν_{max} (KBr) 2964, 2188, 1682, 1515, 1379, 1285, 1144 cm^{-1}; δ_H ($CDCl_3$) 1.20 (3H, d, J=6.8 Hz), 2.36 (1H, dd, J_1=7.6 Hz, J_2=7.4 Hz), 2.70 (1H, m), 2.74 (1H, m), 2.77 (2H, t, J=6.2 Hz), 3.71 (2H, t, J=6.2 Hz), 3.80 (3H, s), 3.83 (3H, s), 6.82 (1H, s), 7.62 (1H, s); δ_C ($CDCl_3$) 18.5, 28.1, 38.0, 55.9, 89.0, 110.8, 111.2, 120.0, 120.3, 131.3, 147.1, 147.1, 151.0, 168.2; HRMS (ESI-TOF) calcd for $C_{17}H_{19}N_2O_3$: 299.1396 ([M+H]$^+$), found: 299.1389 ([M+H]$^+$).

*4.2.3.20. 9,10-Dimethoxy-3-methyl-4-oxo-3,4,6,7-tetrahydro-2H-pyrido[2,1-a]isoquinoline-1-carbonitrile (**14c**).* Recrystallization from 2-propanol gave **14c** (74 mg, 58%) as a pale yellow solid, mp 168–169 °C; R_f (50% methyl *tert*-butyl ether/chloroform) 0.60; ν_{max} (KBr) 2187, 1684, 1600, 1513, 1380, 1250, 1206, 1134 cm^{-1}; δ_H ($CDCl_3$) 1.50 (3H, d, J=6.2 Hz), 2.53 (2H, dd, J_1=5.6 Hz, J_2=16.0 Hz), 2.63 (1H, m), 2.79 (2H, m), 3.53 (1H, m), 3.78 (3H, s), 3.80 (1H, m), 3.81 (3H, s), 6.98 (1H, s), 7.66 (1H, s); δ_C ($CDCl_3$) 15.3, 28.0, 30.2, 34.0, 40.3, 56.0, 56.1, 82.0, 111.1, 111.3, 119.9, 121.4, 131.6, 147.2, 147.7, 151.1, 172.0; HRMS (ESI-TOF) calcd for $C_{17}H_{19}N_2O$: 299.1396 ([M+H]$^+$), found: 299.1400 ([M+H]$^+$).

*4.2.3.21. 9,10-Dimethoxy-4-oxo-2-phenyl-3,4,6,7-tetrahydro-2H-pyrido[2,1-a]isoquinoline-1-carbonitrile (**14d**).* Recrystallization from 2-propanol gave **14d** (85 mg, 55%) as a yellow solid, mp 173–174 °C; R_f (EtOAc) 0.50; ν_{max} (KBr disc) 2189, 1641, 1596, 1555, 1462, 1273 cm^{-1}; δ_H ($CDCl_3$) 2.89–3.06 (3H, m), 3.53 (2H, t, J=6.2 Hz), 3.96 (2H, m), 3.96 (3H, s), 4.00 (3H, s), 6.75 (1H, s), 7.38 (5H, m), 8.03 (1H, s); δ_C ($CDCl_3$) 27.83, 38.85, 56.02, 56.21, 78.90, 110.10, 110.39, 111.89, 118.51, 122.81, 124.05, 126.84, 128.26, 128.68, 129.05, 129.83, 131.88, 135.09, 141.32, 147.50, 152.56, 164.11, 187.63; HRMS (ESI-TOF) calcd for $C_{22}H_{21}N_2O_3$: 361.1552 ([M+H]$^+$), found: 361.1560 ([M+H]$^+$).

*4.2.3.22. 2-(6,7-Dimethoxy-3,4-dihydro-2H-isoquinolin-1-ylidene)-5-(4-methoxy-phenyl)-3-oxo-pent-4-enenitrile (**15**).* The solution of β-enaminonitrile **13** (1.0 g, 4.3 mmol) and 4-methoxycinnamoyl

chloride (**2e**) in pyridine (30 mL) was stirred at ambient temperature. After 96 h the mixture was concentrated and the crude product was recrystallized from EtOAc/isopropyl ether to give a white solid (1040 mg, 62%), mp 197–198 °C; R_f (30% hexane/acetone) 0.68; ν_{max} (KBr) 2185, 1593, 1550, 1510, 1435, 1288, 1223, 1169, 832 cm^{-1}; δ_H ($CDCl_3$) 2.87 (2H, qv, J=6.4 Hz), 3.51 (2H, dt, J_1=7.4 Hz, J_2=3.0 Hz), 3.85 (3H, s), 3.95 (3H, s), 4.00 (3H, s), 6.74 (1H, s), 6.89 (1H, s), 6.93 (1H, s), 7.40–7.70 (4H, m), 8.02 (1H, s); δ_C ($CDCl_3$) 27.9, 38.8, 55.2, 56.0, 56.2, 78.7, 110.4, 111.9, 114.2, 118.6, 121.8, 123.0, 127.8, 129.9, 131.9, 141.1, 147.5, 152.4, 161.1, 164.0, 187.8; HRMS (ESI-TOF) calcd for $C_{23}H_{22}N_2O_4$: 391.1658 ($[M+H]^+$), found: 391.1664 ($[M+H]^+$).

*4.2.3.23. 9,10-Dimethoxy-4-(4-methoxy-phenyl)-2-oxo-3,4,6,7-tetrahydro-2H-pyrido[2,1-a]isoquinoline-1-carbonitrile (**16**).* A mixture of **15** (0.1 g, 0.26 mmol) and Cs_2CO_3 (0.34 g, 1.4 mmol, 4 equiv) in methanol (25 mL) was stirred and heated to reflux for 24 h. The cooled solution was acidified with concd hydrochloric acid (0.2 mL) and evaporated under reduced pressure at 40 °C. After removal of cesium chloride the residue was treated with isopropyl ether yielding **16** (91 mg, 90%) as a pale yellow solid, which was recrystallized from 2-propanol, mp 221–222 °C; R_f (EtOAc) 0.17; ν_{max} (KBr) 2196, 1635, 1610, 1586, 1535, 1253 cm^{-1}; δ_H ($CDCl_3$) 1.12 (1H, qv, J=6.2 Hz), 2.71–2.85 (2H, m), 3.15 (1H, dd, J_1=7.4 Hz, J_2=16 Hz), 3.3–365 (2H, m), 3.80 (3H, s), 3.95 (3H, s), 3.99 (3H, s), 4.82 (1H, dd, J_1=5.6 Hz, J_2=7.2 Hz), 6.72 (1H, s), 6.87 (2H, d, J_1=8.4 Hz), 7.22 (1H, d, J_1=8.4 Hz), 7.94 (1H, s); δ_C ($CDCl_3$) 22.7, 28.6, 42.5, 47.0, 55.3, 56.1, 56.3, 62.9, 81.6, 110.0, 112.8, 114.6, 119.0, 127.6, 129.0, 131.1, 147.6, 152.9, 159.8, 160.9, 187.2; HRMS (ESI-TOF) calcd for $C_{23}H_{23}N_2O_4$: 391.1658 ($[M+H]^+$), found: 391.1659 ($[M+H]^+$).

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