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Dihydropyridine-based MCRs. New reaction pathways in the interaction with ethyl glyoxalate and non-aromatic amines

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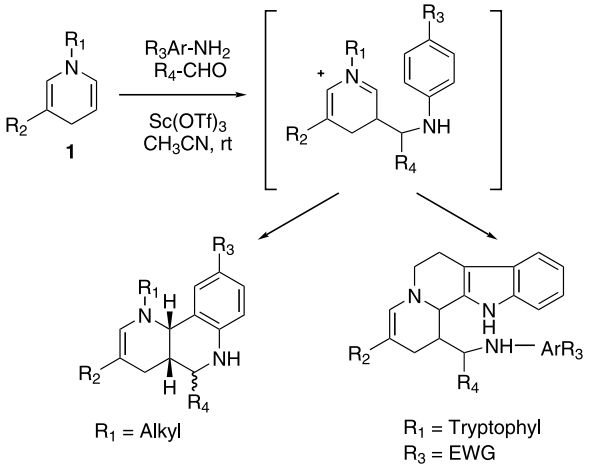
Abstract—The Lewis acid-catalyzed interaction of dihydropyridines with ethyl glyoxalate and primary aliphatic amines yields, depending on the reaction conditions, bicyclic aminals or rearranged tetrahydropyridines in one-pot multicomponent reactions.

We have recently reported the Lewis acid-catalyzed formal [4+2] cycloaddition of 1,4-dihydropyridines (DHPs)[1] with aldehydes and anilines to afford highly functionalized tetrahydroquinoline systems, through readily performed MCRs (multicomponent reactions).[2,3] The stepwise nature of this process[4] allowed deactivated anilines to participate in the reaction, provided that a suitable nucleophilic terminator (tethered to the heterocyclic nitrogen) would trap the iminium ion intermediate, leading to a different indoloquinolizidine scaffold (Scheme 1).



Scheme 1. Scaffolds resulting from the reaction of DHPs with aldehydes and anilines.

In this context, with the aim of broadening the synthetic scope of the process, we reasoned that the interaction of primary aliphatic amines would lead to alternative structures via the same reaction mechanism, which would include this time an intermolecular trapping of the iminium intermediate by another equivalent of the amine, therefore allowing a 4CR to proceed.

The first experiment was the reaction of 1-methyl-3-cyano-1,4-dihydropyridine **1a** with the imine formed in situ by *n*-butylamine and ethyl glyoxalate in the presence of 20% scandium triflate in CH_3CN. We obtained the unexpected compounds **2a** and **3a** in low yields ($\approx$5%) (Scheme 2).

The formation of these new structural motifs (functionalized tetrahydropyridines **2** and partially reduced pyridopyrimidines **3**) prompted us to improve the yield and selectivity of the synthetic process, define the mechanistic and stereochemical features of the reaction and explore, in a preliminary manner, the generality of the transformations.

After some experimentation, involving modifications in the relative stoichiometries of the reagents, reaction times and temperatures, we found that aldehydes **2** were conveniently formed at 60°C, employing 2.2 equiv. of amine and 1.2 equiv. of ethyl glyoxalate, in 3–4 days in 40% yield,[5] whereas bicyclic derivatives **3** were obtained in the presence of 4 Å molecular sieves at room temperature, employing 2 equiv. of amine and 2

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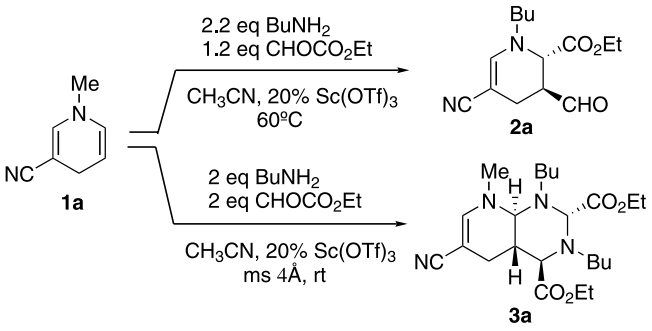


Scheme 2. Interaction of DHP **1a** with ethyl glyoxalate and *n*-butylamine.

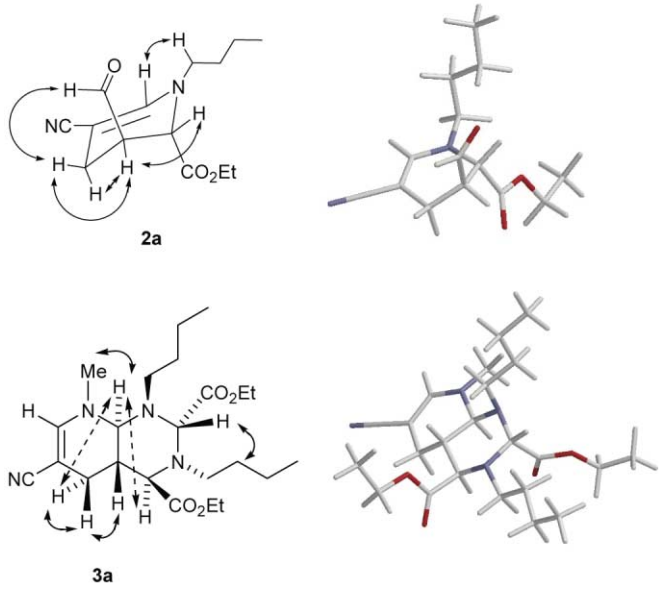


Figure 1. Diagnostic NOEs and optimized geometries (MMFF, AM1) for compounds **2a** and **3a**.

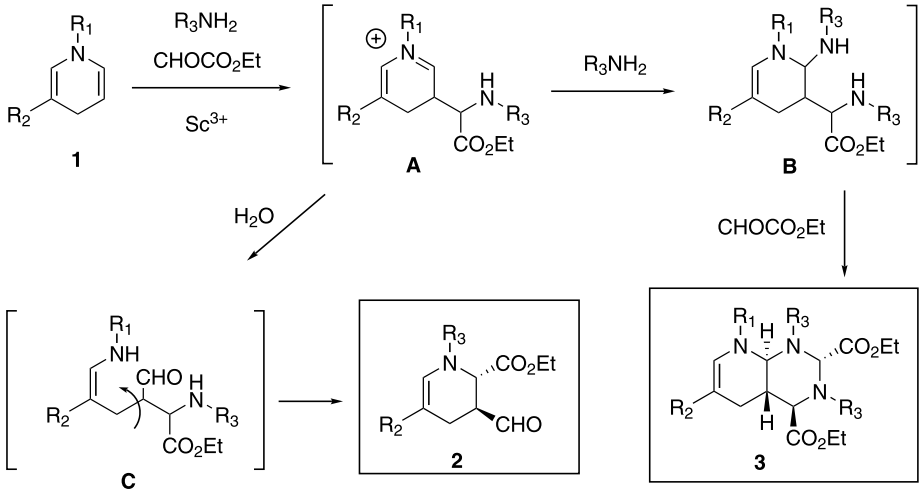
equiv. of ethyl glyoxalate, in 3–5 h (40%).[6] The somewhat modest efficiency of the reactions is probably a result of the multicomponent nature of the process and the high number of bonds formed and broken in the event, which for instance involves the interaction of five molecular units for the final assembly of compound **3**, therefore allowing the introduction of a considerable degree of molecular diversity.[7]

The stereochemical assignment of compounds **2a** and **3a** was performed through NMR methods (coupling constant analysis and diagnostic NOEs), which were in good agreement with the optimized geometries obtained through molecular modeling (using molecular mechanics and semiempirical methods, MMFF and AM1, respectively).[8] Interestingly, the *trans* isomers were observed in both series (whereas in the interaction with aromatic amines, cyclization affords exclusively *cis* compounds). Also the diaxial arrangement of the carbonyl groups at positions 2 and 3 in tetrahydropyridine **2a**, which do not suffer from 1,3-diaxial repulsions is of note. With respect to the pyridopyrimidine **3a**, (which has four stereogenic centers), the only isolated isomer corresponds to the most stable structure, the *trans*-decalin fusion was evident from the coupling constant of the vicinal hydrogen atoms ($J \approx 10$ Hz) and bears an axial butyl group at the nitrogen, probably to relieve steric congestion[9] (Fig. 1).

A reasonable mechanistic scenario which accounts for the formation of the observed compounds may involve the condensation of the amine and the aldehyde components, to generate an imine, which would be activated by the Lewis acid, and attacked by the nucleophilic DHP, to form the iminium ion **A**, which on further nucleophilic attack by another equivalent of the primary amine would furnish a diamino derivative **B**, which may then interact with a second unit of the glyoxalate to form the aminal **3**.[10] The *trans* stereochemistry of the ring fusion may be the consequence of the more favorable attack of the incoming amine nucleophile to the less substituted face of the iminium intermediate **A**, and thermodynamic control may explain the selection at the other two stereogenic centers (presumably by a base-catalyzed epimerization).[11] On the other hand, if water is not efficiently removed (absence of molecular sieves), and both the temperature and reaction time are increased, hydrolysis of the C=N bond in intermediate **A** is promoted to yield aminoaldehyde **C**, which through bond rotation may reach a reactive conformation to allow the interaction of the secondary amine moiety with the conjugated double bond, and through an addition–elimination process the tetrahydropyridine ring will be closed and the R^1–NH moiety would be substituted. This sequence is reminiscent of the Zincke reaction, and the overall process shows similarities with important transformations in the biogenesis of indole alkaloids, like the formation of vallesiachotamine from strictosidine through a 4,21-dehydrocorynantheine aldehyde precursor.[12] Again thermodynamic control may be invoked for the formation of the more stable *trans* isomer. In agreement with this proposal, compounds **3** can be transformed into the corresponding aldehydes **2** by treatment with $Sc(OTf)_3$ in a CH_3CN/H_2O (95/5) mixture at 60°C, probably by hydrolysis of the aminal to the common iminium intermediate **A** (Scheme 3).

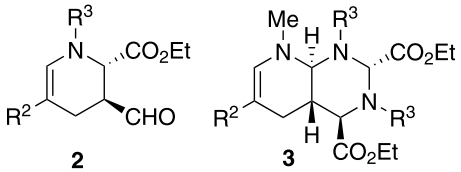
The processes described above seem to be general and different DHPs and primary amines (including benzylamines) form the expected compounds (see Table 1). However, some restrictions apply, and for instance secondary amines and aromatic aldehydes do not furnish the corresponding products under the usual conditions.

In conclusion, the Lewis acid-catalyzed interaction of primary aliphatic amines, aldehydes and DHPs affords the novel heterocyclic systems **2** and **3**, increasing the synthetic scope of this family of MCRs. The extension of the above procedures to different types of activated olefins is currently underway in our laboratory.



Scheme 3. Mechanistic proposal for the formation of the aldehyde **2** and bicycle **3**.

Table 1. List of compounds **2** and **3** obtained in the MCRs



Entry	R^2	R^3	Product	Yield (%)
1	CN	*n*-Bu	**2a**	40
2	CO_2Me	*n*-Bu	**2b**	36
3	CO_2Me	*i*-Pr	**2c**	38
4	CO_2Me	Bn	**2d**	32
5	CO_2Me	3-MeO–$PhCH_2$	**2e**	25
6	CO_2Me	4-MeO–$PhCH_2$	**2f**	21
7	CN	*n*-Bu	**3a**	41
8	CO_2Me	*n*-Bu	**3b**	37

Acknowledgements

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5. Representative procedure: To a solution of *n*-butylamine (140 μL, 1.43 mmol) and ethyl glyoxalate (50% solution in toluene, 155 μL, 0.78 mmol) in dry acetonitrile (3 mL) were added scandium triflate (64 mg, 0.13 mmol), and 1-methyl-1,4-dihydropyridine-3-carboxylic acid methyl ester (100 mg, 0.65 mmol). The reaction mixture was stirred at 60°C for 3 days and then allowed to cool to rt. Satd aq. Na_2CO_3 (5 mL) was added and the mixture extracted with ethyl acetate (3×5 mL). The organic phase was washed with satd aq. Na_2CO_3 (2×10 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by silica gel flash chromatography (ethyl acetate/hexanes) to give **2b** (69 mg, 36%) as an oil. IR (cm^{-1}) 2954, 2864, 1726, 1681, 1620, 1429; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, 3H, $J=7.2$ Hz), 1.22–1.32 (m, 5H), 1.48–1.61 (m, 2H), 2.31 (ddd, 1H, $J=2$, 6.4, 16.8 Hz), 2.94 (dt, 1H, $J=2$, 16.8 Hz), 3.10 (dt, 1H, $J=2$, 6.4 Hz), 3.18–3.22 (m, 2H), 3.67 (s, 3H), 4.17–4.25 (m, 2H), 4.39 (t, 1H, $J=2$ Hz), 7.36 (d, 1H, $J=1.2$ Hz), 9.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 14.1, 18.0, 19.7, 30.5, 45.2, 50.7, 55.3, 56.5, 61.8, 91.4, 145.6, 168.1, 170.7, 199.9; MS: 316 $(M+1+H_2O)^+$, 298 $(M+1)^+$; UV (CH_3CN, λ, log ε_0): 290 (4.2).
6. Typical experimental procedure: To a solution of *n*-butylamine (200 μL, 2.02 mmol), ethyl glyoxalate (50% solution in toluene, 400 μL, 2.01 mmol) and 4 Å molecular sieves in dry acetonitrile (7 mL) were added scandium triflate (98 mg, 0.199 mmol), and 1-methyl-1,4-dihydropyridine-3-carbonitrile (120 mg, 1.00 mmol). The reaction mixture was stirred at rt for 3 h. Satd aq. Na_2CO_3 (5 mL) was added and the mixture extracted with ethyl acetate (3×5 mL). The organic phase was washed with satd aq. Na_2CO_3 (2×10 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by silica gel flash chromatography (ethyl acetate /hexanes) to give aminal **3a** (133 mg, 41%) as an oil. IR (cm^{-1}) 2957, 2931, 2867, 2189, 1728, 1630, 1177; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 3H, $J=7.3$ Hz), 0.94 (t, 3H, $J=7.2$ Hz), 1.27 (t, 3H, $J=7.0$ Hz), 1.30 (t, 3H, $J=7.0$ Hz), 1.32–1.42 (m, 8H), 1.92 (dd, 1H,

$J=5.2$, 15.4 Hz), 2.04–2.11 (m, 1H, $J=1.6$, 11.7, 15.4 Hz), 2.19–2.22 (m, 1H), 2.36–2.44 (m, 2H), 2.49–2.56 (m, 1H), 2.74 (s, 3H), 2.93–2.97 (m, 1H), 3.78 (d, 1H, $J=10$ Hz), 3.86 (d, 1H, $J=10.4$ Hz) 4.16–4.26 (m, 4H), 4.41 (s, 1H), 6.68 (d, 1H, $J=1.6$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 14.1, 14.2, 14.3, 20.1, 20.3, 24.6, 29.5, 31.0, 31.2, 37.2, 42.6, 50.0, 60.5, 61.0, 66.0, 70.2, 72.6, 75.4, 121.9, 148.9, 170.2, 171.8; MS: 434 $(M)^+$, 361 $(M-CO_2Et)^+$; UV (CH_3CN, λ, $\log \varepsilon_0$): 271 (4.2).

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