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Straightforward α-carbamoylation of NADH-like dihydropyridines and enol ethers

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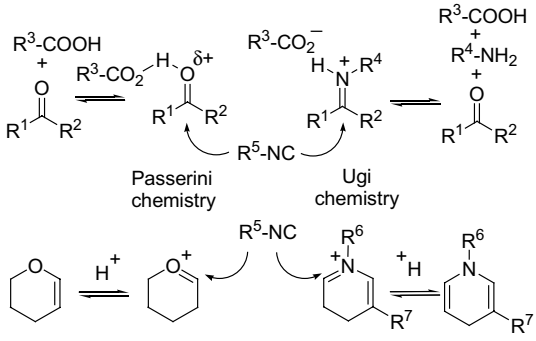
Abstract—The protonation of NADH-like dihydropyridines and cyclic enol ethers generates reactive cationic intermediates, which interact with isocyanides to afford α-carbamoylated heterocycles after an aqueous quenching, in Ugi and Passerini-type reactions, thus broadening the scope of these multicomponent processes.

Multicomponent reactions (MCRs) hold a privileged position among the synthetic strategies in terms of efficiency, particularly regarding the preparation of collections of molecules or in diversity oriented issues.[1] The systematic exploration of the chemical space through this methodology is far beyond the range offered by conventional procedures. Among MCRs, the Ugi and Passerini reactions are the most powerful and versatile processes, and have been intensively used in synthetic and medicinal chemistry.[2] In these reactions, the key step is the nucleophilic attack of the isocyanide upon the iminium ion or the activated carbonyl, which are generated in situ.[3,4] In order to expand the scope of these processes, and make the ready functionalization of fundamental heterocyclic frameworks feasible, we considered alternative ways to generate the reactive intermediates.[5] In this paper we report the study of the protonation of activated olefin moieties, present in dihydropyridines (**1**) and cyclic enol ethers (**2**), as the way to promote the α-carbamoylation of these heterocyclic structures through interaction with isocyanides (Scheme 1).



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

The first experiments involved the reactivity of *N*-alkyldihydropyridines (**1**), as readily available precursors for the preparation of complex piperidine-based compounds.[6–8] Thus, a MeOH solution of dihydropyridine **1a** reacted with *tert*-butylisocyanide (**2a**) in the presence of TFA, and, after an aqueous quenching, afforded the expected α-carboxamide **3a** in low yield (≈20%) together with some byproducts arising from the capture of the iminium ion by the nucleophilic solvent. Thus, 2-methoxytetrahydropyridines and related tetrahydropyridine dimers were isolated in these experiments. Also, the formamides formed by hydrolysis of the isocyanides were detected in some entries.

The parameters of the reaction were modified to improve the outcome. Noteworthy, the reaction performed in the presence of an excess of water with *p*-toluenesulfonic acid in catalytic amounts was not successful and yielded exclusively products derived from the hydrolysis of the isonitriles and the dihydropyridines. The best yields were obtained by using THF (or DCM) as the

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solvent, premixing the dihydropyridine with the isocyanide and adding a stoichiometric amount of a sulfonic acid [methanesulfonic, (±)-camphorsulfonic, or *p*-toluenesulfonic, but not triflic acid which polymerized the dihydropyridine] at −78 °C, stirring the mixture at 0 °C, and quenching with water after 24 h.[9] The process is general and diversely substituted dihydropyridines (the most representative modifications at the *N*-akyl- and the β-electron-withdrawing group positions were examined) underwent the transformation with cyclohexyl-, benzyl-, and *tert*-butylisocyanide in yields ranging from 64% to 97% (Table 1).

On the other hand, the possibility of promoting enantioselective transformations was considered, and carboxamide **3a** was prepared using (+)-camphorsulfonic acid as the catalyst. Unfortunately, we observed practically no enantiomeric excess (2%); however, the enantiomers were separated through routine chiral HPLC, thereby providing a convenient resolution for the racemic mixtures.[10]

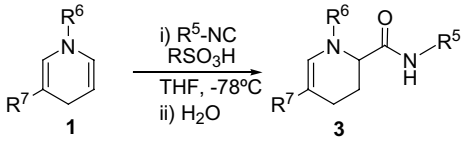
The chemistry of the cyclic enol ethers was tackled next, and essentially the same conditions were effective in the transformation of dihydropyrans and dihydrofurans. However, in these cases, the corresponding formamide (arising from the hydrolysis of the isocyanide) was produced in noticeable yields (up to 15%). Interestingly, the use of *p*-toluenesulfonic acid monohydrate was also efficient and was considered in some cases. 2*H*-Dihydropyran and dihydrofuran were converted into the α-carboxamido derivatives in acceptable yields (Table 2, entries 1, 2, 4, and 5). Interestingly, the substituted pyran **2b** underwent the expected transformation to yield a 60:40 mixture of the *trans* and *cis* diastereomers (entry 3).[11]

No productive transformations were possible under the usual conditions tested with the 3,4-dihydro-6-methyl-2*H*-pyran-2-one, probably because of the less activated olefin system.

On the other hand, after treatment with *tert*-butylisocyanide, the 3,4-dihydro-2-ethoxy-2*H*-pyran afforded a complex mixture in which the expected α-carboxamido derivatives (the diastereomeric mixture) were detected, probably indicating a competing reactivity of the acetal function under the reaction conditions.[12] The formation of α-trisubstituted carboxamides through this method was satisfactorily accomplished, and the α-methyldihydrofuran reacted normally to form the expected adduct, which contains a quaternary stereogenic center (entry 6).

In conclusion, a novel, one-pot, direct α-carbamoylation of enol ethers and dihydropyridines is reported.[13] The

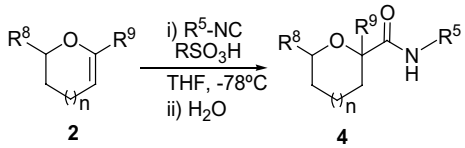
Table 1. α-Carbamoylation of dihydropyridines **1**



Entry	Dihydropyridine	R^6	R^7	R^5	Product	Yield (%)[a]
1	**1a**	Me	CN	*tert*-Bu	**3a**	97
2	**1b**	Me	CO_2Me	C_6H_{11}	**3b**	89
3	**1b**	Me	CO_2Me	Bn	**3c**	75
4	**1c**	Bn	COMe	*tert*-Bu	**3d**	70
5	**1c**	Bn	COMe	C_6H_{11}	**3e**	85
6	**1d**	Bn	$CONH_2$	C_6H_{11}	**3f**	64

[a] Isolated yield.

Table 2. α-Carbamoylation of cyclic enol ethers **2**



Entry	Enol ether	*n*	R^8/R^9	R^5	Product	Yield (%)[a]
1	**2a**	1	H/H	*tert*-Bu	**4a**	71
2	**2a**	1	H/H	C_6H_{11}	**4b**	65
3	**2b**	1	CH_2OAc/H	*tert*-Bu	**4c**	56[b]
4	**2d**	0	H/H	*tert*-Bu	**4d**	65
5	**2d**	0	H/H	C_6H_{11}	**4e**	60
6	**2f**	0	H/Me	*tert*-Bu	**4f**	70

[a] Isolated yield.
[b] Obtained as a 60:40 mixture of *trans* and *cis* isomers.

protocol developed allows the straightforward functionalization of key building blocks in heterocyclic chemistry, and may prove useful in the synthesis of carboxamido-piperidines and -pyrans, scaffolds with relevant presence in bioactive compounds.[14] Further work is underway in order to extend the synthetic methodology described.

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9. Typical experimental procedure: *tert*-butylisocyanide (1.2 mmol) was injected to a dichloromethane solution (20 mL) of dihydropyridine **1a** (1 mmol) and the solution was cooled to −78 °C. (±)-Camphorsulfonic (1 mmol) acid was then added, and the resulting mixture was stirred for 20 h at 0 °C. Water was added and the mixture was extracted twice with dichloromethane. The organic extracts were washed with saturated aqueous Na_2CO_3 solution, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, dichloromethane) to yield the desired α-carbamoylated-tetrahydropyridine **3a** (97%), obtained as a yellow oil. IR (cm^{-1}): 3323, 3015, 2970, 2929, 2184, 1683, 1623, 1558, 1405, 1362, 1098; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.80$ (s, 1H), 5.60 (br s, 1H), 3.57 (br s, 1H), 2.98 (s, 3H), 2.28 (m, 1H), 2.17 (m, 1H), 2.06 (m, 1H), 1.70 (m, 1H), 1.35 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.2$, 146.5, 122.4, 75.9, 61.4, 51.7, 42.6, 28.8, 23.2, 19.1 ppm; MS (EI): *m*/*z* (%): 221 (M^+, 5), 121 (100); UV [λ_{max} nm ($\log\varepsilon$), CH_2Cl_2]: 273 (4.53). HRMS (EI) mass calcd for $C_{12}H_{19}N_3O$: 221.1528, found 221.1539.
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