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Dihydropyridine-Based Multicomponent Reactions. Efficient Entry into New Tetrahydroquinoline Systems through Lewis Acid-Catalyzed Formal [4 + 2] Cycloadditions

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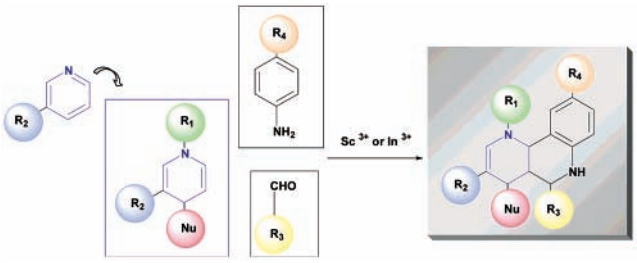
ABSTRACT



The three-component reaction of dihydropyridines, aldehydes, and *p*-methylaniline efficiently forms highly substituted tetrahydroquinolines in a stereoselective manner through a Lewis acid-catalyzed formal [4 + 2] cycloaddition. $InCl_3$ and $Sc(OTf)_3$ are the catalysts of choice for this process. The in situ generation of a reactive 1,4-dihydropyridine through the regioselective nucleophilic addition of cyanide to pyridinium salts allows a one-pot four-component transformation.

Multicomponent reactions (MCR) have emerged as a powerful tool for delivering the molecular diversity needed in the combinatorial approaches for the preparation of bioactive compounds.[1] Nitrogen heterocycles are frequently found in privileged structures (pharmacophores),[2] but their incorporation sometimes poses special problems (multistep sequences, lack of generality, preparation from acyclic precursors, etc.); thus, only a limited number of strategies have been successfully applied in the synthesis of heterocyclic scaffolds.[3] In this context, dihydropyridines (DHPs)[4] show interesting features that make them attractive for use in MCR: the high number of available derivatives (readily prepared from commercial pyridines) and the rich chemistry of the enamine moiety, which may be exploited for a wide variety of

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(1) For recent reviews, see: (a) Ugi, I.; Domling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647. (b) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321. (c) Ugi, I.; Heck, S. *Comb. Chem. High Throughput Screening* **2001** *4*, 1.

(2) (a) Wess, G.; Urmann, N.; Sickenberger, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3341. (b) Muegge, I. *Chem. Eur. J.* **2002**, *8*, 1977.

(3) For recent successful approaches dealing with nitrogen heterocycles, see: (a) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1921. (b) Gordeev, M. F.; Patel, D. V.; Gordon, E. M. *J. Org. Chem.* **1996**, *61*, 924. (c) Lorsbach, B. A.; Bagdanoff, J. T.; Miller, R. B.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 2244. (d) Munoz, B.; Chen, C.; McDonald, I. A. *Biotechnol. Bioeng.* **2000**, *71*, 78. (e) Pelish, H. E.; Westwood, N. J.; Feng, Y.; Kirchhausen, T.; Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 6740. (f) Ding, S.; Gray, N. S.; Wu, X.; Ding, Q.; Schultz, P. G. *J. Am. Chem. Soc.* **2002**, *124*, 1594.

(4) (a) Lounasmaa, M.; Tolvanen, A. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5, p 135. (b) For a recent review, see: Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141.

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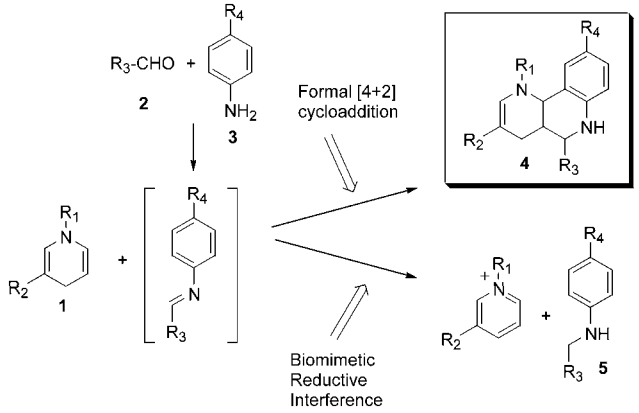
synthetically useful transformations. However, a major drawback seriously hampers their use for synthetic purposes: their easy oxidation to the corresponding pyridinium salts. In fact, nature's prominent role for NADH (a 1,4-dihydropyridine) is to promote the reduction of imines and carbonyl compounds (becoming oxidized to NAD^+ in the event).

Recently, we have shown that is feasible to avoid this oxidative fate and, in what we term *nonbiomimetic transformations*, we have achieved alternative oxidation routes by bonding with electronegative atoms in chemically productive processes.[5] With these thoughts in mind, we decided to test the participation of dihydropyridines (as electron-rich olefins) in acid-catalyzed imino Diels−Alder reactions. This versatile process for the synthesis of substituted tetrahydroquinolines (including interesting bioactive compounds), has elicited enormous interest in recent times.[6] Thus, the three-component interaction of an *N*-alkyl-1,4-dihydropyridine (**1**) with an aldehyde (**2**) and an aniline (**3**) would lead (through the in situ formation of the corresponding imine) to the benzonaphthyridine-type adduct **4**, in a formal [4 + 2] cycloaddition process (Scheme 1).

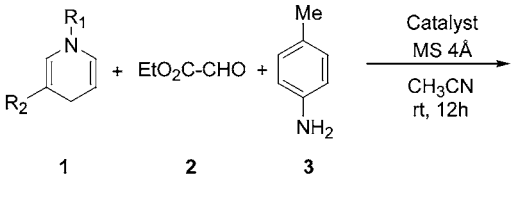
Scheme 1. Competing Reaction Pathways in the DHP−Imine Interaction

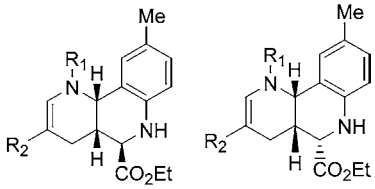


It has to be considered that such reactions, although perfectly defined for alkenes, enol-ethers, and enamines, may here display a redox interference caused by the known ability of DHPs to reduce imines.[7]

After discouraging experiments with different Lewis or protic acids (TFA and BF_3 caused the decomposition of the dihydropyridine, whereas $Mg(ClO_4)_2$ efficiently promoted the reductive pathway leading to the isolation of the pyridinium salts and the secondary amines **5**), we turned our attention to the use of $InCl_3$ and $Sc(OTf)_3$,[8,9] and we were delighted to find that stirring a solution of dihydropyridine (**1a**),[10] ethyl glyoxalate (**2**), and *p*-methylaniline (**3**) with $InCl_3$ (20%) as a catalyst in dry CH_3CN[11] in the presence of molecular sieves cleanly afforded a 2:1 mixture of the desired compounds **4a**−**4a′**[12] in 65% overall yield (entry 1, Table 1). The reaction

Table 1. Multicomponent Reactions of *N*-Alkyl-1,4-dihydropyridines





entry	R_1	R_2	compd	catalyst	yield (%)	dr (**4**:**4′**)
1	Me	CN	**4a**−**4a′**	$InCl_3$	65	2:1
2	Me	CO_2Me	**4b**−**4b′**	$InCl_3$	63	1:2
3	Me	CO_2Me	**4b**−**4b′**	$Sc(OTf)_3$	86	1:2
4	Bn	$CONH_2$	**4c**−**4c′**	$Sc(OTf)_3$	67	1.5:1

seems to be general, and works well with different substituents attached to the dihydropyridine nitrogen (Me and Bn) and with several electron-withdrawing groups at position 3 (CN, CO_2Me, $CONH_2$). The use of $Sc(OTf)_3$ as the catalyst slightly increased the yield to 86%, while the stereoselectivity remained unchanged (entries 2 and 3).

The structural diversity of the process is further increased by using *N*-acyldihydroazines (conveniently prepared through the reduction of the *N*-acylpyridinium salts). Thus, from *N*-methoxycarbonyl-1,2-dihydropyridine, naphthyridine **6** (37%, Figure 1) is obtained as a single isomer under the usual conditions (CH_3CN, $InCl_3$), whereas the corresponding dihydroisoquinoline derivative affords the benzo analogues

(5) (a) Lavilla, R.; Coll, O.; Kumar, R.; Bosch, J. *J. Org. Chem*. **1998**, *63*, 2728. (b) Lavilla, R.; Kumar, R.; Coll, O.; Masdeu, C.; Spada, A.; Bosch, J. Espinosa, E.; Molins, E. *Chem. Eur. J*. **2000**, *6*, 1763 and references therein.

(6) For some relevant examples of this process, also called the Poparov reaction, see: (a) Grieco, P. Bahsas, A. *Tetrahedron Lett*. **1988**, *29*, 5855. (b) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195. (c) Kiselyov, A. S.; Smith, L., II; Armstrong, R. W. *Tetrahedron* **1998**, *54*, 5089. (d) Ma, Y.; Qian, C.; Xie, M.; Sun, J. *J. Org. Chem*. **1999**, *64*, 6462. (e) Stevenson, P. J.; Nieuwenhuyzen, M.; Osborne, D. *Chem. Commun*. **2002**, 444. (f) Powell, D. A.; Batey, R. A. *Org. Lett*. **2002**, *4*, 2913.

(7) Interestingly, $Sc(OTf)_3$ seems to promote also the reductive pathway: Itoh, T.; Nagata, K.; Kurihara, A.; Miyazaki, M.; Ohsawa, O. *Tetrahedron Lett*. **2002**, *43*, 3105. For a general overview, see ref 4.

(8) (a) Babu, G.; Perumal, P. T. *Aldrichimica Acta* **2000**, *33*, 16. (b) Kobayashi, S. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 2, p 883.

(9) Other lanthanide Lewis acids were preliminarily tested (cerium, ytterbium, and lanthanum triflates) and also showed good reactivity profiles. Interestingly, the stereoselectivity of the process is affected by the nature of the catalyst. Details on these reactions will be reported in due curse.

(10) Dihydropyridines **1** were prepared by $Na_2S_2O_4$ reduction of the corresponding *N*-alkylpyridinium salts.

(11) Other solvents like THF or CH_2Cl_2 were ineffective, no cycloadducts being detected in these experiments.

(12) Products are racemic mixtures. Only one enantiomer is depicted. The stereochemical assignment was performed on purified compounds (column chromatography) through NOE experiments, molecular modelling and coupling constant analysis.

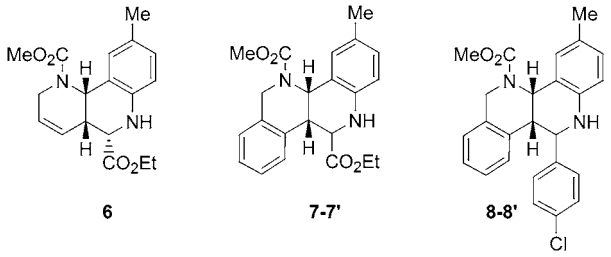


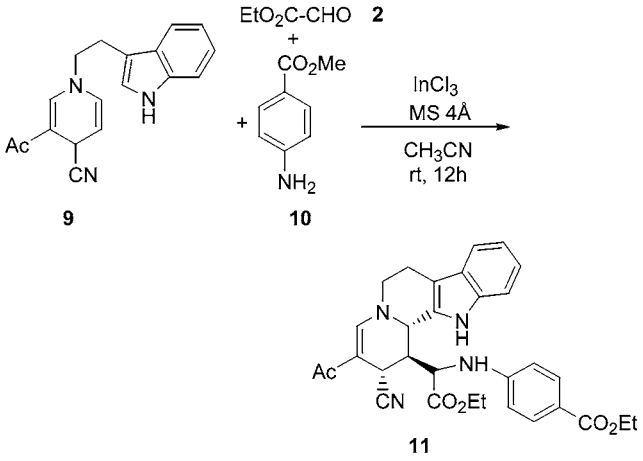
Figure 1. 3CR products from *N*-methoxycarbonyl-1,2-dihydroazines.

7−**7′** [63%, $Sc(OTf)_3$, 4:1]. The use of 4-chlorobenzaldehyde required more energetic conditions [CH_3CN, $InCl_3$, reflux temperature, 48 h][13] but also furnished the desired products **8**−**8′** (25%, 1.5:1).[14]

The scope of the process with regard to further modifications on the aldehyde and aniline components was preliminarily studied. The use of paraformaldehyde, glyoxylic acid, and chloral hydrate was not successful; only the biomimetic reduction products were detected. On the other hand, the reaction with the highly activated 3-methoxyaniline coursed through the aniline addition upon the intermediate imine,[15] bypassing in this way the interaction with the dihydropyridine. The reaction of electron-deficient aromatic amines (for instance 4-aminopyridine) was not satisfactory either. It has to be considered that the reaction although a formal [4 + 2] cycloaddition presumably proceeds through a stepwise ionic mechanism, involving the enamine addition upon the in situ-formed imine and the subsequent cyclization of the aromatic amine upon the iminium ion thus generated.[6b] The reduced nucleophilicity of deactivated anilines, however, opens the possibility of an internal trapping of the iminium intermediate by an electron-rich aromatic ring suitably located at the dihydropyridine nitrogen, leading to alternative structural types.

Thus, dihydropyridine **9** (generated by cyanide addition upon the corresponding *N*-tryptophylpyridinium salt) reacted with ethyl glyoxylate (**2**) and ethyl *p*-aminobenzoate (**10**), under $InCl_3$ catalysis, to stereoselectively afford the indoloquinolizidine derivative **11** (66%, 4:1 mixture of epimers at the α-aminoester center, stereochemistry not determined) (Scheme 2). The stereochemical outcome can be rationalized by considering the preferential attack of the dihydropyridine from its less hindered face and the final indole cyclization

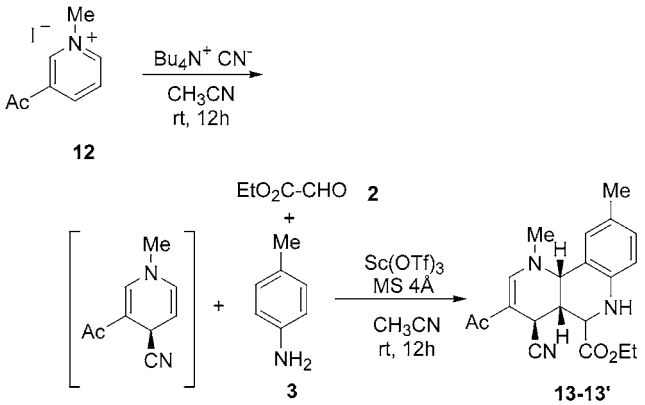
Scheme 2. Intramolecular Approach to Indoloquinolizidine **11**



upon the iminium ion taking place in a stereocontrolled manner to yield a *trans*-indoloquinolizidine.[16]

This result suggested the extension of the above methodology to more complex dihydropyridines, and we envisaged the in situ generation of a γ-substituted dihydropyridine, which would interact with the aldehyde and the aniline in a sequential mode in a one-pot four-component process (Scheme 3).[17,18]

Scheme 3. Four-Component One-Pot Tandem Cyclization Protocol



In this way, the reactive dihydropyridine was generated through the regioselective cyanide addition to the pyridinium salt **12** in a CH_3CN solution, and then the *p*-methylaniline (**3**) and the glyoxylate (**2**) together with the Lewis acid were added to promote the cycloaddition, which nicely afforded

(13) To speed up the processes, the reactions involving the more labile DHPs **1** were conducted at 60 °C. The isolated yields were somewhat lower, probably due to partial decomposition of the starting DHPs. Other activation techniques (for instance, high pressure, microwave irradiation) are under study and may result in faster reactions. On the other hand, the use of ionic liquids (Yadav, J. S.; Reddy, B. V. S.; Uma Gayathri, K.; Prasad, A. R. *Synthesis* **2002**, 2537) or microencapsulated scandium triflate (Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc*. **1998**, *120*, 2985) can also be considered for catalyst immobilization.

(14) Interaction of aromatic aldehydes with *N*-alkylDHPs (**1**) under the same conditions affords the expected addition compounds. The influence of the substituents in the aromatic ring on the reactivity and the stereoselectivity is under study.

(15) Huang, T.; Li, C.-J. *Tetrahedron Lett.* **2000**, *41*, 6715.

(16) For the related interaction of a dihydropyridine with the Eschenmoser's salt, see: Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3597.

(17) Direct 4CR would probably result in the interception of the imine by the nucleophile in a Strecker-type reaction.

(18) Attempted in situ generation of DHPs **1** by $Na_2S_2O_4$ reduction of pyridinium salts and subsequent reaction with ethyl glyoxalate and *p*-methylaniline resulted in failure, and no adducts (**4**−**4′**) were detected.

the highly substituted naphthyridine **13**−**13′** (72%, 1.2:1) as an epimeric mixture at the α-aminoester stereogenic center.

In summary, a multicomponent reaction involving the Lewis acid-catalyzed interaction of dihydropyridines, anilines, and aldehydes to form diversely substituted tetrahydroquinolines has been developed. The process, which can include an additional component in a tandem protocol, allows the incorporation of a wide range of commercially available pyridines into the final structure. A systematic survey of the reaction (catalyst and substrate range, improvement of the stereoselectivity, etc.) is currently under way in our laboratories.

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Supporting Information Available: Experimental procedures and spectral data of the compounds disclosed in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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