Synthetic Methods

DOI: 10.1002/anie.200605070

Double Insertion of Isocyanides into Dihydropyridines: Direct Access to Substituted Benzimidazolium Salts**

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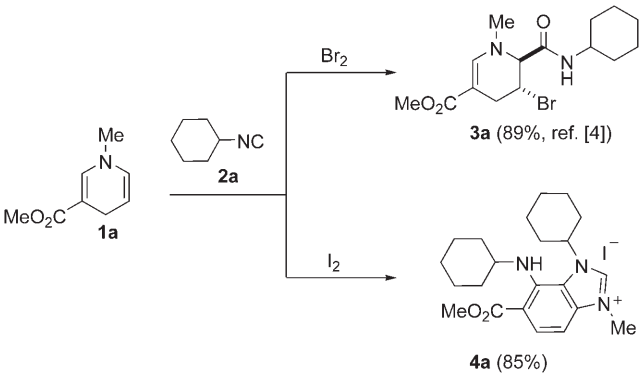
In memory of Marcial Moreno-Mañas

The chemistry of isocyanides has witnessed impressive developments in recent years. Since the pioneering work of Ugi,[1] who completely reshaped the field of multicomponent reactions (MCRs),[2] the famous four-component reaction (4CR) has become pivotal in modern synthetic methodology, especially in medicinal and combinatorial chemistry.

Continuing our efforts on the straightforward functionalization of heterocycles through MCRs,[3] our attention was drawn to the halo-carbamoylation of the electron-rich double bonds of dihydropyridines (DHPs). Although the interaction of DHP **1a** with bromine and cyclohexyl isocyanide (**2a**) afforded the expected β-bromo-α-carbamoyl tetrahydropyridine **3a** (89%; Scheme 1),[4] a similar reaction with iodine gave only traces of the analogous compound, and the major component was determined to be the benzimidazolium salt **4a** (40% with one equivalent of isocyanide, 85% with two equivalents).[5]



Scheme 1. Interaction of DHP **1a** with isocyanide **2a** and halogens.

The striking and clean formation of this benzimidazolium salt can be envisaged as the result of a formal double insertion of two isocyanide molecules into the DHP ring, which is rearranged to the benzimidazole core. This process involves the generation of four bonds (three C–C and one C–N) in a highly efficient and atom-economical manner, HI being the only side product formed. The process is worthy of interest as it deals with unprecedented reactivity pathways for both partners (isocyanides and DHPs[6]), and allows direct and easy entry into an important class of compounds: benzimidazole derivatives displaying a previously undescribed substitution pattern. In this respect, it should be remarked that benzimidazolium salts are synthesized by alkylation of benzimidazoles, and the synthesis of these compounds relies, almost exclusively, on transformations from anilines and *ortho*-diaminobenzenes, thus restricting the access to polysubstituted series.[7] Recently, benzimidazolium salts have gained relevance not only as N-heterocyclic carbene precursors (with implications in organocatalysis and as transition-metal ligands),[8] but also as ionic liquids[9] and bioactive compounds with remarkable presence in several therapeutic areas.[10]

To gain information on the mechanism of this transformation and to determine the relative disposition of the atoms belonging to the isocyanide units in the final adduct (where they could be adjacent to or flanking a central C atom from the DHP), we decided to perform the synthesis of salt **4a** with a cyclohexyl isocyanide labeled with ^{13}C at the C1 position (Figure 1).[11] Inspection of the (^{1}H-decoupled) ^{13}C NMR spectrum of doubly labeled **4a** clearly showed that the insertion pattern was contiguous (C3a–C4), as the major signals were doublets with a coupling constant in the range of the $^{1}J_{C-C}$ value (75.6 Hz).[12] In addition, we performed the reaction with DHP **1a** doubly deuterated at C4,[13] to yield the expected adduct **4a** labeled with deuterium at C6, which neighbors the CO_2Me group (Scheme 2).

Although the mechanism is far from well established, the following proposal can account for the main features of this transformation (Scheme 3). The process begins with the interaction of iodine[14] with the more reactive double bond of the DHP, in a new example of nonbiomimetic oxidation of DHPs.[15] The addition of isocyanides to the in situ generated α-haloiminium ion has also been reported,[4] but in this case the process continues with another nucleophilic attack on the first intermediate **A** to generate a new nitrilium ion **B**.[16] This intermediate can be trapped by interaction with an enamine-type double bond of the heterocyclic moiety to furnish a

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[**] This work was supported by DGICYT (Spain, project BQU 2006-03794) and Almirall-Prodesfarma (Barcelona). We thank Prof. Ludger A. Wessjohann (Leibniz Institute of Plant Biochemistry, Halle) for useful comments.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

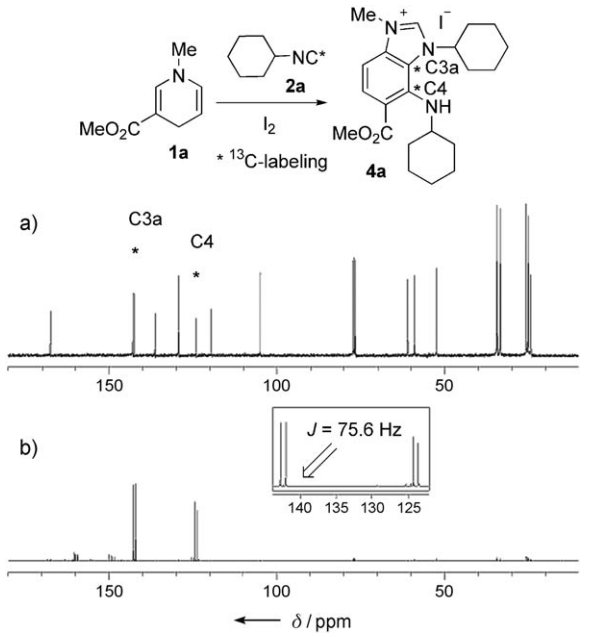
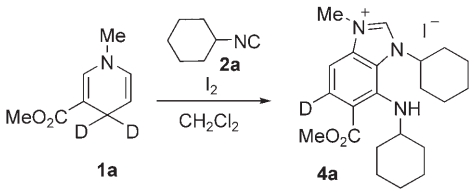
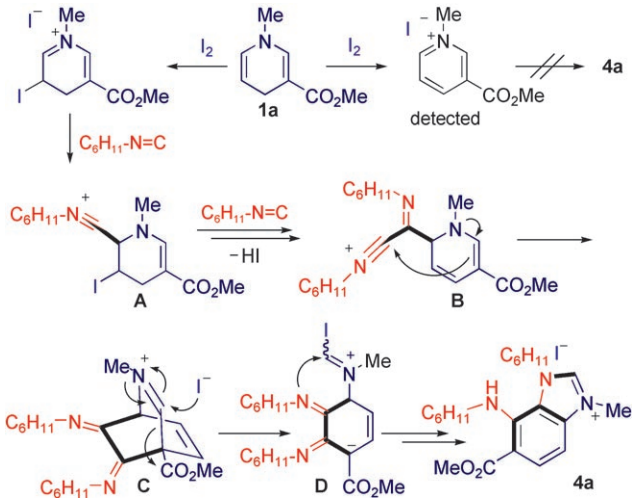


Figure 1. Insertion pattern for the isocyanide units in benzimidazolium salt **4a**, from the synthesis with ^{13}C-labeled isocyanide **2a** (top). ^{1}H-decoupled ^{13}C NMR spectra of a) unlabeled and b) labeled salt **4a**.



Scheme 2. Synthesis of deuterated **4a** from 4,4-dideuterated DHP **1a**.



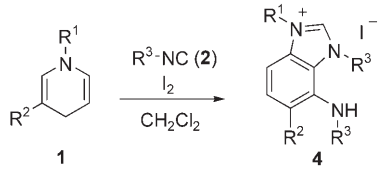
Scheme 3. Mechanistic proposal for the formation of **4a**.

bicyclic system **C**,[17] which may experience an iodide-promoted fragmentation to yield a delocalized anion **D**. Subsequent imidazole ring formation and aromatization may lead to the final adduct. The overall thermodynamic gain and the progressive manner in which all the new bonds are generated presumably make this orchestrated sequence feasible. The subtle distinction between the nucleophilicity and nucleofugacity of bromide and iodide may account for the different stabilization of the nitrilium intermediates, as well as the capacity to promote the ring opening and recyclization from intermediates **C** and **D**, respectively. Interestingly, pyridinium salts do not undergo the observed transformation (unambiguously tested in independent experiments). We have also observed a kinetic competition to some extent between the nonbiomimetic oxidation (ultimately ending in the benzimidazolium salt) and the formation of the corresponding pyridinium salt.

The influence of bases was analyzed next: the presence of anhydrous Na_2CO_3 resulted in lower yields and purities, whereas Et_3N prevented the reaction. On the other hand, small amounts of water (form nonanhydrous solvents) seem to be well-tolerated by the process. It has to be remarked that the outcome of this cascade reaction[18] is unrelated to processes in which an imidazole ring is generated from isocyanides.[19]

We next established the applicability range for this reaction, and in this way systematic variations on the two components were examined (Table 1). With respect to the scope of reactive DHPs, we determined that a broad range of N-substituents allows efficient transformations, including simple alkyl (Me, Et; Table 1, entries 1–3, 9, 13), functionalized (benzyl (Bn), phenethyl; Table 1, entries 4, 5, 10, 14, 15), aromatic (*p*-tolyl; Table 1, entry 6), cyclic (cyclohexyl; Table 1, entry 7), and even homochiral (α-methylbenzyl; Table 1, entry 8) groups. The latter result constitutes a new entry into chiral benzimidazolium salts. No attempts were

Table 1: Range of DHPs **1** and isocyanides **2**.[a]



Entry	R^1	R^2	R^3	Adduct	Yield [%][b]
1	Me	CO_2Me	*c*-C_6H_{11}	**4a**	85
2	Me	CO_2Allyl	*c*-C_6H_{11}	**4b**	61
3	Et	CO_2Allyl	*c*-C_6H_{11}	**4c**	58
4	Bn	CO_2Me	*c*-C_6H_{11}	**4d**	46
5	phenethyl	CO_2Me	*c*-C_6H_{11}	**4e**	25
6	*p*-tolyl	CO_2Me	*c*-C_6H_{11}	**4f**	30
7	*c*-C_6H_{11}	CO_2Me	*c*-C_6H_{11}	**4g**	40
8	α-methylbenzyl[c]	CO_2Me	*c*-C_6H_{11}	**4h**	31
9	Me	CN	*c*-C_6H_{11}	**4i**	34
10	Bn	COMe	*c*-C_6H_{11}	**4j**	52
11	Bn	$CONH_2$	*c*-C_6H_{11}	–	–
12	Me	CHO	*c*-C_6H_{11}	–	–
13	Me	CO_2Me	Bn	**4k**	43
14	Bn	CO_2Me	Bn	**4l**	46
15	Bn	CO_2Allyl	Bn	**4m**	39
16	Me	CO_2Me	*p*-$MeOC_6H_4$	**4n**	35

[a] All reactions were performed following the standard procedure. [b] Yield of isolated product. [c] Homochiral: the corresponding enantiopure DHP was prepared by the Zincke reaction from (*R*)-(+)-α-methylbenzylamine.

made to increase the yields by adding more isocyanide equivalents. The nature of the electron-withdrawing group at the β position, that is mandatory to guarantee the stability of the starting DHP, spans from alkoxycarbonyl (Table 1, entries 1–8, 13–15) to cyano (Table 1, entry 9) and acetyl (Table 1, entry 10) groups, whereas the corresponding carboxamido- and formyl-DHPs failed to yield the expected adducts (Table 1, entries 11 and 12, respectively). These restrictions probably reflect oxidative interferences, in the former case because of the faster I_2-promoted oxidation of the amide-DHP (a NADH analogue) to the corresponding pyridinium salt.[20] The reluctance of the formyl-DHP to yield the corresponding adduct **4** may be related to the oxidation of the aldehyde moiety during the cascade process.

The range of suitable isocyanides explored to date includes the commercially available cyclohexyl (Table 1, entries 1–10) and benzyl (Table 1, entries 13–15) isocyanides. Tosylmethyl isocyanide (TosMIC) afforded complex mixtures in which the β-iodo-α-carbamoylated compounds **3** were detected. Sterically encumbered isocyanides, such as 2,6-dimethylphenyl and *tert*-butyl derivatives, were considerably less reactive; however, even in these cases the adducts were formed, although in low yields, and detected by HPLC-mass spectrometry (MS). 4-Methoxyphenyl isocyanide (Table 1, entry 16) reacted as expected to yield adduct **4n**. The possibility of incorporating nonidentical residues at positions 3 and 4 in salts **4**, which may overcome an apparent limitation of the protocol, was explored by using mixtures of isocyanides; in this way heteroadducts have been identified, together with the expected homoadducts.[21]

In conclusion, we have described a protocol for the synthesis of benzimidazolium salts from DHPs and isocyanides. The process involves an unprecedented double insertion of the isocyanide unit into the heterocyclic ring, and constitutes a straightforward access to a broad range of derivatives through a cascade reaction.

Experimental Section

Typical procedure: Cyclohexyl isocyanide (**2a**, 240 μL, 1.96 mmol) and a solution of I_2 (248 mg, 0.98 mmol) in anhydrous CH_2Cl_2 (10 mL) were added to a solution of DHP **1a** (150 mg, 0.98 mmol) in anhydrous dichloromethane (5 mL) kept under an inert atmosphere at −78 °C (dry ice–acetone bath). The reaction mixture was stirred for 20 h and gradually warmed to room temperature (no further dry ice was added). H_2O (20 mL) was added and the mixture was extracted twice with CH_2Cl_2. The combined organic extracts were washed with an aqueous solution of $Na_2S_2O_3$ (5%, 2 × 10 mL) and brine (25 mL), and then dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH) to yield the pure benzimidazolium salt **4a** (415 mg, 85%) as a brown powder.

For further experimental details, see the Supporting Information.

Received: December 15, 2006
Revised: February 1, 2007
Published online: March 13, 2007

Keywords: cascade reactions · heterocycles · insertion · isocyanides · synthetic methods

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