ORGANIC LETTERS

2006
Vol. 8, No. 25
5789−5792

Isocyanide Addition to Pyridinium Salts. Efficient Entry into Substituted Nicotinonitrile Derivatives

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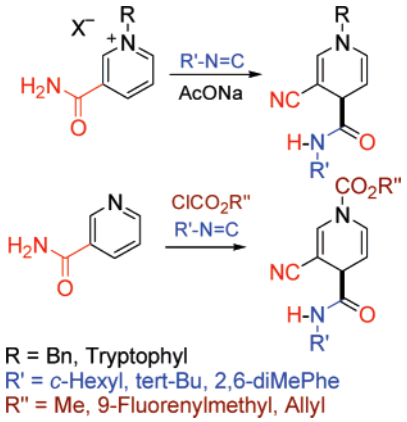
Received September 21, 2006

ABSTRACT



The addition of isocyanides to pyridinium salts is studied. The process takes place efficiently when a carboxamido group is present in the 3 position of the pyridine ring. The outcome of the reaction involves the stabilization of the nitrilium intermediate by the amide, which suffers a mild dehydration, leading regioselectively to *β*-cyano-*γ*-carbamoyl-1,4-dihydropyridines. In this way, a variety of nicotinamide derivatives were carbamoylated. Extension to quinolinium, isoquinolinium, and *N*-acylpyridinium salts is also reported.

The efficient functionalization of pyridine derivatives is of foremost importance in organic synthesis and particularly in medicinal chemistry.[1] In this context the carbamoylation of pyridine derivatives can be achieved only through stepwise protocols. Continuing our studies on the direct functionalization of fundamental heterocyclic systems, here we report our results on the interaction of isocyanides and pyridinium derivatives. We recently disclosed the carbamoylation of isoquinolines, dihydropyridines, and cyclic enol ethers through the addition of isocyanides to these heterocycles.[2] Isocyanide chemistry has become one of the most productive areas in organic synthesis, with deep implications for the preparation of natural products and bioactive compounds.[3] Particularly interesting is the involvement of isocyanides in multicomponent reactions (MCRs).[4]

Given the reactivity of pyridinium salts with nucleophiles, which usually leads to dihydropyridines, often with good regioselectivity,[5] we tested the interaction of isocyanides with

(1) Spitzner, D. Product Class 1: Pyridines. In *Science of Synthesis*; Black, D. StC., Ed.; Thieme Verlag: Stuttgart, 2005; Vol. 15, pp 11−284.

(2) (a) Díaz, J. L.; Miguel, M.; Lavilla, R. *J. Org. Chem.* **2004**, *69*, 3550. (b) Masdeu, C.; Díaz, J. L.; Miguel, M.; Jiménez, O.; Lavilla, R. *Tetrahedron Lett.* **2004**, *45*, 7907. (c) Masdeu, C.; Gómez, E.; Williams, N. A.; Lavilla, R. *QSAR Comb. Sci.* **2006**, *25*, 465.

(3) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.

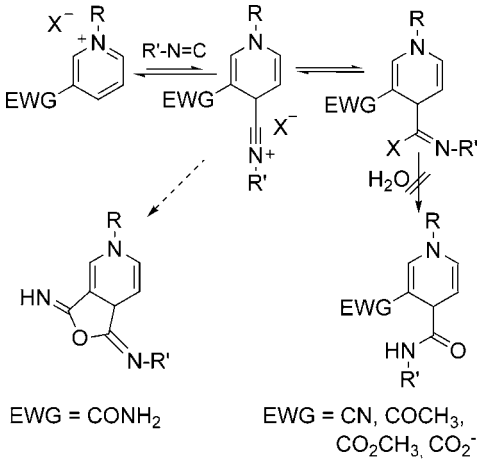
(4) (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (b) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133. (c) For an overview, see: *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-WCH: Weinheim, 2005.

(5) (a) For a review, see: Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141. (b) For additions to *N*-triflylpyridinium salts, see: Corey, E. J.; Tian, Y. *Org. Lett.* **2005**, *7*, 5535.

10.1021/ol062327w CCC: $33.50
Published on Web 11/09/2006

N-alkylpyridinium salts. Although similar addition processes with cyanide yielded the corresponding 1,4-adducts,[6] all attempts to perform the transformation upon reactive β-substituted pyridinium salts (CN, $COCH_3$, CO_2CH_3) under a range of reaction conditions (protic or aprotic solvents, different quenching protocols, and a range of temperatures) resulted only in the detection (HPLC-MS) of traces of the expected adducts. It has to be remarked that pyridines are reluctant to undergo Reissert reactions, requiring special conditions,[7] and do not suffer the analogous isocyanide process.[2a,8] An important difference with the cyanide addition arises here: the initial adduct is now a nitrilium ion, presumably in equilibrium with the starting materials, which may require further stabilization to proceed to the carbamoylated final compounds (Scheme 1). Several experiments

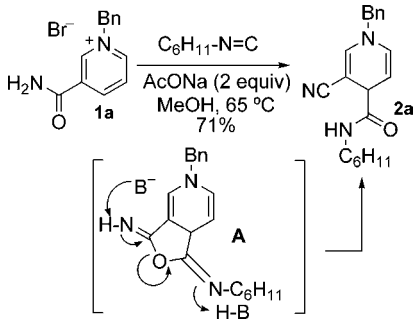
Scheme 1. Addition of Isocyanides to *N*-Alkylpyridinium Salts



were run to explore this point: an external source of chloride ions or the intramolecular trapping with a β-carboxylate pyridinium zwitterion. Unfortunately they failed to yield the expected compounds.

Recently, in a series of elegant studies, Zhu and co-workers disclosed that a carboxamido group attached to the isocyanide moiety efficiently traps the nitrilium intermediate to furnish oxazoles and iminooxazines, versatile synthetic intermediates that are useful in manifold MCRs.[9] The application of this methodology to our synthetic problem would involve the use of nicotinamide salts (structures with relevant roles in biology, chemistry, and medicine),[10] where the carboxamido group is linked to the iminium ion component. Thus, treatment of the *N*-benzyl salt **1a**[11] with cyclohexylisocyanide in MeOH with 2 equiv of AcONa nicely yielded the γ-carbamoylated-β-cyano-1,4-dihydropyridine **2a** regioselectively (71%) (Scheme 2).

Scheme 2. Reaction of Nicotinamide Salt **1a**



Several features deserve comment: the mild conversion (a formal dehydration) of the amide group to the cyano substituent, the need for more than 1 equiv of a base (AcONa being preferred to Et_3N or K_2CO_3, the reaction fails to yield any adduct in the absence of base and with 1.2 equiv the yield drops to 20−30%), and the regioselectivity of the process, favoring the 1,4-isomer.

The rationale for this result probably involves the initial formation of the bisiminofuran-type adduct (**A**), which in the basic medium, rearranges to the thermodinamically more stable product, the β-cyano-γ-carbamoyl-1,4-dihydropyridine **2a**. This type of behavior is precedented in Ugi-type processes with α-aminoacetamides.[12]

The process described here seems to be general, and several nicotinamide salts and isocyanides afforded the expected adducts in respectable yields. In this way, the 1,4-dihydropyridines **2b** (67%), **2c** (63%), and the *N*-tryptophyl derivative **2d** (66%) were prepared (Scheme 3).

This mechanistic outcome for the trapping of the nitrilium ion[13] paves the way for the challenging carbamoylation of pyridine derivatives. Satisfactorily, *N*-acylpyridinium derivatives also reacted under these conditions, probably helped by the enthalpic gain in the rearrangement. Thus, nicotinamide was reacted with methyl chloroformate and cyclohexyl isocyanide to give the 3CR adduct **2e** (66%) in a regioselecive manner. In this case the presence of a base (DIPEA, 1 equiv) resulted in the formation of less clean reaction mixtures and lower yields. Similarly, the interaction with

(6) For instance, see: Bunting, J. W.; Sindhuatmadja, S. *J. Org. Chem.* **1980**, *45*, 5411.

(7) Pyridines only react in Reissert processes under special conditions. See: Ichikawa, E.; Suzuki, M.; Yabu, K.; Albert, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 11808 and references therein.

(8) Recently, the reactivity of *N*-fluoropyridinium salts with isocyanides has been described: Kiselyov, A. S. *Tetrahedron Lett.* **2005**, *46*, 2279.

(9) (a) Janvier, P.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 2560. (b) Bonne, D.; Dekhane, M.; Zhu, J. *Org. Lett.* **2005**, *7*, 5285. (c) Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2006**, *8*, 4145 and references therein.

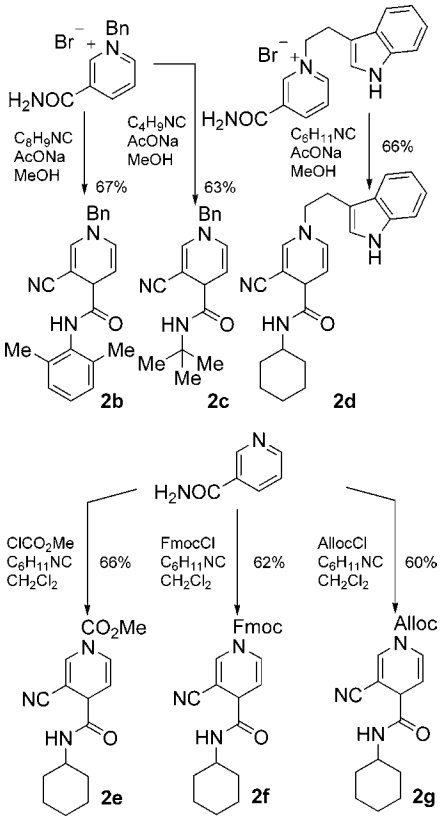
(10) (a) NAD; Chemistry and Its Role in Biology and Medicine. Pankiewicz, K. W., Ed.; In *Curr. Med. Chem.* **2004**, *11* (7). (b) Yang, J.; Klaidman, K.; Adams, J. D. *Med. Chem. Rev.* **2004**, *1*, 13. (c) Ogata, S.; Takeuchi, M.; Teradaira, S.; Yamamoto, N.; Iwata, K.; Okumura, K.; Taguchi, H. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 641. (d) Girgis, A. S.; Hosni, H. M.; Barsoum, F. F. *Bioorg. Med. Chem.* **2006**, *14*, 4466. (e) Broussy, S.; Bernardes-Génisson, V.; Quémard, A.; Meunier, B.; Bernadou, J. *J. Org. Chem.* **2005**, *70*, 10502. (f) Argyrou, A.; Vetting, M. W.; Aladegbami, B.; Blanchard, J. S. *Nat. Struct. Mol. Biol.* **2006**, *13*, 408.

(11) Lutz, J.; Hollmann, F.; Ho, T. V.; Schnyder, A.; Fish, R. H.; Schmid, A. *J. Organomet. Chem.* **2004**, *689*, 4783.

(12) Behnke, D.; Taube, R.; Illgen, K.; Nerdinger, S.; Herdtweck, E. *Synlett* **2004**, 688.

(13) For different trappings, see: Livinghouse, T. *Tetrahedron* **1999**, *55*, 9947.

Scheme 3. Nicotinamide-Isocyanide Adducts



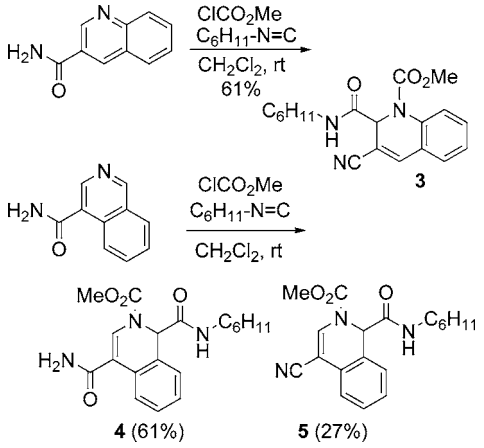
FmocCl and AllocCl allowed the introduction of these useful protecting groups in derivatives **2f** (62%) and **2g** (60%), respectively.

The participation of other heterocycles was considered, and we explored the coexistence of the carboxamido trapping group in a quinoline or isoquinoline nucleus. In these systems, the Ugi−Reissert reaction takes place without the need for any susbtituent.[14] Although the reaction of the *N*-methyl-*β*-carboxamidoquinolinium and isoquinolinium salts afforded unstable dihydroderivatives, the corresponding transformation with the *N*-acyl salts (interaction of the azines with cyclohexylisocyanide and methyl chloroformate) gave the carbamoylated adducts in good yields. The reaction of quinoline-3-carboxamide[15] cleanly afforded adduct **3** (61%) (Scheme 4).

In this case, the presence of the benzo-fused ring promoted a shift in regioselectivity, and the addition at the α-position was the only process observed. The reaction of isquinoline-4-carboxamide[16] under these conditions was more complex and afforded compounds **4** (61%) and **5** (27%). Although regioselectivity was as expected in this series, the major compound **4** seems to arise from the straightforward carbamoylation of the isoquinolinium salt at the more reactive α-position, which is in good agreement with previous results.[2a] However, the presence of the dehydrated compound **5** indicates the participation of the carboxamido group.[17] The

(14) (a) For a Ugi-type process upon a quinolininium salt, see: Ugi, I.; Böttner, E. *Liebigs Ann. Chem.* **1963**, *670*, 74. (b) Also see ref 2a.

Scheme 4. 3CR of Quinoline and Isoquinoline Derivatives



structure of this compound was confirmed by the identity with the product of the 3CR involving 4-cyanoisoquinoline, cyclohexylisocyanide, and methyl chloroformate, which yielded again **5** (63%) in a selective manner. It should be noted that *N*′-substituted nicotinamides (*N*′-phenyl and *N*′-benzyl) afforded complex mixtures when reacted under the usual conditions.

Next we explored a number of post-condensation transformations for some of the compounds thus prepared, exploiting the synthetic versatility of the DHP moiety present in their structures. Thus, **2a** was reduced (H_2/Pd−C) to give the corresponding tetrahydropyridine **6** (80%), and **2e** was DDQ-oxidized to the pyridine **7** (86%) (Figure 1).

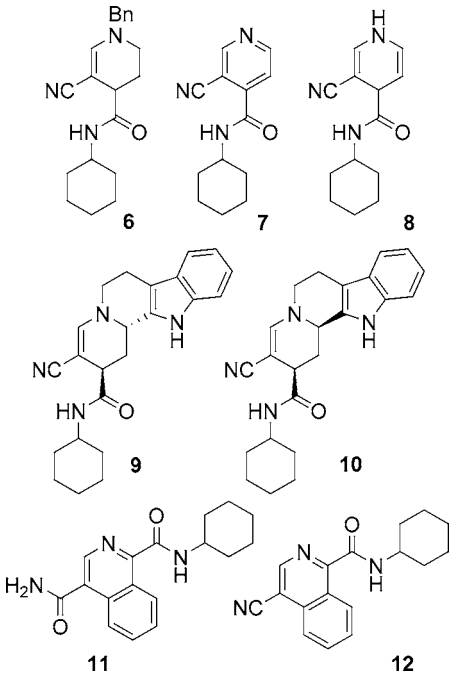


Figure 1. Post-condensation products.

Removal of the Fmoc and Alloc groups in **2f** and **2g** gave access to the N-H dihydropyridine **8** (90% and 75%, respectively).[18] The TFA-promoted cyclization of the triptophyl-dihydropyridine **2d** nicely afforded a 3:1 mixture of the *trans*- and *cis*-indoloquinolizidines **9** (63%) and **10** (21%), respectively. This represents a formal *umpolung* process that allows a suitable two-step carbamoylation of this privileged structure, present in many natural products and bioactive compounds. Interestingly, this methodology complements the Wenkert protocol, in which a nucleophilic malonate is attached to the γ-position of a pyridinium salt, thereby yielding valuable intermediates for the total synthesis of complex indole alkaloids.[19] Finally, the oxidation of the dihydroisoquinoline adducts **4** and **5** gave the corresponding aromatic derivatives **11** (62%) and **12** (50%, unoptimized yields) (Figure 1).

In conclusion, here we describe a flexible and straightforward protocol for the carbamoylation of nicotinamide derivatives. This approach allows the efficient preparation of diversely substituted nicotinonitriles, a group of compounds with relevant presence in medicinal chemistry.[20]

Acknowledgment. This work was supported by DGICYT (Spain, project BQU2003-00089) and Almirall Prodesfarma (Barcelona).

Supporting Information Available: Experimental details, characterization data, and copies of the ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062327W

(15) Ma, Z.; Hano, Y.; Nomura, T.; Chen, Y. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 1193.

(16) Bergstrom, F. W.; Rodda, J. H. *J. Am. Chem. Soc*. **1940**, *62*, 3030.

(17) This may take place through the addition at the α' position of the isoquinoline ring, to generate an *o*-quinodimethane intermediate (attempts to trap such species by Diels−Alder reactions resulted in failure), which may rearrange (1,5-sigmatropic shift) to the final compound **5**, although an intermolecular process cannot be ruled out. Another interesting possibility, suggested by a referee, involves the isocyanide addition to the α position and the trapping of the nitrilium ion by the carboxamido group to yield a strained (but precedented) anti-Bredt intermediate, which would rearrange to **5**.

(18) For an approach to this structural class, see: Lavilla, R.; Gotsens, T.; Guerrero, M.; Bosch, J. *Synthesis* **1995**, 382.

(19) (a) Wenkert, E. *Heterocycles* **1984**, *21*, 325. (b) Amann, R.; Spitzner, D. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 1320.

(20) (a) More than 75,800 substances with the nicotinonitrile core are listed in *SciFinder* (2006), most of them in biomedical patents. (b) Interestingly the cyano substituent is the synthetic precursor for the tetrazole moiety. For a recent result, see: Lukyanov, S. M.; Bliznets, I. V.; Shorshnev, S. V.; Aleksandrov, G. G.; Stepanov, A. E.; Vasil'ev, A. A. *Tetrahedron* **2006**, *62*, 1849.