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Synthesis of isocyanides through dehydration of formamides using XtalFluor-E

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ABSTRACT

The formation of isocyanides from formamides using XtalFluor-E, $[Et_2NSF_2]BF_4$, is presented. A wide range of formamides can be used to produce the corresponding isocyanides in up to 99% yield. In a number of cases, the crude products showed good purity (generally >80% by NMR) allowing to be used directly in multi-component reactions.

Introduction

Isocyanides (also called isonitriles)[1] are key building blocks in organic synthesis.[2] They are well known for their use in the Ugi reaction (or other multicomponent reactions),[3] but they are also utilized in many other synthetic transformations.[4] They can act as ligands for transition metals.[5] Finally, a few natural products contain this functionality.[6]

As isocyanides are somewhat unstable, they are normally prepared just before their use, although some are commercially available. A straightforward approach for their preparation consists in the dehydration of formamides.[7] Numerous reagents can affect this transformation including phosphoryl chloride,[8] chlorophosphate derivatives,[9] Vilsmeier reagent,[10] TsCl,[11] Burgess reagents[12] chlorodimethylformiminium chloride,[10] phosgene,[13] CCl_4/PPh_3,[14] cyanuric chloride,[15] and TfOH.[16] Unfortunately, some of these reagents are expensive and not available on a large scale, in addition most are either hygroscopic, moisture sensitive, highly toxic or thermally unstable.

We have recently described the synthesis of various *N*-containing heterocycles[17] through dehydration using diethylam inodifluorosulfinium tetrafluoroborate ($[Et_2NSF_2]BF_4$), XtalF luor-E,[18] a crystalline solid initially developed as a deoxofluorinating agent with enhanced thermal stability. In particular, we have reported the preparation of 1,3,4-oxadiazoles from 1,2-diacylhydrazines (Fig. 1).[17a] As a potential extension of this work, we imagined that if formamides (i.e., $R^1 = H$) were used as starting substrate, upon activation with XtalFluor-E and in the presence of a base, isocyanides would be generated.

Herein, we report the feasibility of this transformation. A wide range of formamides can be used to produce the corresponding isocyanides in up to 99% yield. In a number of cases, the crude

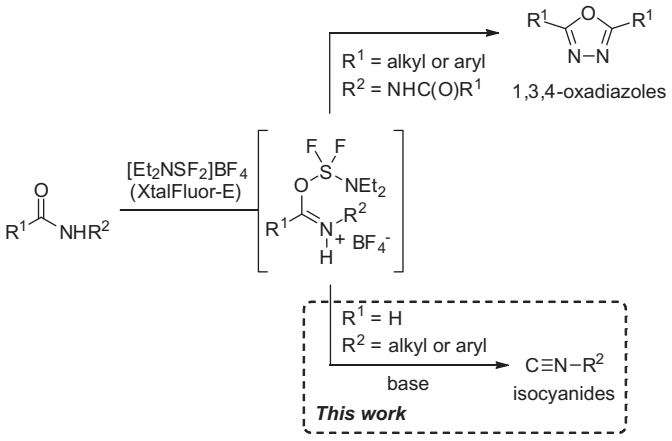

Figure 1. Activation of amides with $[Et_2NSF_2]BF_4$ for the synthesis of 1,3,4-oxadiazoles and isocyanides.

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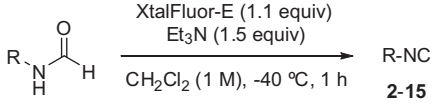
products showed good purity (generally >80% by NMR) allowing to be used directly in multi-component reactions.

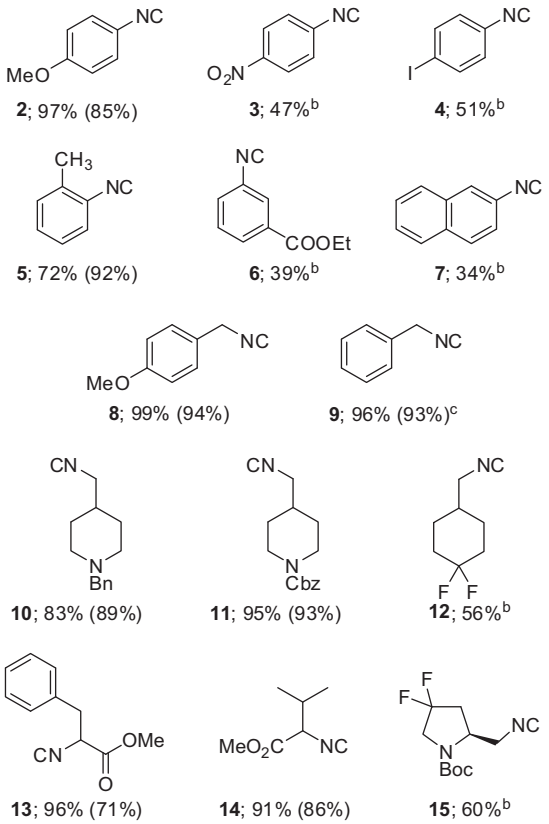
Results and discussion

We optimized the reaction conditions using **1** as the formamide and selected results are shown in Table 1. First, using 1 equiv of XtalFluor-E and Et_3N as the base, it was found that 1.5 equiv of Et_3N was optimal (entries 1–3). Other organic bases (entries 4–5) or an inorganic base (entry 6) was less effective. Using Et_3N as the base, other solvents were examined but all proved less effective than CH_2Cl_2 (entries 7–10). Using a slight excess of XtalFluor-E (1.1 equiv) provided almost a quantitative yield (entry 11). Finally, fine-tuning of the reaction temperature (not shown) revealed that running the transformation at −40 °C for 1 h provided a cleaner product (less side-products observed by ^1H NMR analysis of the crude product).

These optimized conditions were then used to examine the scope of this reaction (Table 2). In a number of cases, the crude isocyanide was pure enough so that it could be used directly in a subsequent transformation (vide infra). In those cases, no further purification was performed and the estimated NMR purity is indicated in parentheses.[19] When the crude isocyanides showed numerous impurities, purification using flash chromatography was performed; this often resulted in lower yields due, most likely, to the instability of the product on silica gel. Hence, a wide range of isocyanides could be generated including ones derived from aromatic (**2**–**7**), benzylic (**8**–**9**), aliphatic (**10**–**12**) or amino acid-based formamides (**13**–**15**). Also, these results show that various functional groups including ether, ester, and protected amines (benzyl, Cbz or Boc) are well tolerated. In the case of the phenylalanine-based isocyanide (**13**), chiral HPLC analysis showed that complete racemization occurred when starting from the enantioenriched formamide.[20] For the crude isocyanides with good purity, the crude yield varied between 72% and 99%. For the isocyanides that required purification, the isolated yields were lower, that is, between 34% and 60%. Surprisingly, for a few formamides (Fig. 2), no desired product could be isolated. For *N*-pentylformamide and *N*-(4-trifluoromethylphenyl)formamide, complete degradation was observed. With *N*-*tert*-butylformamide, no conversion

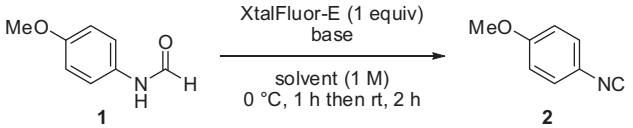
Table 2
Scope of the dehydration of formamides with XtalFluor-E[a]





[a] Crude yield after work-up with purity estimated by ^1H NMR analysis in parenthesis.
[b] Isolated yield.
[c] Reaction time was 2 h.

Table 1
Selected optimization results for the dehydration of the formamide **1**



Entry	Base	Solvent	Yield[a] (%)
1	Et_3N (1.2 equiv)	CH_2Cl_2	64
2	Et_3N (1.5 equiv)	CH_2Cl_2	90
3	Et_3N (2.5 equiv)	CH_2Cl_2	92
4	iPr_2EtN (1.5 equiv)	CH_2Cl_2	23
5	2,4,6-Collidine (1.5 equiv)	CH_2Cl_2	<20[b]
6	K_2CO_3 (1.5 equiv)	CH_2Cl_2	0[c]
7	Et_3N (1.5 equiv)	THF	41
8	Et_3N (1.5 equiv)	CH_3CN	36
9	Et_3N (1.5 equiv)	Toluene	55
10	Et_3N (1.5 equiv)	EtOAc	50
11[d]	Et_3N (1.5 equiv)	CH_2Cl_2	99

[a] Determined by ^1H NMR analysis of the crude using *p*-xylene as an internal standard.
[b] Estimated value as spectral interferences prevented a more accurate measurement.
[c] Starting material was recovered.
[d] 1.1 equiv of XtalFluor-E was used.

was observed (even at higher temperature) and the starting formamide could be fully recovered. Finally, for *N*-formylglycine ethyl ester, the major product was not the desired isocyanide, although we have not been able to isolate and characterize this compound. We suspect an intramolecular reaction with the activated amide similarly to what has been observed with 1,2-diacylhydrazines.[17a] This side-reaction may be slowed down with an α-substituent (cf. compounds **13**–**14**).

With respect to the reaction mechanism, the formation of isocyanides would most likely proceed with a mechanism similar to that which occurs for the cyclodehydration of 1,2-diacylhydrazines (Figs. 1 and 3).[17a] Hence, nucleophilic attack of the amide carbonyl group to $[Et_2NSF_2]BF_4$ at the electrophilic sulfur would generate intermediate **16**. Loss of HF and diethylaminosulfinyl fluoride[21] would lead to the protonated isocyanide (**17**) that would rapidly generate the isocyanide in the presence of Et_3N.

Finally, we explored the possibility of using the crude isocyanides directly in multi-component reactions. First, Passerini reaction[22] using crude isocyanides **2**, **5**, **8**, **9**, **11**, or **14** with a benzaldehyde and a carboxylic acid provided the corresponding α-acyloxyamide **18**–**25** in moderate to good yield from formamides over two steps (Table 3). Using this particular protocol, a simple filtration allows the isolation of the final product. This reaction is particularly effective with benzylic isocyanides. At this

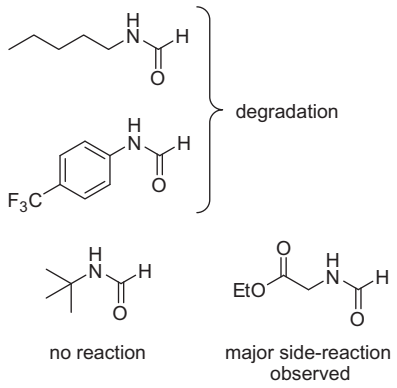


Figure 2. Unproductive formamides.

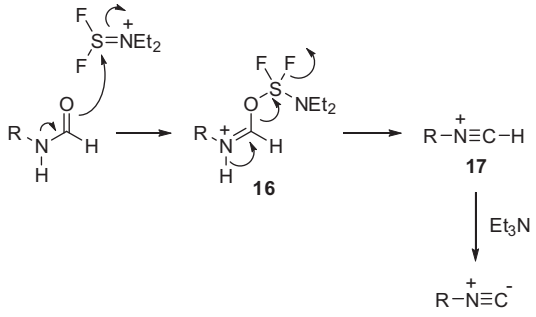
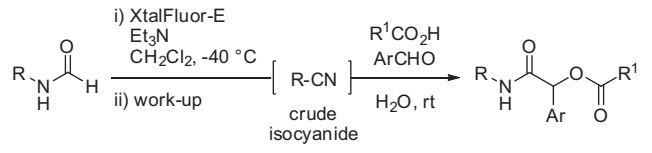
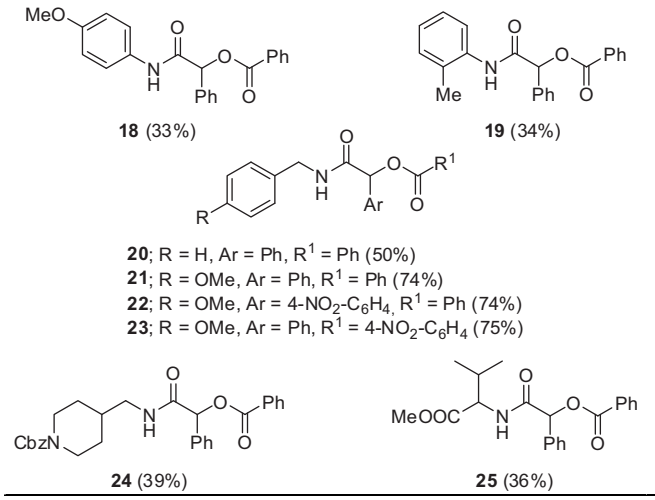


Figure 3. Mechanistic proposal for the dehydration reaction. The BF_4^- counter-ion has been omitted for clarity.

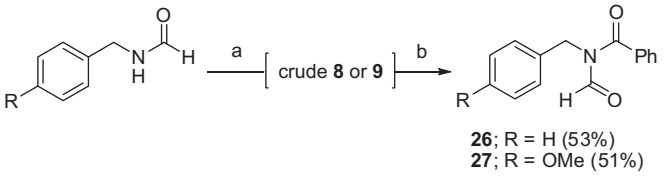
Table 3
Synthesis of α-acyloxyamide using crude isocyanides[a,b]



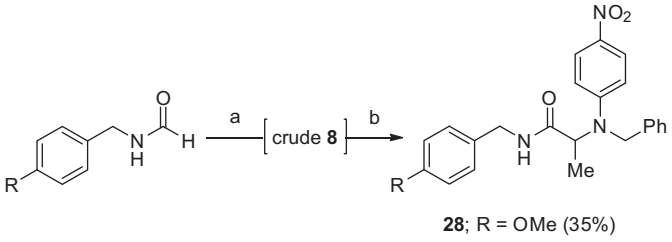


[a] See Supplementary Material for details on the reaction conditions.
[b] Isolated yield by filtration over two steps.

point, no attempts were made to further improve the yield though additional product may be present in the filtrate.[23] This represents 57–87% per step, which is satisfactory considering the crude yield



Scheme 1. Synthesis of *N*-formyl amides with crude isocyanides. Reagents and conditions: (a) XtalFluor-E, Et_3N, CH_2Cl_2 (1 M), −40 °C, 1–2 h followed by an aqueous work-up. (b) $PhCO_2H$, $CHCl_3$, 150 °C (MW), 30 min. Yields from products **26** and **27** are calculated from formamides (over two steps).



Scheme 2. Ugi-Smiles with a crude isocyanide. Reagents and conditions: (a) XtalFluor-E, Et_3N, CH_2Cl_2 (1 M), −40 °C, 1 h followed by an aqueous work-up. (b) CH_3CHO, $BnNH_2$, 4-nitrophenol, rt, 16 h. The yield from products **28** is calculated from the formamide (over two steps).

and purity of isocyanides and the fact that the Passerini is not a quantitative reaction, even with pure isocyanide.[22]

Then, synthesis of *N*-formyl amide under conditions reported by Danishefsky[24] with crude isocyanides **8** or **9** and benzoic acid gave the desired products **26** and **27** in moderate yields over two steps (Scheme 1).

Finally, a phenol Ugi–Smiles reaction[25] with crude isocyanide **8** is also possible albeit in moderate yield (Scheme 2).

Overall, the results obtained for those two multi-component reactions show that the presence of minor impurities in the isocyanide does not affect significantly the subsequent transformation and suggest that extension to other multi-component reactions may be possible.

Conclusion

We have reported the synthesis of isocyanides from formamides using XtalFluor-E. A number of isocyanides can be prepared in up to 99% yield from readily available formamides. In a number of cases, the crude products showed good purity (generally >80% by NMR) allowing to be used directly in multi-component reactions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.128.

References and notes

1. Although still used, isonitrile is an obsolete term that should be replaced with isocyanides, see Moss, G. P.; Smith, P. A. S.; Tavernier, D. *Pure Appl. Chem.* **1995**, *67*, 1307–1375.
2. *Isocyanide Chemistry: Applications in Synthesis and Materials Science*; Nenajdenko, V., Ed.; Wiley-VCH: Weinheim, Germany, 2012.
3. Reviews: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210; (b) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 56–66; (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89; (d) Koopmanschap, G.; Ruijter, E.; Orru, R. V. A. *Beilstein J. Org. Chem.* **2014**, *10*, 544–598.
4. Reviews: (a) Lygin, A. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9094–9124; (b) Gulevich, A. V.; Zhdanko, A.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235–5331; (c) Vlaar, T.; Ruijter, E.; Maes, B. U. W.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 7084–7097.
5. Reviews: (a) Yamamoto, Y. *Coord. Chem. Rev.* **1980**, *32*, 193–233; (b) Singleton, E.; Oosthuizen, H. E. *Adv. Organomet. Chem.* **1983**, *22*, 209–310; (c) Hahn, F. E. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 650–665.
6. Review: Garson, M. J.; Simpson, J. S. *Nat. Prod. Rep.* **2004**, *21*, 164–179.
7. For selected alternative procedures, see (a) Atkinson, R. S.; Harger, M. J. P. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2619–2622; (b) Kitano, Y.; Manoda, T.; Miura, T.; Chiba, K.; Tada, M. *Synthesis* **2006**, 405–410; (c) Pirrung, M. C.; Ghorai, S. *J. Am. Chem. Soc.* **2006**, *128*, 11772–11773; (d) Pirrung, M. C.; Ghorai, S.; Ibarra-Rivera, T. R. *J. Org. Chem.* **2009**, *74*, 4110–4117.
8. Ugi, I.; Meyr, R. *Chem. Ber.* **1960**, *93*, 239–248.
9. Kobayashi, G.; Saito, T.; Kitano, Y. *Synthesis* **2011**, 3225–3234.
10. Walborsky, H. M.; Niznik, G. E. *J. Org. Chem.* **1972**, *37*, 187–190.
11. (a) Okada, I.; Kitano, Y. *Synthesis* **2011**, 3997–4002; (b) Guchhait, S. K.; Priyadarshani, G.; Chaudhary, V.; Seladiya, D. R.; Shah, T. M.; Bhogayta, N. P. *RSC Adv.* **2013**, *3*, 10867–10874.
12. Creedon, S. M.; Crowley, H. K.; McCarthy, D. G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1015–1017.
13. Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 472–484.
14. Maillard, M.; Faraj, A.; Frappier, F.; Florent, J.-C.; Grierson, D. S.; Monneret, C. *Tetrahedron Lett.* **1989**, *30*, 1955–1958.
15. Porcheddu, A.; Giacomelli, G.; Salaris, M. *J. Org. Chem.* **2005**, *70*, 2361–2363.
16. Baldwin, J. E.; O'Neil, I. A. *Synlett* **1900**, 603–604.
17. (a) Pouliot, M.-F.; Angers, L.; Hamel, J.-D.; Paquin, J.-F. *Org. Biomol. Chem.* **2012**, *10*, 988–993; (b) Pouliot, M.-F.; Angers, L.; Hamel, J.-D.; Paquin, J.-F. *Tetrahedron Lett.* **2012**, *53*, 4121–4123.
18. (a) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; Laflamme, F.; L'Heureux, A. *Org. Lett.* **2009**, *11*, 5050–5053; (b) L'Heureux, A.; Beaulieu, F.; Bennet, C.; Bill, D. R.; Clayton, S.; Laflamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* **2010**, *75*, 3401–3411.
19. The impurities have not been structurally identified, but originate from XtalFluor-E as peaks most likely assigned to the diethyl portion of the reagent can be observed on the crude ^{1}H NMR spectra.
20. Zhu, J.; Wu, X.; Danishefsky, S. J. *Tetrahedron Lett.* **2009**, *50*, 577–579.
21. (a) Brown, D. H.; Crosbie, K. D.; Darragh, J. I.; Ross, D. S.; Sharp, D. W. A. *J. Chem. Soc. A* **1970**, 914–917; (b) Keat, R.; Ross, D. S.; Sharp, D. W. A. *Spectrochim. Acta* **1971**, *27A*, 2219–2225.
22. Pirrung, M. C.; Das Sarma, K. *J. Am. Chem. Soc.* **2004**, *126*, 444–445.
23. For instance, in the case of **21**, ^{1}H NMR analysis of the filtrate showed the presence of ca. 20% of **21** along with numerous impurities.
24. Li, X.; Danishefsky, D. *J. Am. Chem. Soc.* **2008**, *130*, 5446–5448.
25. El Kaïm, L.; Grimaud, L.; Oble, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 7961–7964.