Multicomponent Reactions

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IBX-Mediated Oxidative Ugi-Type Multicomponent Reactions: Application to the N and C1 Functionalization of Tetrahydroisoquinoline**

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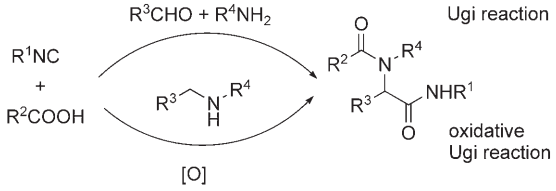
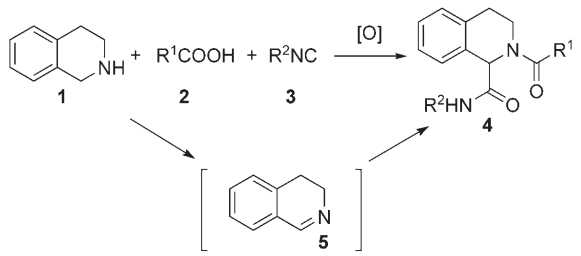
Direct functionalization of the α-carbon atom of amines in general and of tetrahydroisoquinolines in particular has attracted great attention in recent years,[1] and some of the most important C–C bond-forming processes such as Mannich,[2] Strecker,[3] aza-Henry,[4] and Friedel–Crafts[5] reactions can now be performed directly from amines under mild oxidative conditions. All these protocols involve the formation of incipient imine/iminium species followed by addition of suitable nucleophiles. The development of mild oxidation protocols compatible with the nucleophiles is essential for the success of the one-pot process.[6] One of the many options that has been actively pursued recently is the use of a catalytic amount of transition metal in combination with a stoichiometric amount of peroxide as a terminal oxidant. To date, a number of oxidative protocols that tolerate nucleophiles such as malonates, nitroalkanes, electron-rich aromatics, and cyanide have been developed.[2–5] However, multicomponent reactions involving a key amine oxidation step is, to the best of our knowledge, unknown.

Ugi four-component reactions (U-4CRs, Scheme 1) which combine an amine, an aldehyde, an isocyanide, and a carboxylic acid to give an α-acylamino amide have been intensively researched over the past few decades and have found wide applications in the synthesis of medicinally relevant heterocycles.[7] The key C–C bond-forming step in this reaction involves nucleophilic addition of the carbon of an isocyanide to the imine/iminium formed in situ by condensation of an amine and aldehyde. As a continuation of our interest in the development of oxidative multicomponent reactions (MCRs),[8] we became interested in the development of oxidative Ugi-type reactions wherein the electrophilic iminium species was generated by in situ oxidation of amines. Here we report the first examples of oxidative three-component Ugi-type reactions that allow, for the first time, a dual acylation of the nitrogen and α-carbon centers of tetrahydroisoquinoline (**1**) by a carboxylic acid and an isocyanide under mild conditions (Scheme 2).



Scheme 1. Ugi reaction versus an oxidative Ugi-type reaction.



Scheme 2. Three-component reaction of an amine, a carboxylic acid, and an isocyanide for the dual functionalization of tetrahydroisoquinoline (**1**).

To begin our study, tetrahydroisoquinoline (**1**) was selected as a substrate because of its importance in medicinal and natural products chemistry. As 2-iodoxybenzoic acid (IBX) in dimethyl sulfoxide (DMSO) can oxidize secondary amines to imines as demonstrated by Nicolaou and coworkers,[9,10] the three-component condensation of **1**, benzoic acid (**2a**), and benzyl isocyanide (**3a**) was first performed in DMSO in the presence of IBX (Table 1).[11,12] Although it did provide the desired three-compound adduct **4**, the yield of **4** was moderate (22%, entry 1, Table 1).[13] Careful examination of the reaction mixture at different time intervals indicated that the oxidation of **1** to 3,4-dihydroisoquioline (**5**) took place smoothly. It was the slow reaction of **5** with **2a** and **3a** in DMSO that diminished the overall efficiency. On the basis of this observation, the reaction of **1**, **2a**, and **3a** was carried out in different organic solvents (Table 1). Performing the reaction in MeOH, the solvent of choice for the Ugi reaction, improved the yield of **4** to 50% (entries 2, 3, Table 1). This is noteworthy as it indicates that oxidation of amine **1** proceeds much faster than that of methanol in contrast to the dominant notion.[14] Further increasing the polarity and acidity of the

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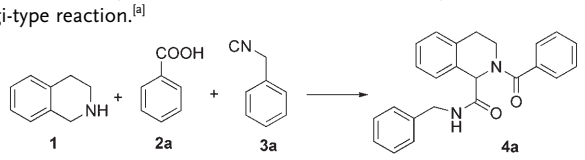
Supporting information for this article, including details of experimental procedures and product characterization for all compounds **4a–4q**, is available on the WWW under http://www.angewandte.org or from the author.

Table 1: A survey of reaction conditions for the IBX-promoted oxidative Ugi-type reaction.[a]



Entry	Solvent	*T* [°C]	*t* [h]	Yield [%][b]
1	DMSO	25	72	22
2	MeOH	25	72	50[c]
3	MeOH	60	21	63[c]
4	TFE[d]	25	72	19
5	Toluene	25	72	29
6	MeCN	25	72	26
7	DMF[d]	25	72	43
8	CH_2Cl_2	25	72	36
9	Et_2O	25	72	20[c]
10	THF	25	72	51
11	THF	40	28	83
12	THF	60	20	87
13	THF[e]	60	20	80
14	THF[f]	60	6	51
15	DMSO/THF (19:1)	60	20	85

[a] General conditions: **1**/**2a**/**3a**/IBX = 1.5:1.5:1.0:2.0, concentration *c* = 0.5 M. [b] Yields refer to the pure isolated compound after silica gel chromatography. [c] Contaminated with a small amount of IBA. [d] TFE = trifluoroethanol; DMF = *N*,*N*-dimethylformamide. [e] 4-Å molecular sieves were added. [f] *c* = 2.0 M.

solvent (TFE) provided a mediocre result (entry 4, Table 1). Only a low to moderate yield of adduct **4** was isolated when the reaction was performed in toluene,[15] MeCN, DMF, CH_2Cl_2, and diethyl ether (entries 5–9, Table 1).[16,17] However, THF turned out to be an excellent reaction media for the present domino oxidation/Ugi-type 3CR process (entry 12, Table 1). A similar result was obtained when a mixture of DMSO and THF (19:1) was used as solvent (entry 15, Table 1).[18] Under optimized conditions (THF, 60 °C, *c* = 0.5 M), compound **4** was isolated in 87% yield (entry 12, Table 1).[19] Note that IBX is poorly soluble in THF, and consequently the oxidative U-3CR was realized under heterogeneous conditions. The excess of IBX as well as its reduced form IBA were removed by a simple filtration through a short pad of Celite.

Using IBX as oxidant and THF as solvent, the scope of this oxidative Ugi reaction was next examined. A variety of carboxylic acids including benzoic acid, acetic acid, and functionalized acids such as 2-iodobenzoic acid, cinnamic acid, (*E*)-4-ethoxy-4-oxobut-2-enoic acid, phenylpropiolate, and N-Cbz-glycine can be used as reaction partners to acylate the secondary amine. Isocyanides with different steric and electronic properties such as benzyl isocyanide, 2-iodobenzyl isocyanide, cyclohexyl isocyanide, *tert*-butyl isocyanide, and α-benzyl-α-isocyanoacetamide[20] can be used to directly acylate the α-carbon atom (Figure 1). As expected, no diastereoselectivity was observed when chiral α-isocyano-α-benzyl isocyanoacetamide was used as an input. Interestingly, the N_α-unprotected tetrahydro-β-carboline can be similarly functionalized to afford N and C double-acylated derivative **4o**. The indole nucleus is stable although its reaction with

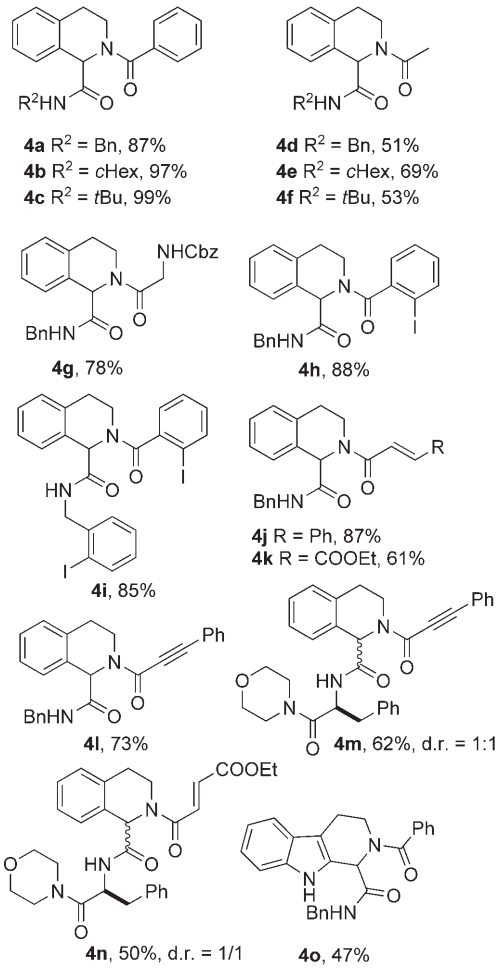
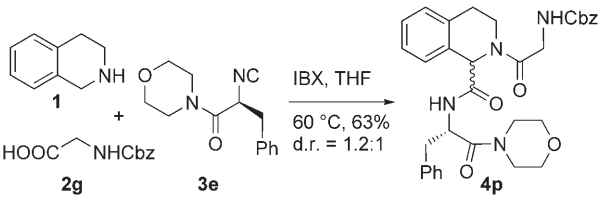


Figure 1. Structures of functionalized tetrahydroisoquinolines. Bn = benzyl; Cbz = carbobenzyloxy.

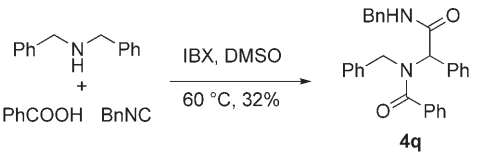
(diacetoxyiodo)benzene has been reported.[21] The higher nucleophilicity of the secondary amine relative to the indolyl nitrogen might ensure the chemoselective oxidation of the former without affecting the indole moiety.

The one-step three-component synthesis of tripeptide **4p** highlighted the potential of the present protocol in the preparation of tetrahydroisoquinoline-containing peptidomimetics (Scheme 3). Interestingly, note that in this reaction a non-proteinogenic amino acid was synthesized with the concomitant formation of a peptide bond. The formation of oxazole resulting from the internal trap of the nitrilium intermediate by amide oxygen was not observed under these



Scheme 3. Three-component reaction to synthesize a tetrahydroisoquinoline-containing tripeptide.

reaction conditions.[22] A preliminary experiment indicated that direct functionalization of an acyclic amine was also feasible. Thus the reaction of dibenzylamine with benzoic acid and benzyl isocyanide in DMSO afforded the α-acyloxy amide **4q** in 32% yield (Scheme 4).



Scheme 4. Double (N and C) acylation of dibenzylamine.

In conclusion, we have documented a highly efficient IBX-mediated Ugi-type reaction of secondary amines. To the best of our knowledge, it constitutes the first examples of dual acylation of the α-carbon and NH group of tetrahydroisoquinoline. Mild conditions, simple experiment procedure, and good to excellent yields characterize the present oxidative three-component reaction. We believe this transformation is of significant synthetic value and are working to extend it.[23]

Experimental Section

Typical procedure: The carboxylic acid (1.5 equiv), secondary amine (1.5 equiv), and isocyanide (1.0 equiv) were added successively to a suspension of IBX (2.0 equiv) in dry THF (0.5 M). The mixture was then heated at 60 °C and monitored by TLC (6–72 h). When the reaction was complete, the mixture was cooled to room temperature, hydrolyzed with HCl (1N), and stirred for 10 min. The mixture was then diluted with dichloromethane and filtered through a short pad of Celite, and the filtrate was evaporated to dryness. The crude product was dissolved in saturated $Na_2S_2O_3$ solution, and the aqueous phase was extracted with dichloromethane. The combined organic layers were washed with saturated $NaHCO_3$, water, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to afford the desired compound.

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[1] a) M. North, *Angew. Chem.* **2004**, *116*, 4218–4220; *Angew. Chem. Int. Ed.* **2004**, *43*, 4126–4128; b) Z. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8928–8933; c) K. Godula, D. Sames, *Science* **2006**, *312*, 67–72.

[2] a) H. M. L. Davies, C. Venkataramani, T. Hansen, D. W. Hopper, *J. Am. Chem. Soc.* **2003**, *125*, 6462–6468; b) Z. Li, C.-J. Li, *Eur. J. Org. Chem.* **2005**, 3173–3176; c) A. J. Catino, J. M. Nichols, B. J. Nettles, M. P. Doyle, *J. Am. Chem. Soc.* **2006**, *128*, 5648–5649; d) J.-C. Matsuo, Y. Tanaki, H. Ishibashi, *Org. Lett.* **2006**, *8*, 4371–4374.

[3] a) D. H. R. Barton, A. Billion, J. Boivin, *Tetrahedron Lett.* **1985**, *26*, 1229–1232; b) S.-I. Murahashi, N. Komiya, H. Terai, T. Nakae, *J. Am. Chem. Soc.* **2003**, *125*, 15312–15313; c) S.-I. Murahashi, N. Komiya, H. Terai, *Angew. Chem.* **2005**, *117*, 7091–7093; *Angew. Chem. Int. Ed.* **2005**, *44*, 6931–6933.

[4] Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3672–3673.

[5] Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 6968–6969.

[6] For a recent overview, see: R. J. K. Taylor, M. Reid, J. Foot, S. A. Raw, *Acc. Chem. Res.* **2005**, *38*, 851–869.

[7] a) C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51–80; b) R. V. A. Orru, M. De Greef, *Synthesis* **2003**, 1471–1499; c) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133–1144; d) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89; e) for a monograph, see: *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**.

[8] a) T. Ngouansavanh, J. Zhu, *Angew. Chem.* **2006**, *118*, 3575–3577; *Angew. Chem. Int. Ed.* **2006**, *45*, 3495–3497; b) for a comprehensive review on the Passerini reaction, see: c) L. Banfi, R. Riva in *Organic Reactions*, *Vol. 65* (Ed.: A. B. Charette), Wiley, New York, **2005**, pp. 1–140.

[9] a) K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *Angew. Chem.* **2003**, *115*, 4211–4216; *Angew. Chem. Int. Ed.* **2003**, *42*, 4077–4082; b) K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *J. Am. Chem. Soc.* **2004**, *126*, 5192–5201.

[10] For highlights, see: a) T. Wirth, *Angew. Chem.* **2001**, *113*, 2893–2895; *Angew. Chem. Int. Ed.* **2001**, *40*, 2812–2814; b) T. Wirth, *Angew. Chem.* **2006**, *118*, 4510–4512; *Angew. Chem. Int. Ed.* **2006**, *45*, 4402–4404.

[11] For selected examples of recent innovative variations of the Ugi reaction, see: a) L. El Kaim, L. Grimaud, J. Oble, *Angew. Chem.* **2005**, *117*, 8175–8178; *Angew. Chem. Int. Ed.* **2005**, *44*, 7961–7964; b) G. B. Giovenzana, G. C. Tron, S. D. Paola, I. G. Menegotto, T. Pirali, *Angew. Chem.* **2006**, *118*, 1117–1120; *Angew. Chem. Int. Ed.* **2006**, *45*, 1099–1102.

[12] For Dess–Martin periodinane (DMP)- or IBX-initiated tandem oxidation/Wittig reactions, see: a) C. C. Huang, *J. Labelled Compd. Radiopharm.* **1987**, *24*, 675–681; b) A. G. M. Barrett, D. Hamprecht, M. Ohkubo, *J. Org. Chem.* **1997**, *62*, 9376–9378; c) D. Crich, X. S. Mo, *Synlett* **1999**, 67–68.

[13] For Ugi reactions for the functionalization of azines, see: a) J. L. Diaz, M. Miguel, R. Lavilla, *J. Org. Chem.* **2004**, *69*, 3550–3553; b) G. C. Tron, J. Zhu, *Synlett* **2005**, 532–534.

[14] For selective oxidations of amino alcohols to amino ketones in DMSO, see: M. Frigerio, M. Santagostino, S. Sputore, G. Palmisano, *J. Org. Chem.* **1995**, *60*, 7272–7276.

[15] For Ugi reactions in toluene in the presence of weak Brønsted acids or Lewis acids, see: a) P. Cristau, J. P. Vors, J. Zhu, *Org. Lett.* **2001**, *3*, 4079–4082; b) A. Fayol, J. Zhu, *Angew. Chem.* **2002**, *114*, 3785–3787; *Angew. Chem. Int. Ed.* **2002**, *41*, 3633–3635; c) P. Janvier, H. Bienaymé, J. Zhu, *Angew. Chem.* **2002**, *114*, 4467–4470; *Angew. Chem. Int. Ed.* **2002**, *41*, 4291–4294; d) A. Fayol, J. Zhu, *Org. Lett.* **2005**, *7*, 239–242; e) D. Bonne, M. Dehkane, J. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 6926–6927; see also: f) V. Z. Parchinsky, O. Shuvalova, O. Ushakova, D. V. Kravchenko, M. Krasavin, *Tetrahedron Lett.* **2006**, *47*, 947–951; g) A. G. Neo, R. M. Carrillo, S. Barriga, E. Momán, S. Marcaccini, C. F. Marcos, *Synlett* **2007**, 327–329; h) M. Umkehrer, G. Ross, N. Jäger, C. Burdack, J. Kolb, H. Hu, M. Alvim-Gaston, C. Hulme, *Tetrahedron Lett.* **2007**, *48*, 2213–2216.

[16] For the acidity of IBX and IBA, see: M. J. Gallen, R. Goumont, T. Clark, F. Terrier, C. M. Williams, *Angew. Chem.* **2006**, *118*, 2995–3000; *Angew. Chem. Int. Ed.* **2006**, *45*, 2929–2934.

[17] For the oxidation of alcohols in different organic solvents, see: J. D. More, N. S. Finney, *Org. Lett.* **2002**, *4*, 3001–3003.

[18] This experiment was suggested by one of the referees.

[19] IBX is able to oxidize THF at elevated temperature (80 °C and above); see Ref. [17] and K. C. Nicolaou, P. S. Baran, R. Kranich, Y. L. Zhong, K. Sugita, N. Zou, *Angew. Chem.* **2001**, *113*, 208–212; *Angew. Chem. Int. Ed.* **2001**, *40*, 202–206.

[20] a) A. Fayol, C. Housseman, X. Sun, P. Janvier, H. Bienaymé, J. Zhu, *Synthesis* **2005**, 161–165; b) C. Housseman, J. Zhu, *Synlett*

2006, 1777 – 1779; c) A. Dömling, B. Beck, T. Fuchs, A. Yazbak, *J. Comb. Chem.* **2006**, *8*, 872 – 880.

[21] a) R. M. Moriarty, M. Sultana, *J. Am. Chem. Soc.* **1985**, *107*, 4559 – 4561; b) R. M. Moriarty, *J. Org. Chem.* **2005**, *70*, 2893 – 2903.

[22] a) P. Janvier, X. Sun, H. Bienaymé, J. Zhu, *J. Am. Chem. Soc.* **2002**, *124*, 2560 – 2567; b) P. Janvier, M. Bois-Choussy, H. Bienaymé, J. Zhu, *Angew. Chem.* **2003**, *115*, 835 – 838; *Angew. Chem. Int. Ed.* **2003**, *42*, 811 – 814; c) T. Pirali, G. C. Tron, J. Zhu, *Org. Lett.* **2006**, *8*, 4145 – 4148.

[23] Lavilla and co-workers have very recently reported an interesting reaction between isocyanide and dihydropyrine in the presence of iodine; see: C. Masdeu, E. Gómez, N. A. O. Williams, R. Lavilla, *Angew. Chem.* **2007**, *119*, 3103 – 3106; *Angew. Chem. Int. Ed.* **2007**, *46*, 3043 – 3046.

