ORGANIC LETTERS

2009
Vol. 11, No. 4
995−997

New Benzotriazole and Benzimidazole Scaffolds from Ugi−Smiles Couplings of Isocyanides

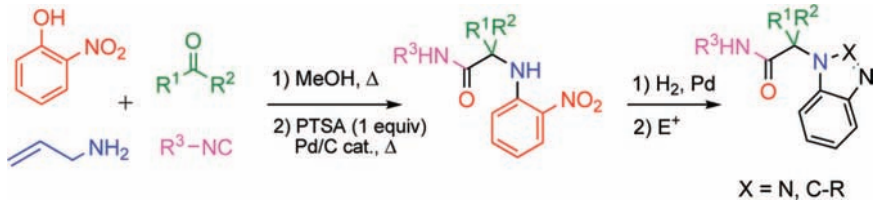
Didier Coffinier, Laurent El Kaim,* and Laurence Grimaud*

Laboratoire Chimie et procédés, Ecole Nationale Supérieure de Techniques Avancées, 32 Bd Victor, 75739 Paris Cedex 15, France

laurent.elkaim@ensta.fr, laurence.grimaud@ensta.fr

Received December 22, 2008

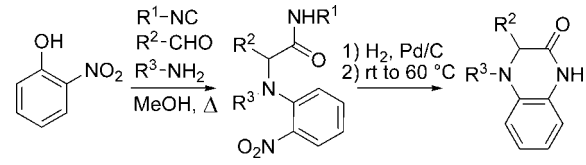
ABSTRACT



When allylamine is used as the amino input in Ugi−Smiles couplings of *o*-nitrophenols, the resulting adducts can be deallylated by a palladium-catalyzed process leading to a formal Ugi−Smiles coupling with ammonia. This new sequence, combined with hydrogenolysis of the nitro group, offers an interesting multicomponent entry to benzotriazole and benzimidazole scaffolds.

Since the pioneering work of Ugi, the use of isocyanides has been strongly associated with the multicomponent formation of peptide derivatives.[1] While carboxylic acids are the most popular acidic components, Ugi demonstrated very early that these couplings could be extended to different acidic partners. We recently disclosed the use of electron-deficient phenols as acidic partners in Ugi-type reactions (Scheme 1).[2] Starting from *o*-nitrophenol, the hydrogenolysis of the Ugi adduct affords an interesting approach to the synthesis of benzofused heterocycles as shown by the preparation of quinoxaline derivatives (Scheme 1).[3] However, the substitution of primary amines by ammonia[4] in such a sequence could afford a much wider access to *o*-phenylene-diamine-related heterocycles.

Scheme 1. Ugi−Smiles Coupling Followed by Azepine Formation



As previously reported for the Ugi reaction, the poor results obtained with ammonia (probably due to the formation of side products)[5] have led chemists to choose "convertible primary amines" such as nitrobenzylamine[6] that can be deprotected after Ugi reaction. In our case, we believed that the electron-

(1) For recent reviews, see: (a) Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1–140. (b) Zhu, J. *Eur. J. Org. Chem.* **2003**, *113*, 3–1144. (c) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53–66. (d) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51–80. (e) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321–3329. (f) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (g) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.

(2) (a) El Kaim, L.; Grimaud, L.; Oble, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 7165–7169. El Kaim, L.; Gizolme, M.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 4169–4180.

(3) Oble, J.; El Kaïm, L.; Gizzi, M.; Grimaud, L. *Heterocycles* **2007**, *73*, 503–517.

(4) Kazmaier, U.; Hebach, C. *Synlett* **2003**, 1591–1594.

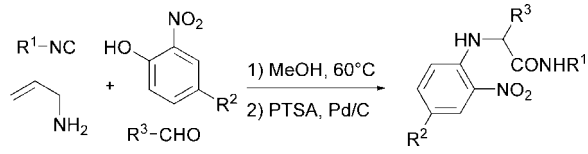
(5) Pick, R.; Bauer, M.; Kazmaier, U.; Hebach, C. *Synlett* **2005**, 757–760.

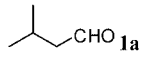
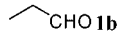
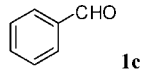
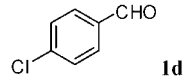
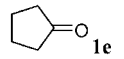
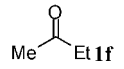
(6) Sung, K. S.; Chen, F. L.; Huang, P. C. *Synlett* **2006**, 2667–2669.

10.1021/ol8029438 CCC: $40.75
Published on Web 01/26/2009

withdrawing effect of the *N*-nitrophenyl group offered interesting opportunities for various primary amines to act as suitable ammonia equivalents. After several deceiving attempts with benzylamines, allylamine was selected owing to its well-known facile deallylation. These deprotections are usually performed under palladium catalysis, the allyl residue being trapped either by the solvent or by an additional nucleophile in the medium.[7] A Pd/C-sulfonic acid system[7b] was selected as it combines the interest of activating the amine while destructing remaining traces of isocyanide.[8] Thus, after completion of the Ugi−Smiles step, the mixture was treated with 1 equiv of *p*-toluenesulfonic acid (PTSA) followed by addition of palladium on carbon (10% Pd/C). After additional heating for 1 day, the expected secondary anilines were isolated in fair to good yields (entries 1−9, Table 1).

Table 1. Ugi−Smiles Formation of Secondary Anilines



entry	R^1	R^2	starting aldehyde	product[a] (yield%)
1	Cy	H	 **1a**	**2a** (88)
2	*t*-Bu	"	**1a**	**2b** (55)
3	Cy	Me	**1a**	**2c** (78)
4	"	"	 **1b**	**2d** (56)
5	4-ClPhCH$_2$	H	**1b**	**2e** (68)
6	*t*-Bu	"	 **1c**	**2f** (73)
7	Cy	"	 **1d**	**2g** (85)
8	4-ClPhCH$_2$	"	 **1e**	**2h** (40)[b]
9	Cy	"	 **1f**	**2i** (36)[b]

[a] Ugi−Smiles reaction (2 mmol scale, 1 M in methanol) was performed with equimolar amount of reagents and left for 1 day at 60 °C. PTSA (1 equiv) in methanol (2 mL) was then added before addition of 10% Pd/C (10 mol %). The resulting mixture was heated at 60 °C for 24 h before workup. [b] The Ugi−Smiles step required a 10 day heating for completion.

o-Phenylenediamine derivatives are important starting materials for the preparation of various benzofused heterocycles such as benzotriazoles[9]or benzimidazoles.[10] These two families have been the focus of many synthetic efforts due to their potential in medicinal chemistry.[11] To reach such scaffolds, adducts obtained after the Ugi−Smiles/deallylation sequence were quantitatively reduced to *o*-phenylenediamine through catalytic hydrogenation under flow conditions. The products were not isolated but directly converted to benzotriazoles under treatment with sodium nitrite and acetic acid (Table 2). Besides their potential biological activities,[12] these new α-benzotriazolyl amides may find interesting applications in the synthesis of pyridones.[13]

Alternatively, two different benzimidazole[14] families have been prepared from these *o*-phenylenediamines either under treatment with CS_2 or by adding aldehydes under oxidative conditions (Table 3). For the preparation of mercaptobenzimidazoles (entries 1 and 2, Table 3), several procedures are available according to the sulfur reagent. Carbon disulfide was preferred over thiocarbonyldiimidazole[15] or thiophosgene.[16] Additions with this reagent are usually performed either in hot DMF[17] or in refluxing ethanol in the presence

(7) (a) Garro-Helion, F.; Merzouk, A.; Guibé, F. *J. Org. Chem.* **1993**, *58*, 6109–6113. (b) Liu, Q.; Marchington, A. P.; Boden, N.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 511–518. (c) Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, *62*, 8932–8936. (d) Karpf, M.; Trussardi, R. *J. Org. Chem.* **2001**, *66*, 2044–2051. (e) Ohmura, N; Nakamura, A.; Hamasaki, A.; Tokunaga, M. *Eur. J. Org. Chem.* **2008**, 5042–5045.

(8) Remaining isocyanide might inhibit the palladium catalytical cycle. For such an effect in a one-pot synthesis of indole, see: El Kaim, L.; Gizzi, M.; Grimaud, L. *Org. lett.* **2008**, *10*, 3417–3419.

(9) (a) Fan; W.-Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 4, pp 101−126. (b) Gillespie, H. B.; Spano, F.; Graff, S. *J. Org. Chem.* **1960**, *25*, 942–944. (c) Plater, M. J.; Greig, I.; Helfrich, M. H.; Ralston, S. H. *J. Chem. Soc., Perkin Trans. 1* **2001**, *20*, 2553–2559. (d) Sasmal, P. K.; Sridhar, S.; Iqbal, J. *Tetrahedron Lett.* **2006**, *47*, 8661–8665.

(10) (a) Grimmett, M. R. Imidazoles and their Benzo Derivatives. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 5, pp 457−487. (b) Tumelty, D.; Cao, K.; Holmes, C. P. *Org. Lett.* **2001**, *1*, 83–86 (O_2-RCHO). (c) Hioki, H.; Matsushita, K.; Kubo, M.; Kodama, M. *J. Comb. Chem.* **2006**, *8*, 462–463 (O_2-RCHO). (d) Raju, B.; Nguyen, N.; Holland, G. W. *J. Comb. Chem.* **2002**, *4*, 320–328. (e) Bahrami, K.; Khodaei, M. M.; Naali, F. *J. Org. Chem.* **2008**, *73*, 6835–6837. (f) Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Otokeshb, S.; Baghbanzadeh, M. *Tetrahedron Lett.* **2006**, *47*, 2557–2560.

(11) For some biologically relevant benzimidazoles and benzotriazoles, see: (a) Salluja, S.; Zou, R.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1996**, *39*, 881–891. (b) Craigo, W. A.; LeSueur, B. W.; Skibo, E. B. *J. Med. Chem.* **1999**, *42*, 3324–3333. (c) Zhao, Z. S.; Arnaiz, D. O.; Griedel, B.; Sakata, S.; Dallas, J. L.; Whitlow, M.; Trinh, L.; Post, J.; Liang, A.; Morrissey, M. M.; Shaw, K. *J. Bioorg. Med. Chem. Lett.* **2000**, *10*, 963–966. (d) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930. (e) Kopanska, K.; Najda, A.; Zebrowska, J.; Chomicz, L.; Piekarczyk, J.; Myjak, P.; Bretner, M. *Bioorg. Med. Chem.* **2004**, *12*, 2617–2624. (f) He, F. Q.; Liu, X. H.; Wang, B. L.; Li, Z. M. *J. Chem. Res.* **2006**, 809–811. (g) Caliendo, G.; Greco, G.; Grieco, P.; Novellino, E.; Perissutti, E.; Santagada, V.; Barbarulo, D.; Esposito, E.; De Blasi, A. *Eur. J. Med. Chem.* **1996**, *31*, 207–213.

(12) Sparatore, F.; Rotonda, M. I.; Caliendo, G.; Novellino, E.; Silipo, C.; Vittoria, A. *Farmaco* **1988**, *43*, 29–48.

(13) For a one-step pyridone formation from α,*β*-unsaturated ketones and α-benzotriazolylamides, see: Katritzky, A. R.; Belyakov, S. A.; Sorochinsky, A. E.; Henderson, S. A.; Chen, J. *J. Org. Chem.* **1997**, *62*, 6210–6214.

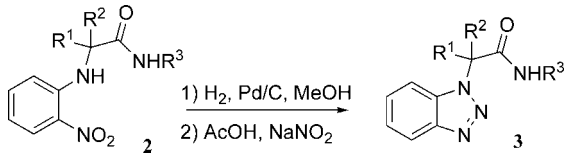
(14) Such substituted benzimidazoles can also be produced by the UDC sequence described by Tempes, Hulme, and co-workers (Tempest, P.; Ma, V.; Thomas, S.; Hua, Z.; Kelly, M. G.; Hulme, C. *Tetrahedron Lett.* **2001**, *42*, 4959–4962.). Formally, similar products could also be formed by a U-3CR of phenylenediamine and condensation or by using *o*-nitroaniline and subsequent reductive cyclization.

(15) Dannhardt, G.; Kohl, B. *Arch. Pharm.* **2000**, *333*, 123–129.

(16) Charles, E. S.; Rao, K. V. B.; Sharma, S. *Pharmazie* **1982**, *37*, 413–415.

(17) Ellsworth, E. L.; Domagala, J.; Vara Prasad, J. V. N.; Hagen, S.; Ferguson, D.; Holler, T.; Hupe, D.; Graham, N.; Nouhan, C.; Tummino, P. J.; Zeikus, G.; Lunney, E. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2019–2024.

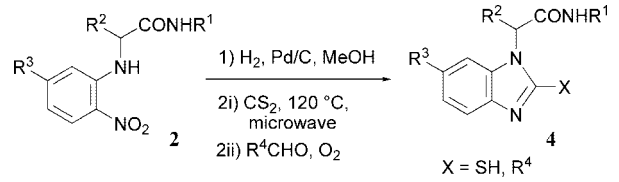
Table 2. Benzotriazoles from Ugi−Smiles Intermediates



entry	starting aniline	R^1	R^2	R^3	product[a] (yield, %)
1	**2a**	H	CH_2iPr	Cy	**3a** (64)
2	**2b**	H	CH_2iPr	tBu	**3b** (91)
3	**2e**	H	Et	4-ClPhCH_2	**3c** (89)
4	**2g**	H	4-ClPh	Cy	**3d** (95)
5	**2i**	Et	Me	Cy	**3e** (74)

[a] Typical procedure: 1 mmol of aniline was treated in MeOH with H_2 under flow conditions on a Pd/C (10%) cartridge (rt, H_2 1 atm, 1 mL/min). Evaporation of the solvent followed by stepwise addition of acetic acid and sodium nitrite afforded product after hydrolysis and extraction of the mixture.

Table 3. Benzimidazoles from Ugi−Smiles Intermediates



entry	starting aniline	R^1	R^2	R^3	X	product (yield, %)
1	**2a**	Cy	CH_2iPr	H	SH	**4a** (84)[a]
2	**2f**	tBu	Ph	H	SH	**4b** (40)[a]
3	**2a**	Cy	CH_2iPr	H	4-NO_2Ph	**4c** (72)[b]
4	**2c**	Cy	4-ClPh	Me	4-ClPh	**4d** (56)[b]
5	**2c**	Cy	CH_2iPr	Me	CH_2-i-Pr	**4e** (52)[c]

[a] Typical procedure: Deallylated Ugi−Smiles adduct (1 mmol) was treated in MeOH with H_2 under flow conditions on a Pd/C (10%) cartridge (rt, 1 atm H_2, 1 mL/min). After evaporation of the solvent, the product was heated under microwave conditions (120 °C, 15 min) with CS_2 (3 equiv) in ethanol (0.3 M). [b] Deallylated Ugi−Smiles adduct was reduced as in footnote a followed by heating overnight at 100 °C with an aromatic aldehyde and catalytic $Pd(OAc)_2$ in DMF under air. [c] Same procedure as footnote b except DMF was replaced by pyridine (rt for 3 days).

of sodium or potassium hydroxide.[18] We found that the addition−cyclization step could be much more easily achieved by simply heating the phenylenediamine under microwave conditions with an excess of CS_2 in ethanol at 120 °C for 15 min. In the case of 2-arylbenzimidazoles (entries 3 and 4, Table 3), the best conversion was obtained with a palladium-catalyzed oxidation in DMF under air. Indeed, **2a** was converted to **4c** in a 72% isolated yield, whereas a lower 50% yield was obtained under heating in nitrotoluene at 160 °C. With aliphatic aldehydes, similar conversion was better achieved at room temperature with pyridine as solvent (entry 5, Table 3). These preparations of benzimidazoles (**4c**, **4d**, **4e**) with three steps involving palladium catalysis illustrate the power of the latter in heterocyclic synthesis.

This study brings forward a new preparation of benzofused heterocycles with four points of diversity, the allyl moiety initially lost being replaced by a new component during the last step of the sequence. In the context of lead discovery, it further demonstrates the utility of multicomponent reactions for the search of efficient synthetic routes toward privileged medicinal scaffolds. We are currently extending these procedures to the use of hydroxypyridines and hydroxypyrimidines in place of *o*-nitrophenol, with the expected formation of scaffolds of higher biological interest.

Acknowledgment. We thank Dr. J. Sancon (GlaxoSmithKline) for fruitful discussions. D.C. thanks the Centre National de la Recherche Scientifique as well as GlaxoSmithKline for a Ph.D. fellowship.

Supporting Information Available: Detailed experimental procedures and spectral data for deallylated Ugi−Smiles adducts, benzotriazoles, and benzimidazoles. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8029438

(18) Devivar, R. V.; Kawashima, E.; Revankar, G. R.; Breitenbach, J. M.; Kreske, E. D.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1994**, *37*, 2942–2949.