ORGANIC LETTERS

2010
Vol. 12, No. 2
324−327

DBU Catalysis of *N,N′*-Carbonyldiimidazole-Mediated Amidations§

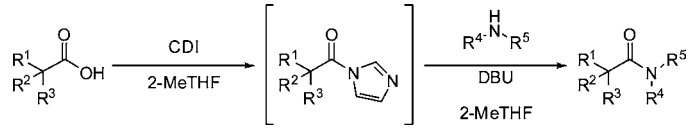
Claude Larrivée-Aboussafy, Brian P. Jones, Kristin E. Price, Mark A. Hardink, Robert W. McLaughlin, Brett M. Lillie, Joel M. Hawkins, and Rajappa Vaidyanathan*

Development Science and Technology, Pfizer Inc., Eastern Point Road, Groton, Connecticut 06340

rajappa.vaidyanathan@pfizer.com

Received November 18, 2009

ABSTRACT

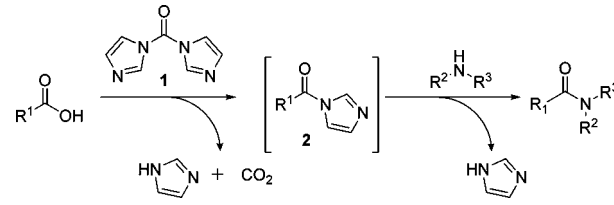


1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) has been found to catalyze the amidation of acyl imidazoles. The rate acceleration is especially evident with traditionally unreactive, electron-deficient anilines. DBU is readily available and offers safety and cost advantages over more commonly employed catalysts such as 1-hydroxybenzotriazole.

N,N′-Carbonyldiimidazole (CDI, **1**) is commonly used for the synthesis of amides from carboxylic acids and amines.[1] CDI-mediated amidations are typically carried out as one-pot procedures, wherein the acid and CDI are stirred until the intermediate acyl imidazole (**2**) is formed. The amine is then added to activated intermediate **2** (Scheme 1). This coupling strategy generates innocuous byproducts—carbon dioxide and imidazole—thereby rendering this an attractive protocol for the synthesis of amides, especially in the pharmaceutical industry.[2−4]

The acyl imidazole intermediates are generally more stable and easier to handle than the corresponding acid chlorides, but are somewhat less reactive. This lower reactivity can cause couplings with hindered acids, hindered amines, or weakly nucleophilic amines to be impractically slow. As a result, many additives have been developed to accelerate these reactions.

Scheme 1. Conversion of Carboxylic Acids to Amides with CDI



One of the most commonly used additives is 1-hydroxybenzotriazole (HOBt, **3**), which has been shown to accelerate couplings that hardly proceed without additives.[5] HOBt provides consistent rate enhancements but has drawbacks

§ Dedicated to the memory of Dr. Bruce A. Pearlman—an exceptional scientist, colleague, and above all, a fantastic human being.

(1) (a) Anderson, G. W.; Paul, R. J. *J. Am. Chem. Soc.* **1958**, *80*, 4423. (b) Paul, R.; Anderson, G. W. *J. Am. Chem. Soc.* **1960**, *82*, 4596–4600. (c) Armstrong, A. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, UK, 1995; Vol. 2, p 1006 and references cited therein.

(2) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.

(3) Dale, D. J.; Dunn, P. J.; Golighty, C.; Hughes, M. L.; Levett, P. C.; Pearce, A. K.; Searle, P. M.; Ward, G.; Wood, A. S. *Org. Process Res. Dev.* **2000**, *4*, 17–22.

(4) Vaidyanathan, R.; Kalthod, V. G.; Ngo, D. P.; Manley, J. M.; Lapekas, S. P. *J. Org. Chem.* **2004**, *69*, 2565–2568.

(5) Dunn, P. J.; Hughes, M. L.; Searle, P. M.; Wood, A. S. *Org. Process Res. Dev.* **2003**, *7*, 244–253.

10.1021/ol9026599
Published on Web 12/16/2009

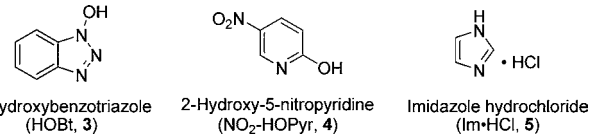


Figure 1. Representative catalysts for CDI-mediated amidations.

including a high cost per mole, highly energetic decomposition, potential for explosion, and transportation restrictions.[6] More recently, other catalysts with improved safety profiles have been introduced (Figure 1) including 2-hydroxy-5-nitropyridine (NO_2−HOPyr, **4**),[7] and imidazole hydrochloride (Im•HCl, **5**).[8] Unlike HOBt, these catalysts offer the advantages of low cost, ease of handling, and chemical stability.

We recently discovered that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, **6**) provided unique rate enhancement in the direct amidation of alkyl cyanoacetates.[9] Traditionally, DBU has been considered a non-nucleophilic base, but it has been shown to function as a better nucleophilic catalyst than the more conventionally employed 1,4-diazabicyclo[2.2.2]octane (DABCO) or 4-dimethylaminopyridine (DMAP) in Baylis−Hillman reactions[10] and in the conversion of carboxylic acids to methyl esters with dimethyl carbonate.[11] Amidines are also known to catalyze the acylation of *sec*-phenethyl alcohol with acetic anhydride.[12] Given these recent developments and our own experience, we sought to examine the effect of DBU on traditionally slow CDI-mediated couplings and directly compare it to known catalysts.

For all of the catalyst comparisons, 2-methyl-2-phenylpropanoic acid (**7**) was used as the carboxylic acid component. The acyl imidazole formed from this substrate (**8**) is hindered and, therefore, a challenging test case.[6] Furthermore, the *gem*-dimethyl groups preclude any side reactions via deprotonation at the α-carbon. Acyl imidazole **8** was treated with both aliphatic amines and anilines. It has been shown that the carbon dioxide evolved during the formation of the acyl imidazole catalyzes the subsequent amidation step.[4] To decouple the effect of carbon dioxide from the catalytic activity of the additives, the reaction mixtures were concentrated in vacuo after the acyl imidazole was formed (to remove CO_2), and fresh solvent was added prior to reaction with the amines and additives (vide infra).

For each amine substrate, the amidation was carried out in the presence and absence of additives, and the reaction rates were compared. The reactions in the absence of additives were compared against those with HOBt (**3**), NO_2−HOPyr (**4**), Im•HCl (**5**), DBU (**6**), as well as *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt) and *N*,*N*-dimethylaminopyridine (DMAP) (Figure 2). The reactions were carried out at 60 or 80 °C in 2-methyltetrahydrofuran (2-MeTHF) with 0.5 equiv of the additive (see the Supporting Information for details).

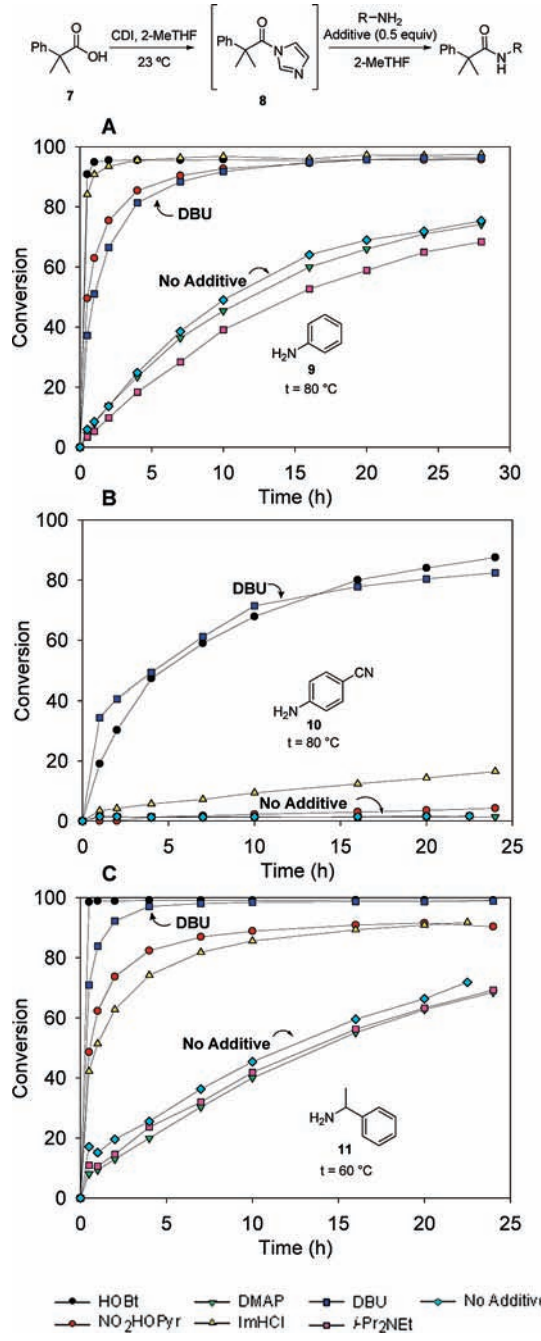


Figure 2. Comparison of various additives in the coupling of acyl imidazole **8** with anilines and aliphatic amines.

In the case of aniline (**9**, Figure 2A), DBU provided approximately the same rate enhancement as NO_2−HOPyr, but the reaction was marginally slower than those with HOBt

(6) (a) Bright, R.; Dale, D. J.; Dunn, P. J.; Hussain, F.; Kang, Y.; Mason, C.; Mitchell, J. C.; Snowden, M. J. *Org. Process Res. Dev.* **2004**, *8*, 1054–1058. (b) Wehrstedt, K. D.; Wandrey, P. A.; Heitkamp, D. *J. Hazard. Mater.* **2005**, *A126*, 1–7.

(7) Dunn, P. J.; Hoffman, W.; Kang, Y.; Mitchell, J. C.; Snowden, M. J. *Org. Process Res. Dev.* **2005**, *9*, 956–961.

(8) Woodman, E. K.; Chaffey, J. G. K.; Hopes, P. A.; Hose, D. R. J.; Gilday, J. P. *Org. Process Res. Dev.* **2009**, *13*, 106–113.

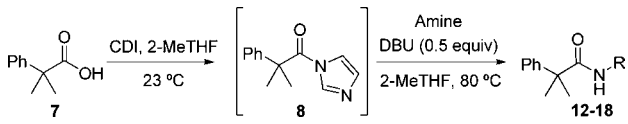
(9) Price, K. E.; Larrivée-Aboussafy, C.; Lillie, B. M.; McLaughlin, R. W.; Mustakis, J.; Hettenbach, K. W.; Hawkins, J. M.; Vaidyanathan, R. *Org. Lett.* **2009**, *11*, 2003–2006.

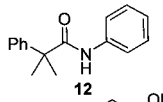
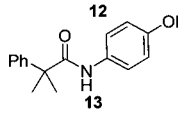
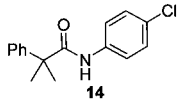
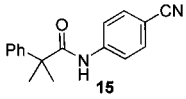
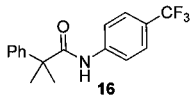
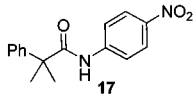
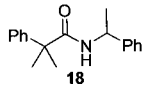
(10) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311–2312.

(11) Shieh, W. C.; Dell, S.; Repic, O. *J. Org. Chem.* **2002**, *67*, 2188–2191.

(12) Birman, V. B.; Li, X.; Han, Z. *Org. Lett.* **2007**, *9*, 37–40.

Table 1. Reaction of Amines with Acyl Imidazole **8** in the Presence and Absence of DBU



entry	product	$t_{1/2}$ (h)[a] with DBU[b]	without DBU	yield (%)[c]
1	 **12**	1	10	73
2	 **13**	0.7	4.3	80
3	 **14**	5.3	> 24[d]	73
4	 **15**	4	>24[e]	86[f]
5	 **16**	17.4	>24[g]	71[f]
6	 **17**	<0.5[h]	>24[i]	82[f]
7[j]	 **18**	< 0.5[k]	12	93

[a] Time taken for the reaction to reach 50% conversion. [b] 0.5 equiv of DBU was added. [c] Isolated yield. [d] 42% conversion in 24 h. [e] <2% conversion in 22.5 h. [f] Isolation experiments used 1.0 equiv of DBU to maximize conversion within a reasonable time period. [g] ~2% conversion in 24 h. [h] 67% conversion in 0.5 h. [i] <1% conversion in 24 h. [j] Reaction run at 60 °C. [k] 71% conversion at 0.5 h.

and Im·HCl.[13] We then examined the amidation using 4-aminobenzonitrile (**10**)—an electron-deficient aniline, and hence an exigent test case (Figure 2B). For this substrate, it was found that *DBU was unique among the practical additives, providing substantial rate enhancement comparable to that of HOBt.* In the case of *sec*-phenethylamine (**11**)—an aliphatic amine—the reaction with DBU was comparable to that with HOBt, and slightly faster than those with NO_2—HOPyr and Im·HCl (Figure 2C). Interestingly, in all of these cases, the background reactions in the absence of additives, as well as the reactions with *i*-Pr_2NEt and DMAP, were substantially slower.

In an effort to explore the generality and scalability of this method, several amines were coupled with **8** in the presence of DBU (Table 1).[14] For all of these reactions, 2-methyltetrahydrofuran[15] was used as the solvent to simplify solvent removal, workup, and product isolation. In all cases, DBU provided appreciable rate enhancement, excellent conversions, and respectable yields. The catalytic effect of

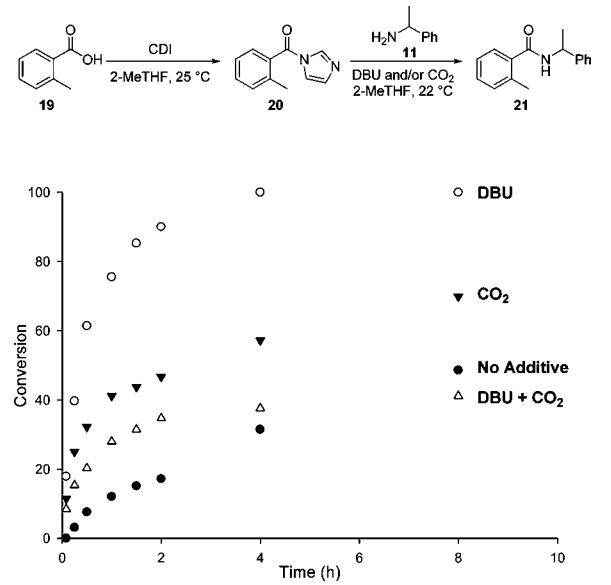


Figure 3. Comparison of DBU and CO_2 addition to the reaction of *o*-toluic acid imidazole with *sec*-phenethylamine (**11**).

DBU was especially pronounced in the case of electron-deficient anilines (entries 4−6, Table 1) wherein the uncatalyzed reactions were <5% complete even after 24 h.

We had previously observed that the CO_2 evolved in the acyl imidazole formation step catalyzed the subsequent amidation step.[4] To better understand the effects of CO_2 and DBU, acyl imidazole **20** derived from *o*-toluic acid (**19**) was treated with *sec*-phenethylamine (**11**).[16] In one case, the reaction was carried out with 0.5 equiv of DBU under a nitrogen blanket. The second experiment was conducted with 0.5 equiv of DBU under a CO_2 atmosphere. Two more experiments were carried out in the absence of DBU under N_2 and CO_2, respectively. It was found that DBU provided approximately 6-fold acceleration over CO_2, and 20-fold acceleration over the reaction with no additive.[17] Interestingly, the reaction with *both* DBU and CO_2 was substantially

(13) For the sake of consistency, 0.5 equiv of the appropriate additive was used for the rate comparison experiments. However, Woodman et al. used 1.5 equiv of Im·HCl in their studies (ref 8).

(14) Most of the preparative examples in Table 1 utilized 0.5 equiv of DBU. In some cases, 1.0 equiv of DBU was added in order to achieve reaction completion within 24 h as indicated by footnote f in Table 1.

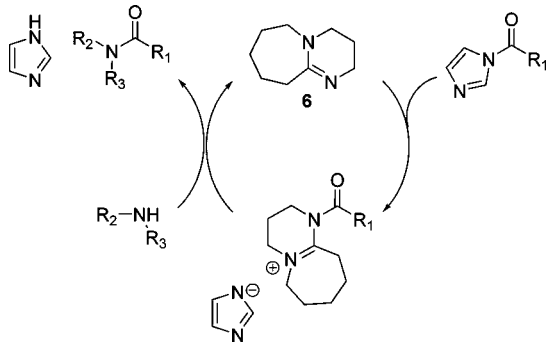
(15) Ripin, D. H. B.; Vetelino, M. *Synlett* **2003**, 2353.

(16) On the basis of prior experience, we knew that the amidation of **20** with **11** would proceed at room temperature. Under these conditions, it was easier to retain the CO_2 in the reaction vessel without recourse to pressure-rated equipment. Therefore, this system was chosen as the test case.

(17) In all cases, the reaction mixtures were concentrated in vacuo after formation of acyl imidazole **20** in order to remove the CO_2 evolved. The residue was then dissolved in 2-MeTHF for the coupling reaction. For reactions with CO_2, the gas was bubbled into a solution of **20** in 2-MeTHF for 1−2 min and the reactions were sealed under a CO_2 atmosphere. The reactions without carbon dioxide were run under a nitrogen atmosphere.

(18) DBU and other amidines are known to form adducts with CO_2. See: (a) Desset, S. L.; Cole-Hamilton, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 1472–1474. (b) Phan, L.; Chiu, D.; Heldebrant, D. J.; Huttenhower, H.; John, E.; Li, X.; Pollet, P.; Wang, R.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. *Ind. Eng. Chem. Res.* **2008**, *47*, 539–545. (c) Heldebrant, D. J.; Jessop, P. G.; Thomas, C. A.; Eckert, C. A.; Liotta, C. L. *J. Org. Chem.* **2005**, *70*, 5335–5338. (d) Pérez, E. R.; da Silva, M. O.; Costa, V. C.; Rodrigues-Filho, U. P.; Franco, D. W. *Tetrahedron Lett.* **2002**, *43*, 4091–4093.

Scheme 2. Proposed Catalytic Cycle



slower than the reactions with either one of them, and stalled at ca. 40% conversion (Figure 3). In other words, the combined presence of CO_2 and DBU negated their individual benefecial effects.[18] Thus, in order to reap the benefits of DBU, it is important to ensure that the CO_2 evolved in the acyl imidazole formation step is removed prior to the addition of DBU and the amine in the amidation step.[19]

(19) The CO_2 evolved in the acyl imidazole formation step can be easily removed from the system by a simple N_2 sweep during or after the acyl imidazole formation, or by heating the reaction mixture. In fact, it is often more difficult to retain the CO_2 than to remove it.

(20) It is unlikely that the rate enhancement for electron-deficient anilines is due to partial deprotonation of the aniline by DBU, given their relative pK_a values in organic solvents. The pK_a values in DMSO for substituted anilines are as follows: *p*-NO_2, 20.9; *p*-CF_3, 27.0; *p*-CN, 25.3; see: (a) Bordwell, F. G.; Algrim, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 2964–2968. (b) Bordwell, F. G.; Algrim, D.; Vanier, N. R. *J. Org. Chem.* **1977**, *42*, 1817–1819. Estimated pK_a for DBU-H^+ in DMSO is 13.9; see: Salvatore, D. L.; Khoram, A.; Bromfield, D. C.; Cohn, P.; Jairaj, V.; Silvestri, M. A. *J. Org. Chem. Soc.* **2005**, *70*, 7443–7446. Useful pK_a data are also provided in the following websites: http://www.chem.wisc.edu/areas/reich/pkatable/ and http://evans.harvard.edu/pdf/evans_pKa_table.pdf .

(21) Rebek, J.; Brown, D.; Zimmerman, S. *J. Am. Chem. Soc.* **1975**, *97*, 454–455.

(22) See: Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglich, W.; Zipse, H. *Chem.—Eur. J.* **2005**, *11*, 4751–4757, and references cited therein.

(23) Baidya, M.; Mayr, H. *Chem. Commun.* **2008**, 1792–1794.

(24) Im·HCl is an excellent catalyst for the reaction of acyl imidazoles with anilines. However, Im·HCl would preferentially protonate aliphatic amines (over acyl imidazoles), thereby decreasing their reactivity. Further experimental data are provided in the Supporting Information.

On the basis of our prior experience[9] and literature precedent,[10,11] we propose that DBU acts as a nucleophilic catalyst in the amidation of acyl imidazoles (Scheme 2).[20] Mechanistically, this pathway is analogous to that proposed for reactions catalyzed by either HOBt[21] or DMAP.[22] The pronounced superiority of DBU relative to DMAP can be ascribed to its higher carbon basicity.[23] This pathway differs from that proposed for Im·HCl, which activates the acyl imidazole via acid catalysis (protonation of the leaving group). This mechanistic difference is especially evident in the reaction of **8** with *sec*-phenethylamine (**11**). In a comparison study, we observed that while the reaction rate increased with increasing DBU concentration, it decreased upon increasing the Im·HCl concentration.[24]

In conclusion, DBU is a safe, effective catalyst for the amidation of acyl imidazoles and can serve as a complement to existing technologies. The rate enhancement provided by DBU is comparable to that of other known catalysts (Im·HCl, NO_2—HOPyr, HOBt) for anilines and aliphatic amines. *In the case of electron deficient anilines, DBU is superior to Im·HCl and NO_2—HOPyr*. While the relatively high basicity of DBU could prove deleterious for certain classes of substrates (e.g., for substrates with base-epimerizable stereocenters), DBU is a useful addition to existing amidation catalysts and should be screened as an additive in reactions that can benefit from nucleophilic catalysis. Further expansion of the scope of DBU catalysis is ongoing in our laboratories, and the results will be communicated in due course.

Acknowledgment. The authors thank the following Pfizer colleagues: Nathan Ide and Stéphane Caron for helpful suggestions and discussions, and Barbara Sitter and David Damon for their assistance with automation experiments.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9026599