Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6943–6945

TETRAHEDRON LETTERS

Accelerated benzylation reaction utilizing dibenzyl carbonate as an alkylating reagent

Wen-Chung Shieh,* Mario Lozanov and Oljan Repič

Chemical and Analytical Development, Novartis Institute for Biomedical Research, East Hanover, NJ 07936, USA

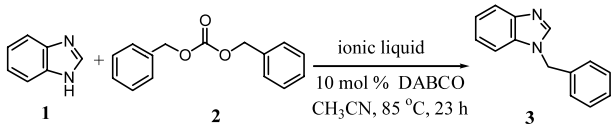
Received 18 June 2003; revised 30 June 2003; accepted 2 July 2003

Abstract—Ionic liquids can effectively accelerate slow *N*-benzylation reactions utilizing dibenzyl carbonate as an alkylating reagent. By applying microwave irradiation in the presence of the same ionic liquid, additional rate enhancement was accomplished.

Recently our laboratory reported a novel DABCO-catalyzed benzylation methodology for a variety of N-, O-, and S-containing compounds utilizing dibenzyl carbonate (DBC) as a replacement for hazardous reagents such as carcinogenic benzyl chloride and lachrymose benzyl bromide.[1] We demonstrated that DABCO, acting as a nucleophilic catalyst, could effectively promote DBC to behave as an alkylating reagent. From our observation, this benzylation protocol seemed to work efficiently (within hours) with several soft nucleophiles. On the other hand, for some nitrogen-containing nucleophiles, such as amide, indole, and aniline derivatives, the benzylation was extremely slow (1–4 days) even at an elevated temperature (135°C). Hence, we had a need to develop a more efficient and expeditious methodology for broader and more practical applications. Herein, we report that by employing an ionic liquid as either a solvent or an additive, significant rate enhancement of the benzylation reaction can be accomplished.

Ionic liquids have been shown to promote a variety of organic transformations effectively. In most of these reported applications, an ionic liquid was employed as a reaction medium in a solvent-free fashion so that volatile organic solvents can be eliminated.[2,3] It has also been reported that ionic liquids can be utilized as catalysts or as additives to enhance the rates of reactions in organic solvents.[4,5] Based on these precedents,

Table 1. Effect of ionic liquids as additives or solvents on the benzylation rate of benzimidazole[a]



1 2 3

Entry	Ionic liquid[b]	% **3**[c]
1	None[d]	64
2	$[emim]^+Cl^-$	77
3	$[emim]^+PF_6^-$	84
4	$[hmim]^+Cl^-$	77
5	$Bu_4N^+Cl^-$	92
6	$Bu_4N^+Br^-$	90
7	$Bu_4N^+I^-$	90
8	$Bu_4N^+OTf^-$	85
9	$Bu_4N^+BF_4^-$	74
10	$Bu_4N^+PF_6^-$	82
11	$Oct_4N^+Br^-$	95
12	$Octadecyl_4N^+Br^-$	88
13	$[hmim]^+Cl^-$ as solvent[e]	90

[a] All reactions, except entries 1 and 13, were conducted with **1** (2 mmol), DBC (3 mmol), DABCO (0.2 mmol, 10 mol%), and an ionic liquid (2 mmol) in 4 mL of CH_3CN at 85°C for 23 h.
[b] [emim] = 1-ethyl-3-methylimidazolium; [hmim] = 1-*n*-hexyl-3-methylimidazolium.
[c] The yields were determined by HPLC analysis of the reaction mixture at the end of the reaction time indicated.
[d] Same as procedure in footnote a, except no ionic liquid was present.
[e] This reaction was conducted with **1** (2 mmol), DBC (3 mmol), DABCO (0.2 mmol, 10 mol%) in $[hmim]^+ Cl^-$ (4 mL) at 85°C for 11 h.

Keywords: nucleophilic catalyst; DABCO; *N*-benzylation; dibenzyl carbonate; ionic liquid; microwave-assisted reactions.
* Corresponding author. E-mail: wen.shieh@pharma.novartis.com

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01711-8

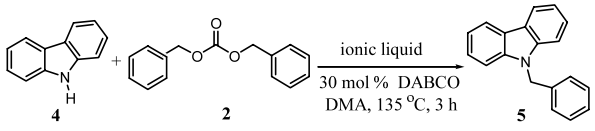
we decided to investigate if the rate of the DABCO-catalyzed benzylation reaction can be enhanced with an ionic liquid. We were particularly interested in examining the advantages of employing stoichiometric amounts of ionic liquid for the benzylation, since most of the imidazolium or pyridinium type ionic liquids are expensive when used as solvents. This study was first conducted by treating benzimidazole **1** with DBC in the presence of 1 equiv. of a variety of ionic liquids at 85°C for 23 h. As shown in Table 1, both imidazolium- and ammonium-type ionic liquids did enhance the rate of reactions moderately. Employing $[hmim]^+Cl^-$ as the solvent, the rate was found to be slightly (however not significantly) faster than when $[hmim]^+Cl^-$ was used as an additive (entries 4 and 13).

Acceleration of the benzylation reaction for carbazole **4** in *N*,*N*-dimethylacetamide (DMA) involving various ionic liquids as an additive at a higher temperature (135°C) was then investigated. Excellent conversion (93%) in 3 h was observed when 1 equiv. of tetrabutylammonium chloride (TBAC) (Table 2, entry 9) was used. In comparison, the imidazolium-series of ionic liquids that we screened were found to be less effective. Ionic liquids that contain a chloride anion consistently out-performed the ones containing different anions (entries 7–9).

Since tetrabutylammonium chloride (TBAC) not only performed well in both cases but also was readily available, we decided to probe the potential of utilizing TBAC as an additive to enhance the rates of several slow benzylation reactions. The results of this study are summarized in Table 3. In a typical experiment, a substrate (2 mmol), DABCO (10–30 mol%), DBC (3 mmol), TBAC (2 mmol) in DMA (4 mL) were heated to 135°C and monitored by HPLC until a trace or no starting material was detected. As promoted by TBAC, the benzylation rates for both 5-bromoindole and the unsubstituted indole were significantly improved as shown by impressive reductions in reaction times to 0.5 (entry 1) and 2 h (entry 2), respectively. In the absence of TBAC, the same reactions took 24 and 45 h under the same conditions of solvent, temperature, concentration, and DABCO loading. A dramatic rate enhancement was observed for the benzylation of a succinimide. In this example, the benzylation time of phthalimide was reduced from 96 to 1 h, which corresponds to a rate increase of more than 96-fold (entry 4).

Microwave irradiation has been employed for the promotion of a variety of organic transformations leading to faster and cleaner reactions when compared to con-

Table 2. Effect of ionic liquids as an additive on the benzylation rate of carbazole[a]



Entry	Ionic liquid[b]	% **5**[c]
1	None[d]	59
2	$[bmim]^+OTf^-$	28
3	$[bmim]^+BF_4^-$	34
4	$[bmim]^+PF_6^-$	28
5	$[bmim]^+Cl^-$	65
6	$[emim]^+BF_4^-$	28
7	$[emim]^+Cl^-$	66
8	$[hmim]^+Cl^-$	79
9	$Bu_4N^+Cl^-$	93

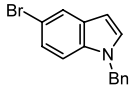
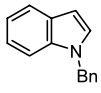
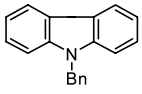
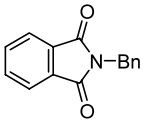
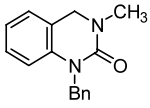
[a] All reactions, except entry 1, were conducted with **4** (2 mmol), DBC (3 mmol), DABCO (0.6 mmol, 30 mol%), and an ionic liquid (2 mmol) in 4 mL of DMA at 135°C for 3 h.

[b] [bmim] = 1-*n*-butyl-3-methylimidazolium [emim] = 1-ethyl-3-methylimidazolium; [hmim] = 1-*n*-hexyl-3-methylimidazolium.

[c] The yields were determined by HPLC analysis of the reaction mixture at the end of the reaction time indicated.

[d] Same as procedure in footnote a, except no ionic liquid was present.

Table 3. Rate enhancement with $Bu_4N^+Cl^-$ for slow benzylation reactions utilizing DBC

Entry	Product[a]	Thermal[b] time, yield[c]	Ionic Liquid[d] time, yield[c]	Microwave[e] time, yield[c]
1	 **6**[f]	24 h, 79%[1]	0.5 h, 83%	6 min, 76%
2	 **7**[g]	45 h, 82%[1]	2 h, 80 %	12 min, 70%
3	 **8**[g]	72 h, 80%[1]	3 h, 89%	18 min, 82%
4	 **9**[f]	96 h, 72%[1]	1 h, 87%	6 min, 84%
5	 **10**[g]	45h, 40%[h]	2 h, 71%	12 min, 41%[i]

[a] The identity of the benzylated products was confirmed by ^1H and ^{13}C NMR and MS.

[b] General procedure using conventional thermal heating: a reaction flask was charged with substrate (2 mmol), DABCO (10–30 mol%), DMA (4 mL), and DBC (3 mmol). The mixture was heated to 135°C, and the reaction was monitored by HPLC until trace or no starting substrate was detected (reaction time).

[c] Isolated yield based on starting substrate.

[d] Same as procedure b, except 1 equiv. of $Bu_4N^+Cl^-$ was charged to the reaction mixture.

[e] General procedure using microwave heating: A solution of substrate (20 mmol), DBC (60 mmol), DABCO (10–30 mol%), $Bu_4N^+Cl^-$ (20 mmol) in CH_3CN (80 mL) was passed through a Milestone ETHOS-CFR continuous-flow reactor preheated to 160°C at 20 bar. The reaction products were analyzed by HPLC after each pass (6 min).

[f] 10 mol% DABCO used.

[g] 30 mol% DABCO used.

[h] 31% of the starting material was recovered.

[i] 21% of the starting material was recovered.

ventional heating.[6] A few laboratories have reported that improvement in yields or reaction times could be achieved for alkylation reactions by combining microwave irradiation with tetraalkylammonium halide either in the absence[7,8] or presence[9–11] of solvents. Since use of both ionic liquid and microwave for organic transformations is still not a widely applied strategy, we decided to probe whether there is any advantage for this approach. By circulating the solution containing a substrate (20 mmol), DBC (60 mmol), DABCO (10–30 mmol), $Bu_4N^+Cl^-$ (20 mmol) in CH_3CN (0.25 M) through a continuous-flow microwave reactor set at 160°C, we observed further rate enhancement for all but one example that we studied (Table 3, entries 1–4). Synthesizing **10** under microwave conditions was fast, however, it led to several by-products as indicated by HPLC, which explained the lower isolated yield. Reproducibility was confirmed for the preparation of **6** at 5 and 25 g scales, which afforded consistent yield of 76 and 74%, respectively.

We have demonstrated that by employing stoichiometric amounts (1 equiv.) of ionic liquids, slow *N*-benzylation reactions that utilize dibenzyl carbonate as the alkylating reagent can be effectively accelerated. The recently developed imidazolium-type ionic liquids have no advantage over the ammonium-type ones such as TBAC, which effectively reduced the benzylation times from several days to hours. A mechanistic study to elucidate the role of TBAC is on going in our lab. By applying microwave irradiation in the presence of the same ionic liquid, further rate enhancements were accomplished from hours to minutes. Preliminary experimental data imply that it is the temperature (thermal heat generated by the microwave), instead of a special microwave effect, that contributes to the rate enhancement of the benzylation reaction. More kinetic studies are underway to verify this account. The new methodology has the advantages of rapid reaction times, ease of operation, use of readily available ionic liquids, and avoiding toxic benzylating reagents. This could make this newly developed chemistry of general interest to organic chemists.

Acknowledgements

We thank Dr. Thomas Blacklock, Dr. Ernst Kuesters, Dr. Gerhard Penn, Dr. Daniel Monti, and Dr. Ching-Pong Mak for their encouragement in pursuing this study.

References

1. Shieh, W.; Lozanov, M.; Loo, M.; Repic, O.; Blacklock, T. *Tetrahedron Lett*. **2003**, *44*, 4563.
2. For recent reviews, see: (a) Welton, T. *Chem. Rev*. **1999**, *99*, 2071; (b) Earle, M. J.; Seddon, K. R. *Pure Appl. Chem*. **2000**, *72*, 1391; (c) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed*. **2000**, *39*, 3772; (d) Zhao, H.; Malhotra, S. *Aldrichimica Acta* **2002**, *35*, 75.
3. Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett*. **2002**, *4*, 3031.
4. Peng, J.; Deng, Y. *Tetrahedron Lett*. **2001**, *42*, 5917.
5. Peng, J.; Deng, Y. *Tetrahedron Lett*. **2001**, *42*, 403.
6. For recent reviews on microwave-assisted organic synthesis, see: (a) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem*. **1995**, *48*, 1665; (b) Caddick, S. *Tetrahedron* **1995**, *51*, 10403; (c) Kingston, H. M.; Haswell, S. J. *Microwave-Enhanced Chemistry. Fundamentals, Sample Preparation, and Applications*; American Chemical Society: Washington, DC, 1997, Chapter 8; (d) Bose, A. K.; Banik, B. K.; Lavlinskaia, N.; Jayaraman, M.; Manhas, M. S. *Chemtech*. **1997**, *27*, 18; (e) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213; (f) Varma, R. S. *Green Chem*. **1999**, 43; (g) Krstenansky, J. L.; Cotterill, I. *Curr. Opin. Drug Discovery Dev*. **2000**, *3*, 454; (h) Perreux, L. Loupy, A. *Tetrahedron* **2001**, *57*, 9199; (h) Lidström, P; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
7. Villa, C.; Genta, M. T.; Bargagna, A.; Mariani, E.; Loupy, A. *Green Chem*. **2001**, *3*, 196.
8. Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J.; Petit, A. *Tetrahedron* **1999**, *55*, 10851.
9. Shieh, W.-C.; Dell, S.; Repic, O. *Org. Lett*. **2001**, *3*, 4279.
10. Shieh, W.; Dell, S.; Repic, O. *Tetrahedron Lett*. **2002**, *43*, 5607.
11. Leadbeater, N. E.; Marco, M. *Org. Lett*. **2002**, *4*, 2973.