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Tetrahedron Letters 44 (2003) 4563–4565

TETRAHEDRON LETTERS

DABCO- and DBU-accelerated green chemistry for *N*-, *O*-, and *S*-benzylation with dibenzyl carbonate

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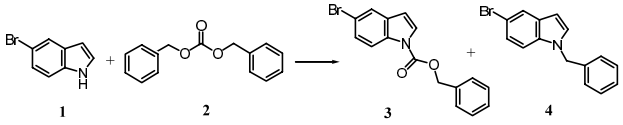
Received 27 March 2003; revised 16 April 2003; accepted 16 April 2003

Abstract—An environmentally friendly process for the benzylation of nitrogen, oxygen, or sulfur atoms with dibenzyl carbonate has been developed. Catalytic amounts of DABCO or DBU can accelerate this 'green' alkylation. © 2003 Elsevier Science Ltd. All rights reserved.

Benzylation of nitrogen, oxygen, or sulfur atoms is an important and frequently utilized protection strategy in organic synthesis. The most commonly used benzylation methodology employs a toxic and carcinogenic reagent benzyl chloride or a lachrymose compound benzyl bromide.[1] Our lab has been engaged in the exploration of practical green chemistry that eliminates the use of substances hazardous to human health and the environment. In our recent study we reported that the green reagent dimethyl carbonate (DMC) can function effectively as a methylating reagent for *N*- and *O*-methylations under mild conditions if DBU is employed as a catalyst.[2,3] We also developed the first catalytic process for the *N*-methylation of indoles using DABCO as the catalyst.[4] We report herein another practical application of DABCO and DBU to the benzylation of *N*-, *O*-, or *S*-atoms with non-toxic dibenzyl carbonate (DBC).

DBC is an excellent acylating agent as demonstrated in a high yielding process for the preparation of Cbz-serine methyl ester under room temperature conditions.[5] It is relatively less active when used as an alkylating reagent. This has been shown in the reported benzylation reactions for anilines[6] and active methylenes,[7] where high energy (130–180°C) and stoichiometric amounts of bases were required to facilitate the benzylation. We were pleased to discover that both DABCO and DBU serve as efficient *nucleophilic catalysts* in promoting DMC as an effective alkylating reagent. Due

Table 1. Effect of DABCO on the benzylation rate of 5-bromoindole[a]



1 2 3 4

Entry	DABCO [mol%]	Temp. [°C]	Time [h]	**1** [%]	**3**[b] [%]	**4**[b] [%]
1	None	95	96	84	11	5
2	10	95	96	20	0	80
3	None	135	24	53	4	43
4	10	135	24	12	6	82

[a] All reactions were conducted with **1** (2.0 mmol), DBC (3.0 mmol) in 4.0 mL of DMA. The product distributions were determined by HPLC analysis of reaction mixture at the end of the reaction time indicated.
[b] The identity of product was confirmed by ^{1}H and ^{13}C NMR and MS.

Keywords: nucleophilic catalyst; DABCO; DBU; benzylation; dibenzyl carbonate; green chemistry.
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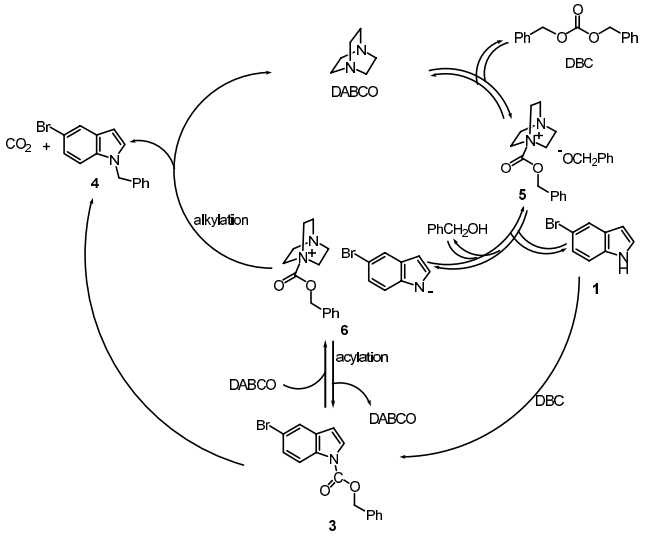
doi:10.1016/S0040-4039(03)00992-4

to structural similarity of DBC to DMC, we decided to investigate if these catalysts may also be effective in activating DBC as a more useful benzylating reagent. Our catalytic benzylation strategy was first evaluated by treating 5-bromoindole (**1**) with DBC (**2**) at 95°C in *N*,*N*-dimethylacetamide (DMA) using catalytic amounts (10 mol%) of DABCO. As revealed in Table 1, this reaction successfully afforded the desired 5-bromo-*N*-benzylindole (**4**) in 80% yield (Table 1, entry 2). Without DABCO, the same reaction generated only 5% of **4** over the same period of time (entry 1).

Although this initial result demonstrates the feasibility of the DABCO-catalyzed benzylation reaction, the rate at 95°C was quite slow. We decided to probe the same reaction at higher temperature (135°C). In the absence of DABCO, benzylation of 4-bromoindole gave 43% of the desired product in 24 h (entry 3). The rate was increased by about twofold when a catalytic amount (0.1 equiv.) of DABCO was employed (entry 4).

We believe that the DABCO-catalyzed indole benzylation proceeds through the pathways illustrated in Scheme 1. DABCO could function as a nucleophilic catalyst and react with DBC to generate an ion pair **5**. Deprotonation of indole **1** with phenylmethoxide ($PhCH_2O^-$) would lead to an ion pair **6**, which could undergo alkylation affording the *N*-benzylated indole **4**. Alternatively, ion-pair **6** could proceed through an acylation pathway yielding indole carbamate **3**, which was isolated from the reaction mixture and supported by ^1H and ^{13}C NMR, MS, and elemental analysis. It was experimentally verified that pure **3** can convert efficiently (96% conversion) into **4** at 95°C within 47 h in the presence of DBC when catalytic amount (0.1 equiv.) of DABCO was employed. Without DABCO, the conversion of **3** into **4** was not facile (only 5% conversion) under the same conditions. Transformation of **3** to **4** became more effective at higher temperature (e.g. 135°C) in the absence of DABCO.

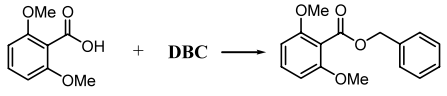


Scheme 1. Plausible mechanism for the indole benzylation.

For the benzylation of a carboxylic acid with DBC, rate enhancement by DBU is also evident. For example, benzylation of 2,6-dimethoxybenzoic acid (**7**) with DBC employing Bu_3N as a proton scavenger is slow and afforded 36% of the benzyl ester after 24 h (Table 2, entry 1). When an additional 0.1 equiv. of DBU was employed for the same reaction, the yield of benzylation was almost tripled (95%) over the same period of time (entry 2). Near quantitative (99%) conversion to the benzyl ester was achieved in 2 h when 1.1 equiv. of DBU was employed as both proton scavenger and catalyst (entry 3). The rate acceleration is presumably attributed to the reaction of DBU with DBC forming a more active benzylating agent (**9**) as shown in Scheme 2.

To investigate the scope and synthetic utility of the DABCO- and DBU-catalyzed benzylation reactions, a variety of compounds were examined at 135°C (Table 3). Employing this protocol, the reaction appears versatile and applicable to several classes of substrates. Excellent to good yields were obtained for the indole compounds (entries 1–3). Presence of an electron-withdrawing group (NO_2) in the aromatic ring seems to enhance the benzylation rate (entry 3). In comparison, benzylation for the unsubstituted indole was very slow (entry 2). The protocol is highly efficient for benzimidazole (entry 4). Introducing a phenyl group at the 2-position slows down the reaction significantly due to increased steric hindrance around the nitrogen. Benzylation for a cyclic carbamate **20** (2-benzoxazolinone) and a mercaptan **24** (2-mercaptobenzothiazole) are fast

Table 2. Effect of DBU on benzylation rate of 2,6-dimethoxybenzoic acid at 135°C[a]

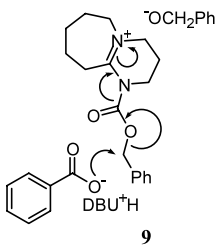


7 8

Entry	Bu_3N [equiv.]	DBU [equiv.]	Time [h]	Yield of **8**[b] [%]
1	1.0	None	24	36
2	1.0	0.1	24	96
3	None	1.1	2	99

[a] All reactions were conducted with **7** (2.0 mmol), DBC (3.0 mmol) in 4.0 mL of DMA.

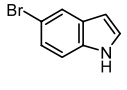
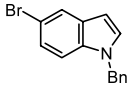
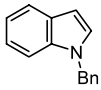
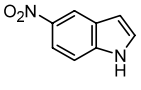
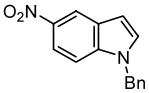
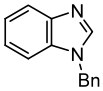
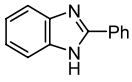
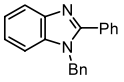
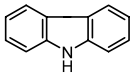
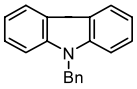
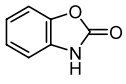
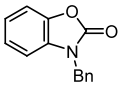
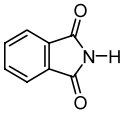
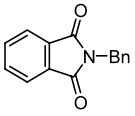
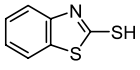
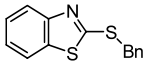
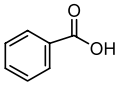
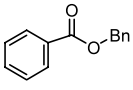
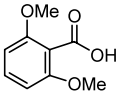
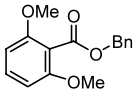
[b] Yield was determined by HPLC analysis of reaction mixture at the end of the reaction time indicated. The identity of product was confirmed by ^1H and ^{13}C NMR and MS.



9

Scheme 2.

Table 3. Catalytic *N*-, O-, and *S*-benzylation with DBC

Entry	Substrate		Time [h][a]	Product[b]		Yield[c] [%]
1		**1**	24		**4**	79
2		**10**	45[d]		**11**[8]	82
3		**12**	1.5		**13**	90
4		**14**	1		**15**[8]	91
5		**16**	45		**17**	83
6		**18**	72[d]		**19**[8]	80
7		**20**	1		**21**[9]	82
8		**22**	96		**23**[10]	72
9		**24**	1		**25**[11]	79
10		**26**	2[e]		**27**[12]	86
11		**7**	2[e]		**8**[13]	89

[a] General procedure: a reaction flask was charged with substrate (2.0 mmol), DABCO (0.2 mmol, 10 mol %), DMA (4.0 mL), and DBC (3.0 mmol). The mixture was heated to 135 °C and the reaction was monitored by HPLC until a trace or no starting substrate is detected (reaction time). [b] The identity of the benzylated products was confirmed by ^{1}H and ^{13}C NMR and MS. [c] Isolated yield based on starting substrate. [d] Same as procedure a, except 30 mol % of DABCO was charged to the reaction mixture. [e] Same as procedure a, except 1.1 equiv of DBU was charged to the reaction mixture.

and high yielding (entries 7 and 9). For a succinimide **22** (phthalimide), the benzylation was extremely slow with moderate yield (entry 8). In a couple of cases, the benzylation reaction had been extremely slow and more DABCO was employed to further accelerate the rate (30 mol% DABCO was used in entries 2 and 6). For the benzylation of aromatic acids, we found DBU a superior catalyst to DABCO. The isolated yields for the two benzyl benzoates are excellent (entries 10 and 11).

In conclusion, we have established a novel, DABCO-catalyzed benzylation methodology for a variety of N-containing compounds and a mercaptan utilizing DBC as the benzylating reagent. Benzylation reactions for carboxylic acids are also effective when DBU is employed as the catalyst. To the best of our knowledge, this is the first reported method of preparing benzyl carboxylates employing DBC. These protocols avoid the use of toxic benzyl halides, eliminate the need of stoichiometric amount of base, and provide green processes for several important chemical transformations.

Acknowledgements

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

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