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A novel, one-step method for the conversion of primary alcohols into carbamate-protected amines

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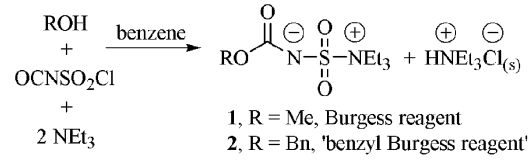
Abstract—A novel process for the one-step conversion of primary alcohols into carbamate-protected amines has been developed using a modified Burgess reagent. Although this letter mainly focuses on the conversion of alcohols into the corresponding Cbz-protected amines, the potential for extending this process to a wide range of carbamates has also been demonstrated. A detailed catalytic cycle has been proposed. While exploring the scope of this new reagent, an *N*-aryl piperidine to an *N*-aryl pyrrolidine rearrangement has been observed and rationalized.

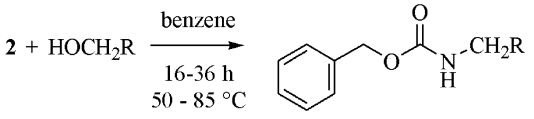
The interconversion of functional groups during synthetic sequences[1] is often necessitated by limitations of reagent chemoselectivity, functional group incompatibility, and the finite number of available starting materials. Frequently, the nascent functional group requires protection to allow subsequent transformations at other sites of the molecule. For example, the classical transformation of a primary alcohol into a protected amine typically requires a four-step process of mesylation, azide displacement, azide reduction, and amine protection. In such cases, it would be particularly attractive to install the desired functionality already conveniently protected. Methods of converting alcohols directly into protected amines often utilize bis-protected ammonia equivalents and require triphenylphosphine and azadicarboxylate reagents.[2] Presented here is a novel class of reagents, based on the Burgess reagent, for the one-step conversion of alcohols into a variety of carbamate-protected amines.

Burgess reagent (**1**, Scheme 1),[3] prepared from methanol, chlorosulfonyl isocyanate and triethylamine, has been shown to be an efficient reagent for the stereospecific *cis*-dehydration of secondary and tertiary alcohols to provide olefins. Also described in that initial publication, albeit in less detail, was the observation that primary alcohols do not undergo elimination due to a competing (and predominant) displacement reaction to form the corresponding methyl carbamates. Although the direct transformation of a primary alcohol into a protected amine was achieved, this reaction has seen limited use due to the harsh conditions required to remove the methyl carbamate in order to access the free amine.[4] However, if the novel 'benzyl Burgess reagent' (**2**) is utilized, the resulting primary amines are obtained bearing the convenient Cbz protecting group. Reagent **2** can be prepared by substituting benzyl alcohol for methanol (Scheme 1) with only minor modifications to the original procedure.[5]

According to Scheme 2, reagent **2** was allowed to react with primary alcohols at elevated temperatures to provide good yields of the Cbz-protected amines shown in Table 1. Various functional groups were found to be compatible with reagent **2**, including esters, nitriles, chlorides and aromatic nitro groups. Entry 6 illustrates the ability of this new reagent to form differentially



Scheme 1.



Scheme 2.

Keywords: Burgess reagent; functional group interconversion; Cbz; carbamate; primary alcohol.

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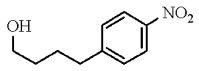
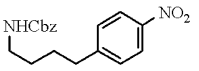
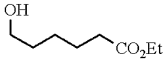
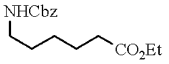
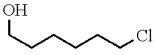
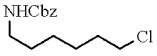
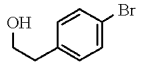
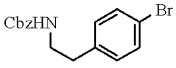
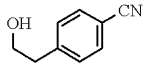
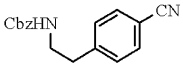
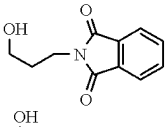
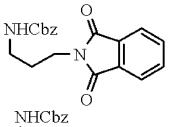
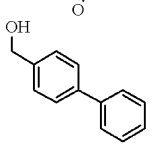
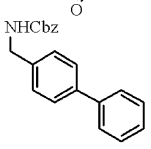
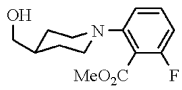
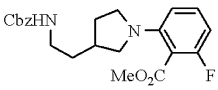
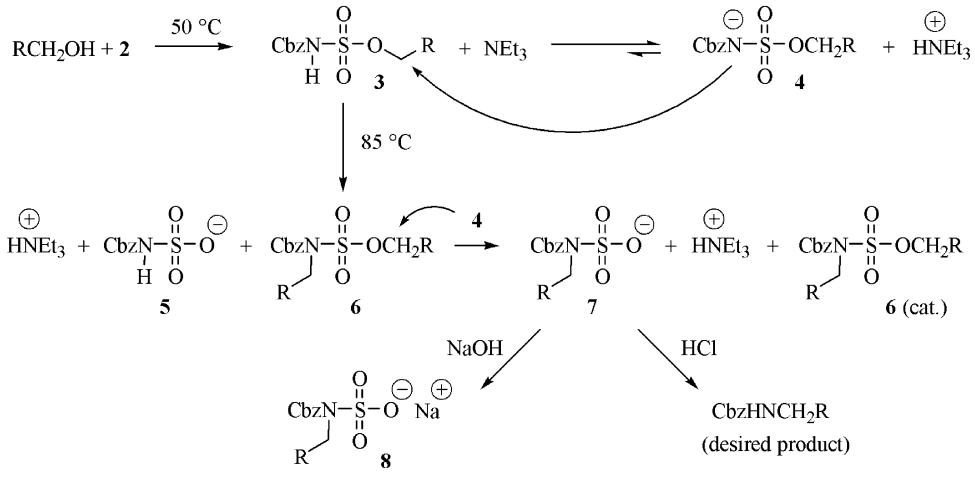
Table 1. Conversion of primary alcohols to Cbz-protected amines

Entry	Substrate	Product	yield[a]
1			77%
2			68%
3			67%
4			71%
5			77%
6			69%
7			60%
8			73%

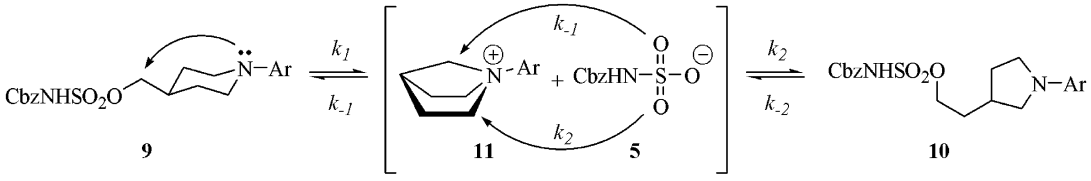
[a] Isolated yields. All compounds were characterized by LCMS (purity, >95%), ^{1}H NMR and HRMS.

protected diamines. Benzylic alcohols such as entry 7, under a variety of conditions, tended to give lower yields, presumably because of their higher reactivity (vida infra).

As proposed in the initial publication,[3] primary alcohols react with this class of reagents (**1**, **2**) via an S_N2 type mechanism. In a typical reaction,[6] a solution of **2** and the primary alcohol is heated to 50°C for 1 h, allowing complete formation of the alkyl *N*-carbobenzyloxysulfamate ester (**3**, Scheme 3). Once formed, compound **3** enters into equilibrium with the reagent-derived triethylamine to form the anion **4** and its triethylammonium counter ion. Although the pK_a for **3** is not known, it is reasonable to propose that this critical equilibrium mostly likely favors the formation of the nucleophilic compound **4** to a great extent. Upon heating to 85°C in a sealed vessel, compound **4** now reacts with the small amount of **3** present to form intermediate **6** and the leaving group *N*-carbobenzyloxysulfamate **5**. The required presence of both components **3** and **4** is supported by the observation that addition of excess base, such as triethylamine, *N*-methyl morpholine or pyridine, shifts this equilibrium further to the right and slows or even halts reaction progression. If a strong base (NaHMDS, 1 equiv.) is added prior to heating, the reaction coordinate does not progress beyond the initial adduct **3**, as determined by LC/MS. Since it is unlikely that compound **5** can serve as a nucleophile,[7] and if this were the major pathway for the formation of **6**, then the maximum possible yield would be 50%. However, once a small amount of intermediate **6** is formed, it enters into a catalytic cycle whereby compound **4**, once again acting as the nucleophile, reacts with **6** to form an equivalent of **7** concomitant with the regeneration of compound **6**. In this manner, all of compound **4** is eventually funneled to compound **7** through reaction with **6**. Necessarily, a catalytic amount of **6** remains at the completion of the reaction, and is detectable by LC/MS prior to work-up. Compound **7** accumulates during the reaction and has been isolated after basic work-up (1 M NaOH) where R = $(CH_2)_3$Ph(4-NO_2) as its insoluble sodium salt, **8**.[8] To isolate the desired products directly, an acidic work-up is preferred, although acids weaker than HCl were not explored. Other observations that support this bimolecular mechanism are that reaction rates and yields increase with higher reaction concentrations. It would also appear that significant positive charge develops at the electrophilic carbon during the transition state because a β-heteroatom prevents the displacement, while switching to a more polar solvent (THF or MeCN) slightly increases yields and rates, and permits reasonable reaction rates at lower temperatures (70–75°C).



Scheme 3. Proposed mechanism for the conversion of primary alcohols to Cbz-protected amines by 'benzyl Burgess reagent'.



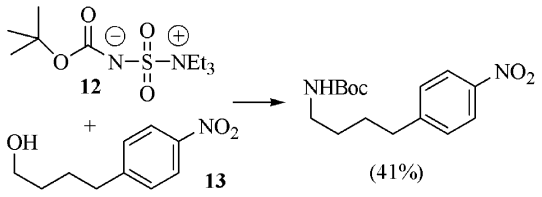
Scheme 4. Proposed mechanism for the rearrangement of the *N*-aryl piperidine to the *N*-aryl pyrrolidine.

This mechanism can be used to help rationalize the routinely observed lower yields and faster reaction rates of benzylic alcohols (Table 1, entry 7). While it is possible that more side reactions occur due to greater ionization at the benzylic carbon, this ionization might also facilitate reaction of compound **3**. If greater than 50% of the material is funneled from **3** plus **4** to **6**, then there will be insufficient **4** remaining to complete the reaction cycle, thereby lowering yields. By contrast, the reaction of benzyl alcohol described by Burgess[3] afforded an 80% yield of the desired methyl carbamate. The higher yield observed by Burgess may be a result of performing the reaction neat at a higher temperature, or the result of fewer steric interactions when forming a methyl carbamate compared to a benzylic carbamate.

Returning to Table 1, entry 8, this unexpected rearrangement of an *N*-aryl piperidine to an *N*-aryl pyrrolidine during the course of the reaction was confirmed by multidimensional $^{1}H/^{13}C$ NMR spectroscopy. In addition to the 73% isolated yield of the pyrrolidine product, a minor amount (ca. 7%) of the desired piperidine isomer was observed by LC/MS. The initial adduct **9** (Scheme 4) forms smoothly and completely as determined by LC/MS. Although this compound should enter into an equilibrium in analogy to that proposed for compound **3** (Scheme 3), an additional equilibration between compounds **9** and **10** must also be proposed. While some of compound **9** reacts as expected to provide the piperidine product (not shown), the majority of compound **9** is slowly converted to compound **10**, and eventually to the observed product, through the intermediacy of the [2.2.1] bicyclic aryl ammonium cation (**11**) and its presumably tightly associated anion (**5**). If ions **11** and **5** were not closely associated and nucleophilic attack on **11** by a nitrogen nucleophile was the actual mechanism, it would be difficult to rationalize the approximately 10:1 selectivity seen for the pyrrolidine product over the piperidine product. The tendency for the equilibrium to favor **10** over **9** might stem from several causes. As a result of geometric constraints, k_1 might be faster than k_{-2}, while k_2 might be faster than k_{-1} for purely stochastic reasons (two equivalent reaction sites for k_2 versus only one reaction site for k_{-1}). In addition, compound **10** might enjoy faster conversion to product due to reduced steric demands on the nucleophile (absence of β-branching). Although not shown for reasons of clarity, a similar equilibration might take place through intermediates analogous to compound **6** (Scheme 3).

Other alcohols may be substituted in place of methanol according to Scheme 1, resulting in the formation of alternate carbamate-forming, Burgess-type reagents. For example, the *tert*-butyl Burgess reagent (**12**, Scheme 5) was prepared and allowed to react with alcohol **13** under slightly milder reaction conditions (70°C, 20 h, benzene). This single, unoptimized attempt yielded 41% of the desired Boc-protected amine, demonstrating the potential for even these very hindered and acid labile Burgess reagents.

In summary, a novel method for the conversion of primary alcohols into Cbz-protected amines has been described. Mechanistic proposals for the overall reaction, as well as an unexpected *N*-aryl piperidine to *N*-aryl pyrrolidine rearrangement have been proposed based on experimental observations. The complete scope of carbamates that can be formed remains to be explored.[9]



Scheme 5. Formation of a Boc-protected amine.

Acknowledgements

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References

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2. (a) Wada, M.; Mitsunobu, O. *Tetrahedron Lett*. **1972**, *13*, 1279–1282; (b) Lee, B. H.; Miller, M. J.; Prody, C. A.; Neilands, J. B. *J. Med. Chem*. **1985**, *28*, 317–325; (c) Dodd, D. S.; Kozikowski, A. P. *Tetrahedron Lett*. **1994**, *35*, 977–980.
3. Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem*. **1973**, *38*, 26–31.
4. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991; pp. 317–318.

5. *Typical procedure for the preparation of reagent* ***2***: To a stirred solution of chlorosulfonyl isocyanate (1.30 mL, 14.9 mmol) in dry benzene (35 mL) under nitrogen in a cool water bath was added anhydrous benzyl alcohol (Aldrich, 1.54 mL, 14.9 mmol) dropwise over 30 min. The water bath was then removed and the solution allowed to warm to ambient temperature for 20 min. The above solution was then transferred via cannula into a rapidly stirred solution of triethylamine (4.20 mL, 30.1 mmol) in dry benzene (17 mL) over the course of 1 h under nitrogen at ambient temperature. A slight exotherm and the formation of solid triethylamine hydrochloride were observed. After an additional 40 min, the contents of the reaction vessel, along with as much precipitate as possible, was transferred via cannula into a dry Schlenk filtration apparatus (medium porosity) to remove the triethylamine hydrochloride. The resulting clear, colorless, benzene solution of **2** thus prepared was estimated to have a final concentration of 0.25 M. This solution could be stored in the freezer for at least a month with no deleterious effect on reaction yields, although a slight yellow color and a small amount of precipitate can develop over time. Attempts to isolate reagent **2** as a crystalline solid, similar to Burgess reagent, were unsuccessful.
6. *Typical procedure for the conversion of a primary alcohol into a Cbz-protected amine* (Table 1, entry 1): To a flame-dried reaction vessel equipped with a stir bar and septum was added 4-(4-nitrophenyl)butan-1-ol (0.21 mL, 1.25 mmol) followed by a benzene solution of **2** (5.0 mL, 1.25 mmol, 0.25 M). The septum was then removed and quickly replaced with a Teflon cap prior to the reaction being placed into a 50°C bath. After 1 h, the bath temperature was increased to 85°C and a small aliquot of the reaction mixture was removed to check for the formation of the initial adduct **3** (LC/MS generally shows M^++18(H_2O): 426). The reaction was stirred for 12–16 h and then periodically monitored, by LC/MS, for the disappearance of **3**. (CAUTION: Remove the reaction vessel from the heating bath and allow its temperature to drop below the boiling point of the solvent prior to removing an analytical sample.) Frequently, LC/MS spectra obtained prior to work-up show numerous side products that disappear after work-up. After complete disappearance of **3**, the reaction was cooled to ambient temperature, benzene was removed in vacuo, and the residue was partitioned between EtOAc and 0.5 M HCl. The organic layer was washed with 5% sodium bicarbonate and brine, then dried over sodium sulfate. Filtration, solvent removal and silica gel chromatography (10–60% EtOAc in hexanes, linear gradient) provided 318 mg (77%) of a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.14 (d, J=8.8 Hz, 2H), 7.48 (d, J=8.8 Hz, 2H), 7.34 (m, 5H), 7.26 (t, J=6.0 Hz, 1H, N*H*), 5.00 (s, 2H), 3.02 (dt, J=6, 6 Hz, 2H), 2.71 (t, J=7.6 Hz, 2H), 1.59 (m, 2H), 1.42 (m, 2H); HRMS calcd for $C_{18}H_{20}N_2O_4$+NH_4^+ 346.1761, found: 346.1791.
7. The formation of a nucleophilic di-anion of **5**, under these reaction conditions, does not seem reasonable.
8. This compound was characterized by LC/MS and ^{1}H NMR in DMSO-d_6, and was stoichiometrically converted into the desired product under acidic conditions.
9. After completion of this work, we became aware of a report using similarly modified Burgess reagents: Nicolaou, K. C.; Huang, X.; Snyder, S. A.; Rao, P. B.; Bella, M.; Reddy, M. V. *Angew. Chem., Intl. Ed. Engl.* **2002**, *41*, 834–838.