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Conversion of Carbamates to Amidosulfones and Amides. Synthesis of the [^{14}C]-Labeled Antiobesity Agent Ro23-7637.

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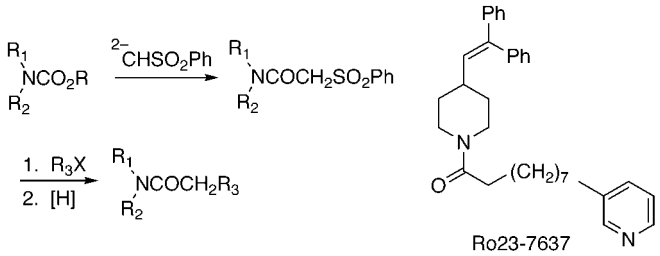
ABSTRACT



Carbamates of primary and secondary amines react with the dianion of methyl phenyl sulfone to yield amidosulfones. Alylation of the amidosulfone followed by reductive removal of the sulfonyl residue gives an amide.

Carbamates are widely used protecting groups for amines because they are easily prepared and are stable to a broad range of reagents used in synthesis yet can be removed under conditions that release the parent amine cleanly and in high yield.[1] Certain carbamates such as the carbobenzyloxy (Cbz) and *tert*-butoxycarbonyl (Boc) derivatives of amines have played a pivotal role as protection devices in peptide synthesis,[2] but beyond the methods available for their preparation and cleavage surprisingly little is known of their more general chemical properties. For conversion of an amine protected as its carbamate to an amide, conventional practice holds that the carbamate is first removed and the liberated amine is reacted with an acylating agent in a subsequent step. An alternative means for accomplishing the same overall transformation would, in principle, invoke nucleophilic attack by an alkyl anion at the carbonyl group of the carbamate with subsequent expulsion of an alkoxide. Ideally, the alkyl group introduced in this manner should be capable of modification, including further substitution, so that amides directly from carbamates are not restricted to structures carrying acyl appendages inherited solely from those alkyl anions that are reactive with carbamates.

The dianion of methyl phenyl sulfone[3] appeared to be a good candidate for reaction with carbamates[4] because (a) this species is highly nucleophilic, (b) the resulting amido-

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 503−547.

(2) Bodanszky, M. *Principles of Peptide Chemistry*; Springer-Verlag: New York, 1984; p 99.

(3) White, J. D.; Avery, M. A.; Choudhry, S. C.; Dhingra, O. P.; Kang, M.-c; Whittle, A. J. *J. Am. Chem. Soc.* **1983**, *105*, 6517.

(4) For other applications of this and related sulfonyl dianions in synthesis, see: Eisch, J. J.; Dua, S. K.; Behrooz, M. *J. Org. Chem.* **1985**, *50*, 3674 and references therein.

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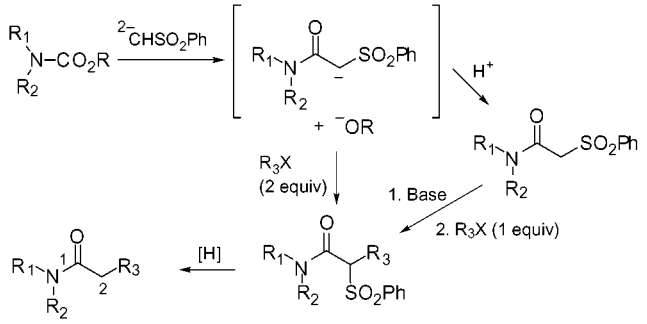
sulfone would be capable of further alkylation, and (c) the sulfonyl substituent can be cleaved to produce an amide. This sequence from carbamate to amide is outlined in Scheme 1,

Scheme 1



where alkylation of the intermediate amidosulfone anion followed by reductive cleavage of the sulfone furnishes an amide in which C1, C2, and the remaining carbons of the acyl chain originate from three different sources. This feature lends the method considerable versatility, for example, by allowing the introduction of labeled carbon via the carbamate carbonyl, the methyl group of methyl phenyl sulfone, or the alkylating agent RX. To illustrate this point, a synthesis of the antiobesity agent Ro23-7637[5] is described in which a ^{14}C label is incorporated via isotopically enriched methyl phenyl sulfone.[6]

Carbamates 1−13 were prepared from a variety of amines by standard methods using either methyl or ethyl chloroformate, or in some cases di-*tert*-butyl dicarbonate.[7] Methyl and ethyl carbamate esters of secondary amines reacted smoothly with the dilithio dianion of methyl phenyl sulfone at 0 °C and gave amidosulfones in good yield (Table 1). However, the reaction of methyl phenyl sulfonyl dianion with *tert*-butyl carbamates was variable, yields with the Boc derivatives of piperidine (**2**) and indoline (**11**) being low. The *N*-Boc derivative of indole gave no amidosulfone but instead returned the parent indole quantitatively. The carbamates **12** and **13** derived from ethylamine and *n*-propylamine, respectively, reacted with the dianion of methyl phenyl sulfone to give an amidosulfone only if the nitrogen was first blocked as its *N*-trimethylsilyl derivative.[8] In these cases, the *N*-silyl group was introduced in situ and was cleaved during workup.

The amidosulfone anion generated by addition of the dianion of methyl phenyl sulfone to a carbamate can be alkylated in situ with an alkyl halide (2 equiv), or the

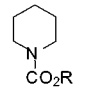
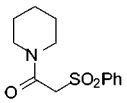
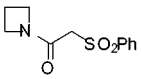
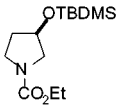
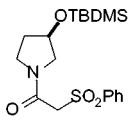
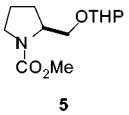
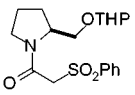
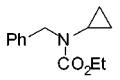
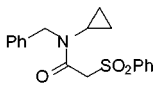
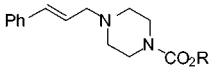
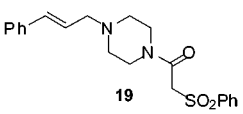
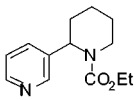
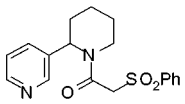
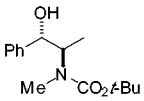
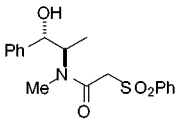
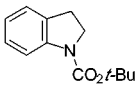
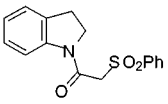
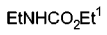
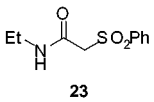
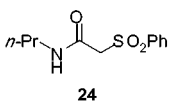
(5) (a) Campfield, L. A.; Smith, F. J.; Mackie, G.; Tenenbaum, R.; Sassano, M. L.; Mullin, J.; Kaiser, K.; Kierstead, R. W. *Obes. Res.* **1993**, *3 Suppl 4*, 5915. (b) Mullin, Jr., J. G.; Kierstead, R. W.; Triscari, J. U.S. Patent 4632925, 1986.

(6) Choudhry, S. C.; Serico, L.; Liebman, A. A. *Synth. Appl. Isotop. Label. Comp.* **1981**, 218.

(7) Pope, B. M.; Yamamoto, Y.; Tarbell, D. S. *Proc. Natl. Acad. Sci. U.S.A.* **1972**, *69*, 730.

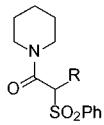
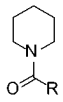
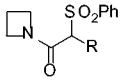
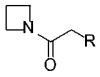
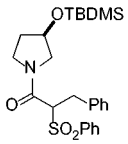
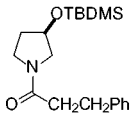
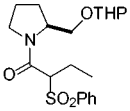
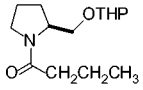
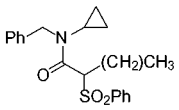
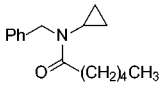
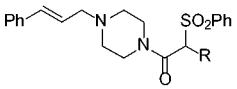
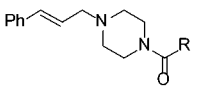
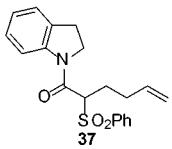
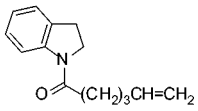
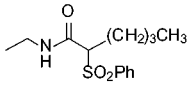
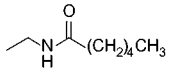
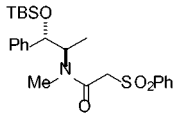
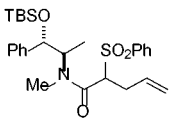
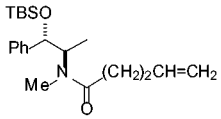
(8) (a) Ghiron, C.; Piga, E.; Rossie, T.; Tamburini, B.; Thomas, R. *Tetrahedron Lett.* **1996**, *37*, 3891. (b) Burkhart, J. P.; Holbert, G. W.; Metcalf, B. W. *Tetrahedron Lett.* **1984**, *25*, 5267.

Table 1. Preparation of Amidosulfones from Carbamates

carbamate	amidosulfone	yield (%)
 **1**, R = Me; **2**, R = *t*-Bu	 **14**	93 from **1**; 37 from **2**
 **3**	 **15**	95
 **4**	 **16**	90
 **5**	 **17**	94
 **6**	 **18**	99
 **7**, R = Et; **8**, R = *t*-Bu	 **19**	75 from **7**; 60 from **8**
 **9**	 **20**	85
 **10**	 **21**	64
 **11**	 **22**	13
 **12**	 **23**	88
 **13**	 **24**	77

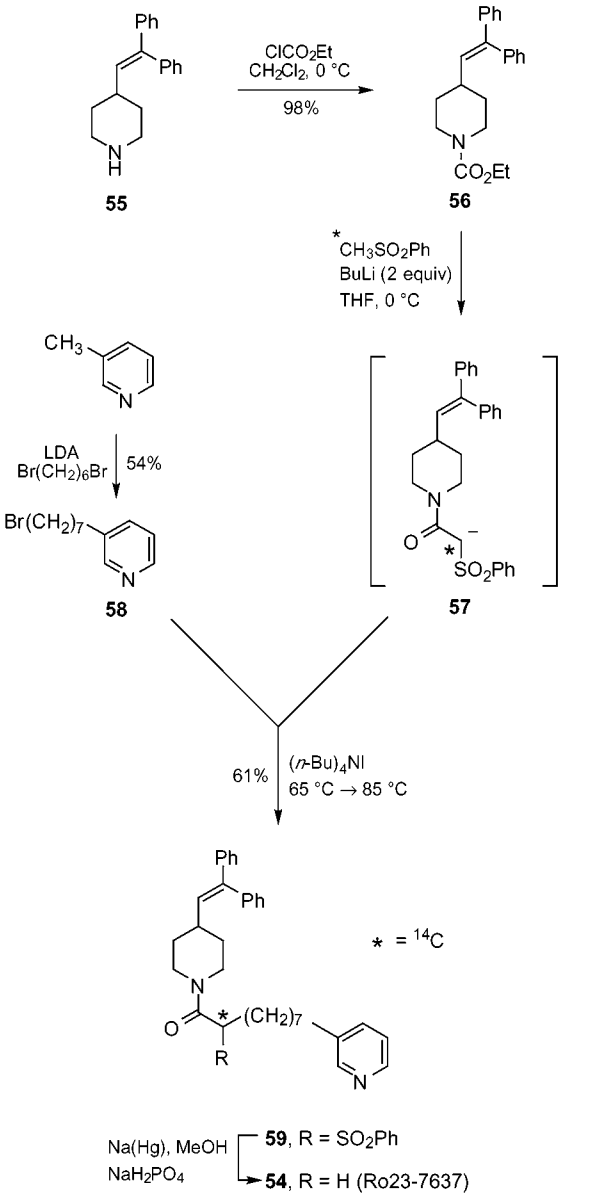
[a] Footnote: (1) the carboxylic acid was reacted with Et_3N/Me_3SiCl (**12**) or with LDA/Me_3SiCl (**13**) before exposure to the dianion of methyl phenyl sulfone.

Table 2. Alkylation of Amidosulfones and Subsequent Reuction[a]

amidosulfone	alkylation product	yield (%)	reducing agent	reduction product	yield (%)
14					
	26, R = Et	87	Na(Hg)	**40**, R = $CH_2CH_2CH_3$	86
	27, R = CH_2CO_2t-Bu	72	SmI_2	**41**, R = $CH_2CH_2CO_2t$-Bu	96
15					
	28, R = $(CH_2)_8CH{=}CH_2$	69	SmI_2	**42**, R = $(CH_2)_3CH{=}CH_2$	92
	29, R = $(CH_2)_{10}CO_2Me$[1]	65	SmI_2	**43**, R = $(CH_2)_{11}CO_2Me$	97
	30, R = CH_2CO_2t-Bu	66	SmI_2	**44**, R = $CH_2CH_2CO_2t$-Bu	91
16	 **31**	99	Na(Hg)	 **45**	85
17	 **32**	90	Na(Hg)	 **46**	89
18	 **33**	81	Na(Hg)	 **47**	97
19					
	34, R = $(CH_2)_8CH_3$	95	SmI_2	**48**, R = $(CH_2)_4CH_3$	90
	35, R = $CH_2CH(CH_3)_2$	80	SmI_2	**49**, R = $CH_2CH_2CH(CH_3)_2$	85
	36, R = CH_2Ph	79	SmI_2	**50**, R = CH_2CH_2Ph	73
22	 **37**	60	SmI_2	 **51**	97
23	 **38**	70	Na(Hg)	 **52**	93
 **25**	 **39**	88[2]	Na(Hg)	 **53**	76

[a] Footnotes: (1) the carboxylic acid was converted to its methyl ester with CH_2N_2 after alkylation; (2) mixture of two diastereomers (ratio not determined).

Scheme 2



amidosulfone can be isolated and alkylated in a separate step with an alkyl halide (1 equiv) in the presence of a base (1 equiv). Thus, alkylation of the α anion of amidosulfones **14**−**19** and **22**, each prepared using potassium *tert*-butoxide in THF, with a variety of alkylating agents in the presence of tetra-*n*-butylammonium iodide gave a good yield of the expected product in all cases (Table 2). Alkylation of **23** was carried out in DMF with potassium carbonate as the base and gave clean C-alkylation with 1-iodobutane. The alkylated amidosulfones **26**, **31**, and **32** were also prepared in comparable yields using the one-pot procedure. In the case of the sulfone **21** derived from ephedrine, it was first necessary to block the hydroxyl function (e.g., **25**) for successful C-alkylation. The amidosulfone **20** derived from the ethyl carbamate of anabasine failed to undergo alkylation α to the sulfonyl group, presumably because of competing N-alkylation at the pyridine nucleus. Reductive removal of the sulfonyl group from alkylated amidosulfones **26**−**39** was carried out with either 6% sodium-amalgam in methanol buffered with disodium hydrogen phosphate[9] or with samarium diiodide in a mixture of methanol and tetrahydrofuran.[10] In all cases, the yield of reduction product was excellent.

The ready availability of methyl phenyl sulfone bearing a ^{14}C label in the methyl group[11] makes the carbamate-to-amide conversion an ideal sequence for incorporating isotopic carbon. This is illustrated in a synthesis of [^{14}C]-labeled Ro23-7637 (**54**), an insulin-lowering antiobesity agent (Scheme 2).[5] Thus, piperidine **55** was converted to its ethyl carbamate **56**,[5b] and the latter was reacted with the dianion of [^{14}C]-methyl phenyl sulfone (specific activity = 30 mCi/mmol) to produce the monoanion of keto sulfone **57**. The latter was alkylated directly with 3-(7-bromoheptyl)pyridine (**58**), prepared from 3-picoline by deprotonation of the methyl substituent and alkylation with 1,6-dibromohexane, to yield keto sulfone **59**.[5b] After reductive removal of the sulfonyl residue with sodium amalgam, **59** furnished [^{14}C]-Ro23-7637 (54) in >98% radiochemical purity.

In summary, a method has been developed for the conversion of carbamates of primary and secondary amines to amides that does not require prior cleavage of the carbamate. The method provides access to a wide variety of amides through alkylation of an intermediate amidosulfone and is especially well-suited to the introduction of an isotopic label into the amide.

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Supporting Information Available: A typical procedure for the preparation of an amidosulfone from a carbamate, alkylation of the amidosulfone, and reductive cleavage of the sulfonyl group to an amide; characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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