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# Stereoselective Synthesis of Protected Amines and Diamines from Alkenes using N,N-Dichloro-t-butylcarbamate

**Barry S. Orlek and Geoffrey Stemp***

SmithKline Beecham Pharmaceuticals, Medicinal Research Centre, Coldharbour Road The Pinnacles, Harlow, Essex CM19 5AD, England.

*Key Words:* Cyclic Alkenes; Aziridines; Vicinal diamines; Boc-amines, N,N-Dichloro-t-butylcarbamate;

***Abstract*** N,N-Dichloro-t-butylcarbamate (**1**) reacts with alkenes (**2**) in a regio- and stereo-selective manner to give the trans-chlorocarbamate adducts (**3**). Treatment of (**3**) with base gives aziridines (**5**), and reaction of (**3**) and (**5**) with sodium azide leads selectively to the versatile diamine precursors (**6**) and (**7**). *In situ* reduction of (**3**) with $Zn/NH_4OAc$ leads directly to Boc-protected amines (**10**)

The stereoselective introduction of amine functionality presents an important synthetic challenge. The vicinal diamine group is present in a number of biologically important molecules[1,2]. 2-Amino-indanes and tetralins also form important pharmacophores for a number of natural and synthetic drug molecules[3].

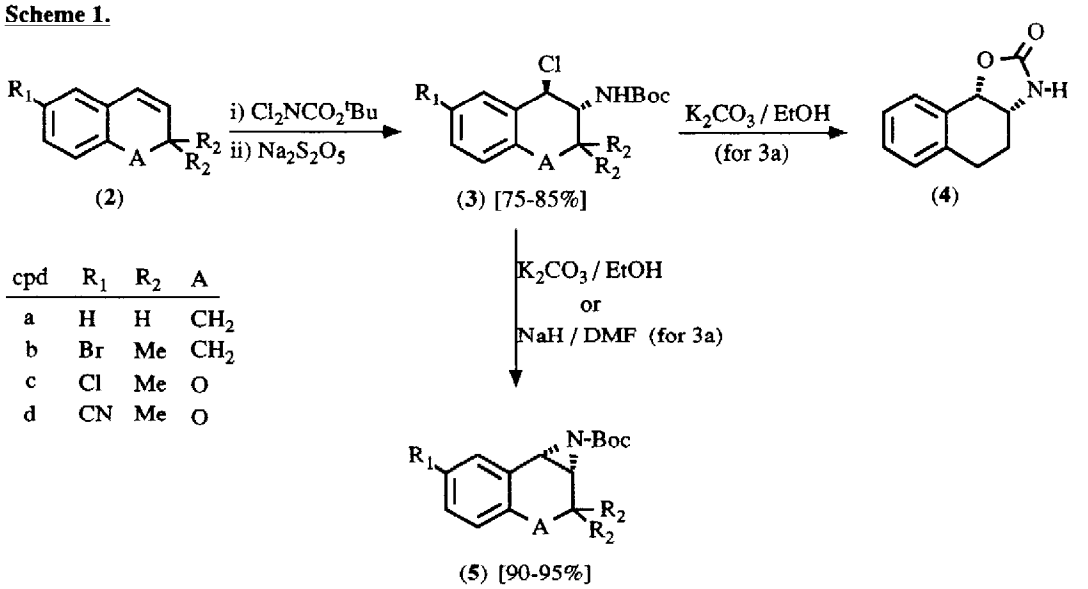
Recently, one of us reported[4] the synthesis of 1,2-diaminoindanes *via* stereoselective trans addition of N,N-dichlorourethane (DCU) to indene followed by displacement of chloride using azide or amines. This work demonstrated the viability of such an approach to vicinal diamines of known relative stereochemistry from cyclic alkenes. One major disadvantage to the use of N,N-dichlorourethane is that, in general, the resulting urethane requires vigorous conditions for deprotection to the free amine, which are not compatible with a wide variety of functional groups[5] In contrast, the t-butoxycarbonyl (Boc) group is readily removed under mild acid conditions In this Letter we report our results using the reaction of N,N-dichloro-t-butylcarbamate (**1**)[6] with a variety of cyclic alkenes (**2**) for the stereoselective synthesis of vicinal diamines and the extension of this methodology to the regioselective synthesis of Boc-protected amines

$$Cl_2NCO_2{}^tBu \quad (1)$$

In agreement with the previous work[4], model experiments with indene and dihydronaphthalene (**2a**) showed that the stereoselective trans addition was maintained with (**1**). It is interesting to note that, in contrast to work reported[7] with DCU and cyclohexene, extension of this methodology to dihydronaphthalene did not result in loss of selectivity We have also extended this reaction to sterically-hindered alkenes such as (**2b-d**) with no loss of regio- or stereo-selectivity. Thus, treatment of (**2a-d**) with (**1**) in toluene at 50°C for 5h, followed by *in situ* reduction with sodium metabisulphite gave trans adducts (**3a-d**) in excellent yield[8]. No products resulting from cis-addition could be detected.

Treatment of (3a) with $K_2CO_3$ in aqueous ethanol resulted in quantitative formation of oxazolidinone (4)[9], presumably *via* an oxazolinium species. More forcing conditions, using NaH in DMF at 50°C, were required for conversion of (3a) to aziridine (5a). In contrast, treatment of (3b-d) with $K_2CO_3$ in aqueous ethanol smoothly led to the Boc-protected aziridines (5b-d) [Scheme 1].

**Scheme 1.**

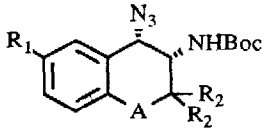



| cpd | $R_1$ | $R_2$ | A |
|---|---|---|---|
| a | H | H | $CH_2$ |
| b | Br | Me | $CH_2$ |
| c | Cl | Me | O |
| d | CN | Me | O |

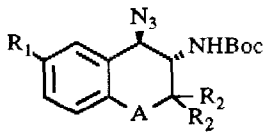
A possible explanation for the different reactivities observed for adducts (3a) and (3b-d) was provided by inspection of their $^1H$ nmr spectra. These showed that for the C(3) and C(4) protons of (3b-d) a coupling constant of 8 Hz was observed, whereas for (3a) this coupling constant was only 2 Hz. These data are consistent with the C(3) and C(4) substituents arranged trans-di-equatorially in (3b-d), which contain the gem-dimethyl group at C(2), and with a trans-di-axial arrangement of these substituents in (3a). These assignments have been confirmed by nuclear Overhauser enhancement (n.O.e) difference experiments on adducts (3a) and (3d). Further evidence was provided by calculation of heats of formation for (3a-d) using the semi-empirical AM1[10] method in the AMPAC[11] program which showed that for (3a) the trans-di-axial conformation is favoured by 2.2 kcal/mol, whereas for (3b-d) the trans-di-equatorial conformation is favoured by approximately 2 5 kcal/mol. Inspection of models shows that in (3a) the trans-di-axial conformer is perfectly set up for either oxazoline or aziridine formation, and in agreement with the work reported previously[4], the product obtained depends upon the base used in the reaction. However, in compounds (3b-d) the trans-di-axial conformer is destabilised by the interaction between the 4-chloro and the axial 2-methyl substituent. Aziridine formation in these cases probably proceeds *via* a twist-boat conformation[12], where the gem-dimethyl grouping prevents the approach of the carbamate oxygen underneath the carbon bearing the 4-chloro substituent

Reaction of trans-adducts (3a-d) and aziridines (5a-d) with sodium azide gave the cis- and trans-azidocarbamates (6) and (7), respectively, in high yield.

| cpd. | $R_1$ | $R_2$ | A |
|---|---|---|---|
| a | H | H | $CH_2$ |
| b | Br | Me | $CH_2$ |
| c | Cl | Me | O |
| d | CN | Me | O |

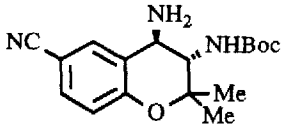


(**6**) [93-96%]

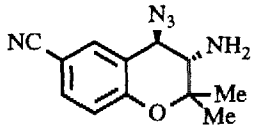


(**7**) [90-98%]

The versatility of these cis- and trans- azidocarbamates as precursors to vicinal diamines of known relative stereochemistry was demonstrated by reduction[13] of (**7d**) to aminocarbamate (**8**) and by treatment of (**7d**) with trifluoroacetic acid to give aminoazide (**9**).

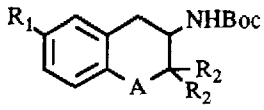


(**8**) [94%]



(**9**) [85%]

Complementary to the preparation of vicinal diamines, it was envisaged that the addition of (**1**) to alkenes (**2**), coupled to an alternative reductive procedure, would lead regioselectively to Boc-protected amines (**10**) in one-pot[14,15].

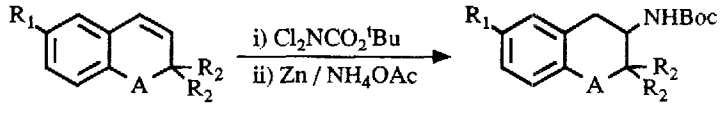


(**10**)

Under typical experimental conditions, a solution of indene (**2e**) and N,N-dichloro-t-butylcarbamate (1.1 eq.) in toluene was heated at 50 °C for 6h. Solvent was replaced with dioxane and aqueous ammonium acetate, the mixture cooled to 0 °C and zinc dust (10 eq.) added portionwise over 15 min. The mixture was stirred vigorously for 14 h, filtered and extracted with ether to give the Boc-protected amine (**10e**) in 85% yield. Similar results were obtained with alkenes (**2a-d**), including the sterically-hindered alkenes (**2b-d**)[16] [Scheme 2].

**Scheme 2.**

| cpd. | $R_1$ | $R_2$ | A |
|---|---|---|---|
| a | H | H | $CH_2$ |
| b | Br | Me | $CH_2$ |
| c | Cl | Me | O |
| d | CN | Me | O |
| e | H | H | bond |




(**2**) (**10**) [60 - 85%]

In conclusion, the addition of N,N-dichloro-t-butylcarbamate (**1**) to alkenes followed by *in situ* reduction with sodium metabisulphite provides a stereoselective route to diamine precursors where each amino substituent can be selectively elaborated further, and changing the reducing agent to zinc and ammonium acetate gives an efficient one-pot synthesis of Boc-protected amines.

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REFERENCES AND NOTES.

1 E T. Michalson and J. Szmuszkovicz, Prog. Drug Res., **1989**, *33*, 135-149.

2 M T Reetz, R. Jaeger, R. Drewlies and M Hübel, Angew Chem. Int Ed. Engl., **1991**, *30*, 103-105; and references therein

3 (a) C.R. Ganellin, Advances in Drug Research, **1967**, *4*, 163-249; (b) D. Beaumont and R.D. Waigh, Prog. Med. Chem., **1981**, *18*, 46-86.

4 B S Orlek, Tetrahedron Lett , **1986**, 1699-1702

5. For the conversion of alkyl carbamates to amines under neutral conditions and discussion of more vigorous conditions see M E Jung and M A. Lyster, J C.S Chem. Comm., **1978**, 315-316; and references therein.

6. R.E. White and P. Kovacic, J. Am. Chem Soc., **1975**, *97*, 1180-1184.

7. (a) T A. Foglia and D. Swern, J. Org. Chem., **1966**, *31*, 3625-3631; (b) B J. Walker and P Wrobel, J C.S Chem. Comm., **1980**, 462-463.

8. All new compounds had satisfactory analytical and/or mass spectral data. $^1$H n.m.r data ($CDCl_3$) at 270 MHz: Compound (3a): δ 1.45 (s, 9H), 1.90 (m, 1H), 2.50 (m, 1H), 2 90 (m, 2H), 4 25 (m, 1H), 4.72 (br s, NH), 5.04, (d, J=2 Hz, 1H), 7.05-7.40 (m, 4H); Compound (3d): δ 1.30 (s, 3H), 1.46 (s, 9H), 1.53 (s, 3H), 4.17 (dd, J=9, 8 Hz, 1H), 4.63 (d, J=9 Hz, NH), 4 88 (d, J=8 Hz, 1H), 6.92 (d, J=9 HZ, 1H), 7.48 (dd, J=9, 2 Hz, 1H), 7.82 (d, J=2 Hz, 1H).

9. The formation of an oxazolidinone under these mild conditions stands in contrast to the vigorous pyrolysis required to convert ethyl-β-chlorocarbamates into the corresponding oxazolidinones. See T.A. Foglia and D. Swern, J. Org. Chem., **1967**, *32*, 75-78

10. M.J.S. Dewar, E.G Zoebisch, E.F Healy, and J.J.P. Stewart, J. Am. Chem. Soc., **1985**, *107*, 3902-3909

11. J.J.P. Stewart, QCPE Bulletin, **1986**, *6*, 24a.

12 J. Sicher, M. Tichy, F. Sipos, and M. Pankova, Coll. Czech Chem Comm , **1961**, *26*, 2418-2434.

13 We have found the method of H. Bayley, D.N. Standring, and J.R. Knowles, Tetrahedron Lett., **1978**, 3633-3634; employing 1,3-propane-dithiol, to be an excellent procedure for the reduction of highly functionalised and sterically hindered azides such as (6) and (7)

14. Traditional approaches based on α- or β- indanones or tetralones can involve lengthy procedures which are not compatible with the presence of a variety of aromatic substituents See A.S Horn, B. Kaptein, N.A. Vernue, J.B De Vries and T B A. Muller, Eur. J. Med. Chem., **1988**, *23*, 325-328; and references therein.

15. For a related approach using the chromous chloride promoted addition of N-chloroamides to alkenes see H. Driguez, J.M Paton and J. Lessard, Can J Chem , **1977**, *55*, 700-719.

16 In all cases, deprotection of (**10**) to the corresponding amine proceeded in 80-90% yield under standard conditions employing TFA in $CH_2Cl_2$ at 0 °C.

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