Pergamon

Tetrahedron Letters, Vol. 38, No. 48, pp. 8425-8428, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10238-6

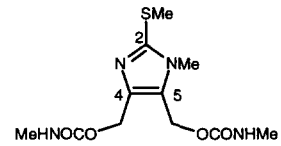
A New Synthesis of Carmethizole and Related Nitrogen Analogues.

Michael P. Hay* and William A. Denny

Cancer Society Research Laboratory
University of Auckland School of Medicine
Private Bag 92019, Auckland, New Zealand

Abstract: A new efficient six-step synthesis of carmethizole, a novel bis-carbamate alkylating agent, and syntheses of related nitrogen analogues are described, using a key 4,5-disubstituted imidazole intermediate **8**. © 1997 Elsevier Science Ltd.

Carmethizole (**1**) is a novel bis-carbamate alkylating agent[1] which forms DNA-protein and DNA-DNA cross-links *in vitro*,[2] and has antitumour activity against murine leukaemias, solid tumours and human tumour xenografts *in vivo*.[1,3] Difficulty with formulation and unacceptable cardiotoxicity halted the advancement of carmethizole (**1**) to clinical trial.[4] Antitumour activity of related bis-hydroxymethylimidazoles was found to be enhanced by electron-donating 2-substituents, while electron-withdrawing 2-substituents led to compounds that were inactive.[1] This relationship was suggested to be a consequence of the ability of the 2-substituent to stabilize the transition state of the S_N1-type activation of the hydroxymethyl groups, which eventually leads to DNA alkylation.[5]

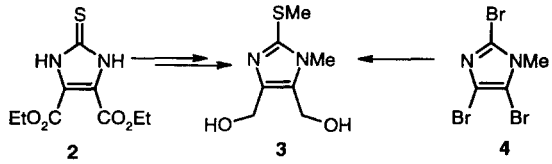


1

These reports led us to consider bis-hydroxymethylimidazole derivatives with 2-nitrogen substituents as interesting drug development targets. We aimed to prepare a range of amino-substituted derivatives including 2-N_3, 2-$NHCO_2R$, and 2-NH_2. While the 2-amino derivative **17** is expected to be more reactive than carmethizole (**1**) on the basis of its electron-donating properties ($\sigma_p(NH_2)$= -0.66, σ_p(SMe) = 0.00)[6] the 2-azido derivative **12** and a bis-BOC derivative **16** contain considerably less electron-donating substituents, ($\sigma_p(N_3)$= 0.15, $\sigma_p(NHCO_2Me)$[7] = -0.15)[6] and may be considered prodrug forms of the 2-amino derivative. The use of the azido group as a masked amine function is well known,[8] and metabolism of aryl azides to amines has been demonstrated.[9,10,11]

The initial synthesis of **1** by Anderson[1] used a ring-formation approach to produce a tri-substituted imidazole intermediate **2** which was elaborated to **1** in several steps via **3** (Scheme 1). Other

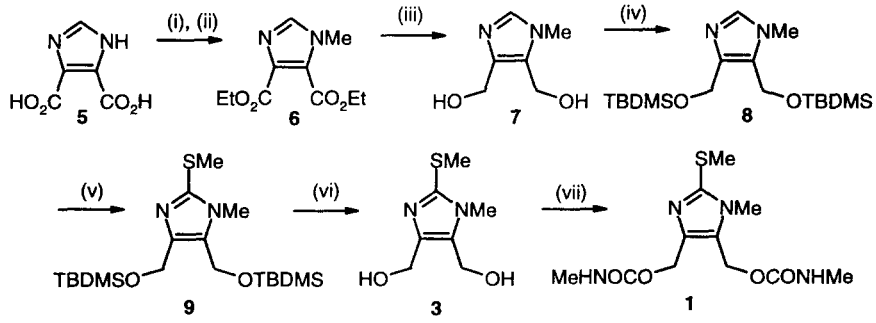
2-substituted derivatives (H, Me, Ph, OMe) were obtained by individual imidazole ring syntheses. More recently, Lipshutz[12] described a one-pot procedure for generating 2-thiomethyl bis-hydroxymethylimidazole (**3**) from tribromo-N-methylimidazole (**4**), using three sequential treatments of nBuLi followed by the appropriate electrophile (Scheme 1). Metallation of imidazoles, followed by reaction with electrophiles, has been the subject of considerable study and provides a useful method for the selective functionalisation of imidazoles.[13]



Scheme 1.

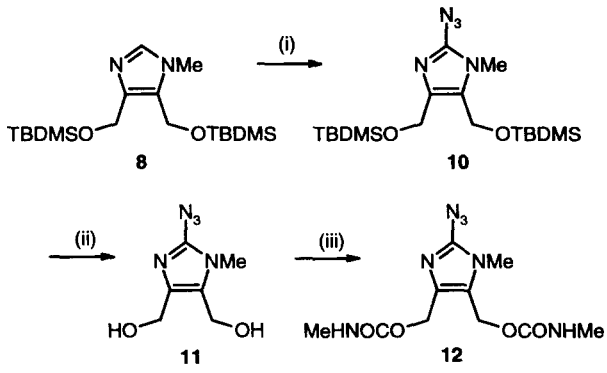
We report an approach that uses electrophilic attack on a 2-lithiated 4,5-disubstituted imidazole to provide a new synthesis of carmethizole (**1**) and also efficient access to a range of nitrogen-based analogues.

Esterification and N-alkylation of commercially available imidazole-4,5-dicarboxylic acid (**5**) gave the diester **6**, which was reduced to the diol **7** with $LiAlH_4$ and protected as the di-TBDMS ether **8**. This key intermediate was converted to the sulfide **9** using standard metallation conditions and dimethyl disulfide.[12] Deprotection of the silyl ether groups with TBAF and reaction with methyl isocyanate and dibutyltin diacetate gave carmethizole (**1**) in good yield[14] (Scheme 2).



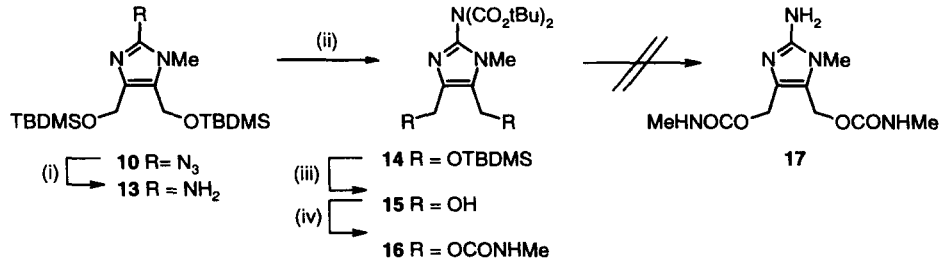
Scheme 2. Reagents: (i) $SOCl_2$, EtOH; (ii) MeI, K_2CO_3, DMF; (iii) $LiAlH_4$, THF; (iv) TBDMSCl, Et_3N, DMF; (v) nBuLi, Me_2S_2, THF; (vi) TBAF, THF; (vii) MeNCO, $nBu_2Sn(OAc)_2$, DCM.

Access to nitrogen analogues was afforded by reaction of the lithiated derivative of **8** with tosyl azide[15] to give the azide **10** which was elaborated to the 2-azido bis-carbamate **12**[16] in a similar manner to the methylthio derivative **1** (Scheme 3).



Scheme 3. Reagents: (i) nBuLi, tosyl azide, THF; (ii) TBAF, THF; (iii) MeNCO, $nBu_2Sn(OAc)_2$.

Reduction of the azide **12** using either Pd/C or Lindlar catalyst[17] under neutral or acidic conditions gave only complex mixtures, emphasising the unstable nature of 2-aminoimidazole derivatives bearing leaving groups in conjugation with the 2-position. Attempts to trap the amine by carrying out the reduction in the presence of $(BOC)_2O$[18] or via a Staudinger reaction[19] were unsuccessful. However, catalytic hydrogenation of the bis-silylether azide **10** using Pd/C gave a quantitative yield of the amine **13**, which was protected as the bis-BOC compound **14**. Deprotection of **14** with HF.pyridine and formation of the bis-carbamate as described above gave the protected amino derivative **16**.[20] Reaction of **16** with HCl/MeOH, TFA, or anhydrous HCl in EtOAc[21] failed to give the 2-amino bis-carbamate **17**. NMR analysis of the product mixture indicated loss of methyl carbamate groups in addition to the removal of the *t*-butyloxycarbonyl group, again emphasising the instability of such compounds (Scheme 4).



Scheme 4. Reagents: (i) H_2, Pd/C, EtOH; (ii) $(BOC)_2O$, DMAP, THF; (iii) HF.pyr; (iv) MeNCO, $nBu_2Sn(OAc)_2$.

Thus a versatile synthetic route to carmethizole (**1**), 2-azido- (**12**), and protected 2-amino analogue (**16**) has been established. Failure to isolate the 2-amino bis-hydroxymethyl carbamate (**17**)

underlines the reactivity of such derivatives. The utilisation of (**12**) and (**16**) as prodrugs of reactive 2-amino bis-hydroxymethyl carbamate (**17**) will be reported in due course.

Acknowledgements.

The authors acknowledge support from the Auckland Division of the Cancer Society of New Zealand and Contract NO1-CM 47019 from the National Cancer Institute, NIH.

References and Notes.

1. Anderson, W.K.; Bhattacharjee, D.; Houston, M.D. *J. Med. Chem.* **1989**, *32*, 119-127.
2. Elliot, W.L.; Fry, D.W.; Anderson, W.K.; Nelson, J.M.; Hook, K.E.; Hawkins, P.A.; Leopold III, W.R. *Cancer Res.* **1991**, *51*, 4581-4587.
3. Waud, W.R.; Plowman, J.; Harrison Jnr, S.D.; Dykes, D.J.; Anderson, W.K.; Griswold Jnr, D.P. *Cancer Chemother. Pharmacol.* **1992**, *30*, 261-266.
4. Beijnen, J.H.; Flora, K.P.; Halbert, G.W.; Henrar, R.E.C.; Slack, J.A. *Brit. J. Cancer* **1995**, *72*, 210-218.
5. Jarosinski, M.A.; Reddy, P.S.; Anderson, W.K. *J. Med. Chem.* **1993**, *36*, 3618-3627.
6. Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley Interscience: New York, 1979, p49.
7. A substituent constant for $N(CO_2R)_2$ was not available from Reference 6 and the value for $NHCO_2Me$ used is an approximation
8. Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297-368.
9. Nicholls, D.; Gescher, A.; Griffin, R.J. *Xenobiotica* **1991**, *21*, 935-943.
10. Bliss, E.A.; Brown, T.B.; Stevens, M.F.G.; Wong, C.K. *J. Pharm. Pharmacol.* **1979**, *31 (S)*, 66P.
11. Stevens, M.F.G. Griffin, R.J. Wong, S.K. *Anti-Cancer Drug Des.*1987 *2*, 311-318.
12. Lipschutz, B.H.; Hagan, W. *Tetrahedron Lett.* **1992**, *33*, 5865-5868.
13. For a recent review see Iddon, B.; Ngochindo, R.I.; *Heterocycles* **1994**, *38*, 2487-2568
14. Data for compound **1**: mp (EtOAc) 127.5-128.0 °C (lit. (see ref. 1) mp (dichloromethane/hexanes) 125-126 °C).
15. Regitz, M.; Hocker, J.; Liedhegener, A. *Org. Synth.* **1968**, 48, 36.
16. Data for 1-methyl-2-azido-4,5-bis(hydroxymethyl)imidazole bis(*N*-methylcarbamate) (**12**): (86%) mp (EtOAc) 126 °C (d); IR (KBr) 3424, 3368, 2963, 2172, 2130, 1707, 1560, 1506, 1491, 1273 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.13 (s, 2 H, CH_2O), 5.04 (s, 2 H, CH_2O), 4.75 (br. s, 2 H, OCONH), 3.38 (s, 3 H, NCH_3), 2.77-2.80 (m, 6 H, $2CH_3$); ^{13}C NMR ($CDCl_3$) δ 156.8, 156.4, 141.6, 134.9, 124.9, 59.1, 54.8, 29.6, 27.6, 27.5. MS (DEI) 297 (M^+, 5%), 269 (8), 223 (20), 155 (30), 137 (40), 58 (75), 42 (100). HRMS (DEI) calcd for $C_{10}H_{15}N_7O_4$ 297.1189 (M^+), measured 297.1188. Anal. calcd for $C_{10}H_{15}N_7O_4$: C, 40.4; H, 5.1; N, 3.0; found C, 41.1; H, 5.2; N, 3.2%.
17. Corey, E.J.; Nicolaou, K.C.; Balanson, R.D.; Machida, V. *Synth.* **1975**, 590-591.
18. Saito, S.; Nakajima, N.; Inaba, M.; Morikawa, T. *Tetrahedron Lett.* **1989**, *30*, 837-838.
19. Afonso, C.A.M. *Tetrahedron Lett.* **1995**, *36*, 8857-8858.
20. Data for 1-methyl-2-(N,N-di-*t*-butyloxycarbamoyl)-4,5-bis(hydroxymethyl)imidazole bis(*N*-methylcarbamate) (**16**): (69%) oil; IR (thin film) 3380, 1800, 1767, 1721, 1514, 1251 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 7.09 (q, J = 4.3 Hz, 1 H, OCONH), 6.99 (q, J = 4.3 Hz, 1 H, OCONH), 5.10 (s, 2 H, CH_2O), 4.89 (s, 2 H, CH_2O), 3.37 (s, 3 H, NCH_3), 2.51 (br d, J = 4.3 Hz, 6 H, $2CH_3$), 1.40 (s, 18 H, $2C(CH_3)_3$); ^{13}C NMR ($(CD_3)_2SO$) δ 156.5, 156.1, 149.8, 138.0, 133.9, 126.0, 83.5, 58.0, 54.0, 29.5, 27.3 (2); MS (DEI) 471 (M^+, 10%), 397 (10), 315 (30), 223 (40), 165 (100); HRMS (DEI) Calc. for $C_{20}H_{33}N_5O_8$ (M^+) 471.2329, found 471.2337.
21. Gibson, F.S.; Bergmeier, S.C.; Rappoport, H. *J. Org. Chem.* **1994**, *59*, 3216-3218.

(*Received in UK* 8 *September* 1997; *accepted* 26 *September* 1997)