Alternative Syntheses of the Antitumour Drug Temozolomide avoiding the Use of Methyl Isocyanate

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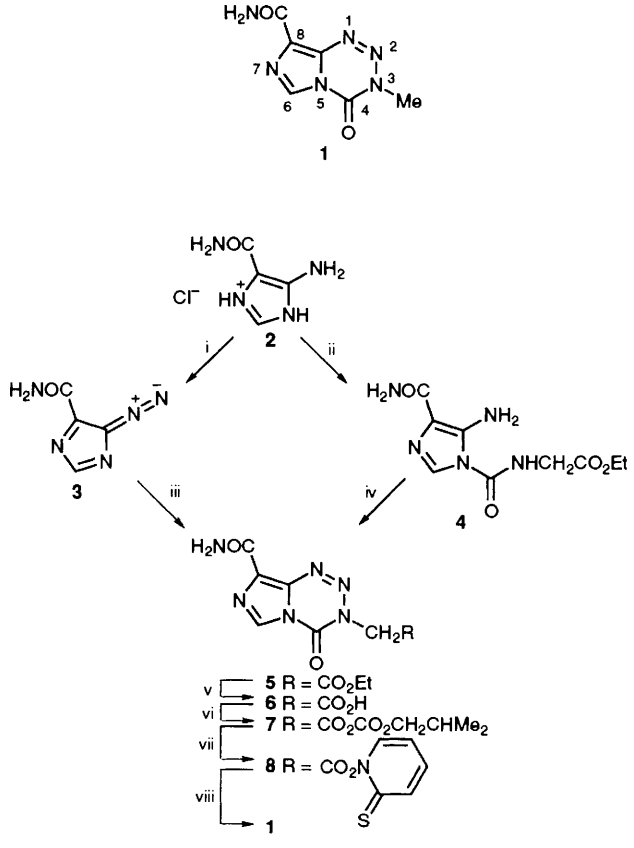
Ethyl (8-carbamoyl-3,4-dihydro-4-oxoimidazo[5,1-*d*]-1,2,3,5-tetrazin-3-yl)acetate **5** can be prepared by two routes starting from 5-aminoimidazole-4-carboxamide **2**; hydrolysis of **5** to the corresponding carboxylic acid **6** followed by Barton radical decarboxylation gives the antitumour imidazotetrazinone temozolomide **1**.

The antitumour drug temozolomide, 8-carbamoyl-3-methylimidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one **1**, is currently undergoing clinical trials in Europe and the USA following encouraging initial results in patients with malignant melanoma, mycosis fungoides or brain tumours.[1] Detailed NMR[2] and crystallographic and molecular modelling studies[3] have confirmed that temozolomide is an effective molecular device (MW 194 Da) for targeting an electrophilic and fugitive methyldiazonium fragment to the major groove of guanine-rich sequences in DNA. Clinical activity correlates with methyl group transfer to a guanine O^6-position of DNA since tumour types which can repair this lesion are less sensitive to the drug.[4]

The original synthesis of temozolomide involved conversion of the aminoimidazole **2** to 5-diazoimidazole-4-carboxamide **3** followed by cyclisation with methyl isocyanate in dichloromethane at 25 °C:[5] although this synthesis was slow it had the merit of giving clinical grade temozolomide in high yield. We now report the first alternative synthesis of temozolomide which does not employ volatile methyl isocyanate (bp 39 °C), a molecule of ill repute.[6] In designing a synthetic strategy we were mindful to exploit the robust stability of imidazotetrazines to acids:[7] we chose to exploit the Barton radical decarboxylation[8] of the carboxylic acid precursor **6** as a preferred route to temozolomide (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) $NaNO_2$ (excess), 2N-HCl, 0 °C; (ii) EtO_2CCH_2NCO, DMSO, pyridine, 20 °C; (iii) EtO_2CCH_2NCO, DMSO, 25 °C; (iv) $NaNO_2$, 2N-HCl, 0 °C; (v) 5N-HCl, 45 °C; (vi) Me_2CHCH_2OCOCl, *N*-methylmorpholine, DMF, −15 °C; (vii) 2-mercaptopyridine *N*-oxide, Et_3N, −15 °C; (viii) Bu_3SnH, AIBN (catalyst), DMF, hv, 25 °C

Interaction of commercially available non-volatile ethyl isocyanatoacetate and diazoimidazole-4-carboxamide **3** in dry Me_2SO at 25 °C overnight gave the ester **5**† in 80% yield. Hydrolysis of the ester to the acid **6**‡ was accomplished in 80% yield in 5 mol dm^{-3} hydrochloric acid at 45 °C. All efforts to convert ester **5** or acid **6** to temozolomide directly by a range of conventional approaches failed. Accordingly, the carboxylic acid was converted first to the reactive ester **7**§ with isobutyl chloroformate/methylmorpholine in dry DMF at −15 °C under nitrogen and thence to the 1-substituted pyridine-2(1*H*)-thione **8**¶ with 2-mercaptopyridine *N*-oxide in triethylamine at −15 °C. Homolytic cleavage of **8** with AIBN (catalytic amount) and tributyltin hydride in dry DMF, under irradiation with a 100 W tungsten lamp at 25 °C under nitrogen, gave temozolomide **1** in an overall (unoptimised) yield of 26% for the transformation **6** → **1** without isolation of intermediates **7** and **8**. This synthesis, which we have accomplished on a gram scale, highlights the surprising fact that the imidazotetrazine nucleus is sufficiently robust to survive a variety of acidic, basic and radical-generating reagents and points out a range of alternative synthetic strategies which might be applied for bulk synthesis of temozolomide.

We also report an alternative route to ester **5** obviating the use of the potentially unstable diazoimidazole-4-carboxamide **3**. Regioselective carbamoylation of the free base of **2** with ethyl isocyanatoacetate in Me_2SO gave the urea **4**‖ (77% isolated yield). Cyclisation of the urea to the imidazotetrazinone ester **5** was accomplished by sodium nitrite in 2 mol dm^{-3} hydrochloric acid in 93% yield. 5-Amino-4-carbamoyl-1-(*N*-substituted carbamoyl)imidazoles are useful intermediates for the synthesis of imidazotetrazines and other heterocycles but nitrosative cyclisation only proceeds efficiently when electron-withdrawing groups are attached to the methylene group.

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Footnotes

† *Spectroscopic data* for compound **5**: mp 162–164 °C (decomp.); ν_{max} (KBr) cm^{-1} 3412, 3185, 3098, 2999, 1744, 1694, 1611 and 1260; δ_H [$(CD_3)_2SO$] 1.24 (3H, t, CH_2CH_3), 4.22 (2H, q, CH_2CH_3), 5.23 (2H, s, CH_2CO), 7.77 (1H, brs, NH), 7.92 (1H, brs, NH) and 8.92 (1H, s, H-6); [Found: C, 40.2; H, 3.5; N, 32.0%; M + H (FAB, NOBA matrix), 267. $C_9H_{10}N_6O_4$ requires C, 40.6; H, 3.8; N, 31.6%; M + H 267].

‡ *Spectroscopic data* for compound **6**: mp 165 °C (decomp.); ν_{max} (KBr) cm^{-1} 3407, 3249, 3090, 3001, 1755, 1717, 1640 and 1588; δ_H[$(CD_3)_2SO$] 5.13 (2H, s, CH_2), 7.77 (1H, brs, NH), 7.92 (1H, brs, NH), 8.94 (1H, s, H-6); (Found: C, 34.40; H, 2.70; N, 33.97. $C_7H_6N_6O_4 \cdot 0.5H_2O$ requires C, 34.00; H, 2.83; N, 34.00%).

§ *Spectroscopic data* for compound **7**: mp 165–167 °C (decomp.); δ_H ($CDCl_3$) 0.91 (6H, d, 2 × CH_3), 1.95 (1H, m, CH), 3.99 (2H, d, OCH_2), 5.14 (2H, s, CH_2CO), 6.82 (1H, brs, NH), 7.26 (1H, brs, NH), 8.43 (1H, s, H-6).

¶ *Spectroscopic data* for compound **8**: δ_H [$(CD_3)_2SO$] 5.74 (2H, s, CH_2), 7.02 (1H, m, pyridyl CH), 7.56 (1H, m, pyridyl CH), 7.65 (1H, m, pyridyl CH), 7.89 (1H, brs, NH), 8.03 (1H, brs, NH), 9.07 (1H, s, H-6).

‖ *Spectroscopic data* for compound **4**: mp 183–185 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3499, 3426, 3334, 3236, 1727, 1658, 1555, 1505 and 1219; δ_H [$(CD_3)_2SO$] 1.21 (3H, t, CH_2CH_3), 4.00 (2H, d, CH_2O), 4.15 (2H, q, CH_2CH_3), 6.41 (2H, brs, NH), 6.85 (1H, brs, NH), 6.95 (1H, brs, NH), 7.69 (1H, s, H-2), 9.07 (1H, t, NH); [Found: C, 39.3; H, 5.5; N, 25.6%; M + H, 256. $C_9H_{13}N_5O_4 \cdot H_2O$ requires C, 39.5; H, 5.4; N, 25.6%; M + H, 256].

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