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The isolation and use of a benzodiazepine iminochloride for the efficient construction of flumazenil

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Abstract—The benzodiazepine iminochloride **2** has been isolated, characterized and its reaction with a glycinate enolate synthon investigated resulting in an efficient synthesis of the imidazobenzodiazepine flumazenil.

Flumazenil **1**[1] selectively blocks the central effects of the classical benzodiazepines and has attracted much attention for the treatment of benzodiazepine induced sedation and overdosing[2a–d] as well as being evaluated for the improvement of cognitive function in Alzheimer's patients.[2e] Imidazobenzodiazepines of this type have been recently constructed in moderate yields (~20–65%) by the reaction of an isonitrile,[3] or an amidine ester[4] with an in situ[3] formed activated imidoyl derivative of the benzodiazepine, most usually the corresponding iminophosphate,[3,4] or iminochloride.[3e] There remain some drawbacks with this approach however, with the fact that isonitriles are lachrymatory/moisture sensitive and iminophosphates/chlorides are largely unstable[4] making these reagents difficult to handle on a larger scale. To adequately address these problems, we considered the combination of ester and nitrile formamidines as isonitrile equivalents,[4] with the hitherto uncharacterised iminochloride **2** (Fig. 1) on the basis that the latter might be amenable to isolation and therefore allow a detailed evaluation of its transformation into flumazenil (**2**→**1**).

Evaluation and selection of an appropriate isocyanide synthon: Amidine **3**,[5a] the precursor for the synthesis of flumazenil, was chosen for a more detailed investigation. Thus the ester **3** was first deprotonated in accordance with literature precedent[4] with lithium hexamethyldisilylazide at −78°C, then slowly warmed up and treated with D_2O at different temperatures. Above ~−30°C, extensive decomposition was observed. Three bases were then evaluated (*t*BuOK, NaH, LHMDS), and their respective salts quenched with excess benzyl chloride. LHMDS proved superior, providing the corresponding dibenzylated adduct **4** in 82% yield (Scheme 1).

Evaluation and selection of a stable, activated imidoyl derivative of a benzodiazepine: Iminochloride **2** was prepared[6,7] by the dropwise addition of a slight excess of $POCl_3$ to a hot (100°C) toluene solution of the amide **5**[1] in the presence of excess *N*,*N*-dimethyl-*p*-toluidine. After basic work-up, the iminochloride could be freed from its alkaline environment by trituration and washing with diisopropyl ether/*n*-hexane before use. This convenient isolation procedure provided iminochloride

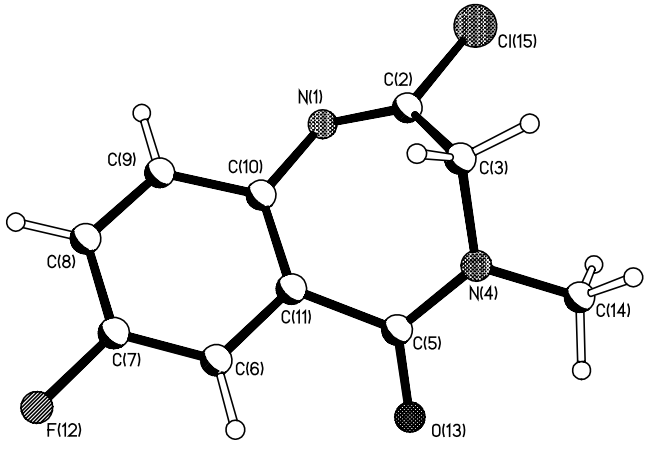

Figure 1. X-Ray structure of compound **2**.

Keywords: diazepine; iminochloride; amidine; imidazole.
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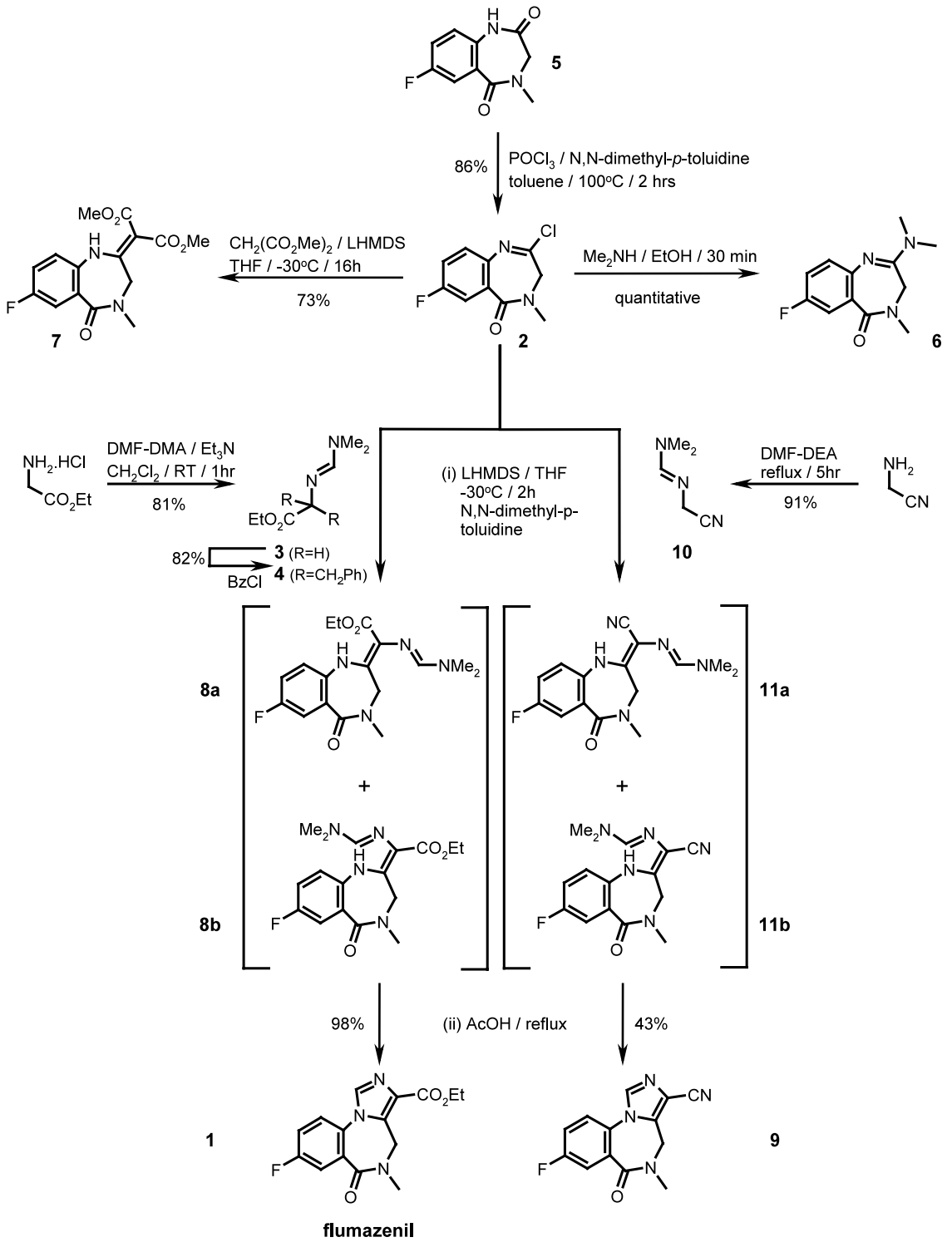

Scheme 1.

2 in 86% yield with a calibrated purity of 97% based upon HPLC analysis of the corresponding amidine adduct **6**.

Compound **2** is very prone to hydrolysis in solution and proved difficult to analyse. For example, ^{1}H NMR analysis showed only starting material **5** unless a small amount of a hindered amine was first added to the $CDCl_3$ solvent; passing the solvent through basic alumina did not suffice. Confirmation of structure was gleaned from an X-ray determination.[7]

The reactivity of iminochloride **2** with nucleophiles was confirmed by its smooth reaction with dimethylmalonate,[4c] giving adduct **7** in 73% yield. Treatment of isolated iminochloride **2** with 2 equiv. of the lithiated

amidine derived from **3** at −35°C gave rise to a mixture of the open chain intermediate **8a** and flumazenil **1** (~20:1, pH 7 quench). Although such intermediate 2-dehydroglycinates are believed not to be isolatable in systems where subsequent intramolecular cyclisations are possible,[4a] a non-aqueous work-up permitted the isolation of **8a**. Subsequent acidification with AcOH in THF or dioxane to pH 5 with heating facilitated the isomerisation of **8a** to **8b** followed by spontaneous cyclisation and elimination of dimethylamine to produce flumazenil **1**. This method was applied directly to the original reaction mixtures containing **8a** which gave reproducible, isolated yields of **1** of 98% from iminochloride **2** after recrystallisation. If this protocol was not followed, a normal aqueous work-up led to hydrolysis of any remaining uncyclised **8a**, resulting in variable yields. Reactions using non-isolated imino chloride (i.e. as a crude solution in toluene) resulted in reduced yields of ca. 70% of **1**. Application of this process to the synthesis of nitrile **9** using amidine **10**[5b] as the requisite building block resulted in an overall yield of only 43% from iminochloride **2**. The reaction could be interrupted at an intermediate stage to afford a ca. 1:1 mixture of cyano amidines **11a** and **11b**. Upon standing or in solution, **11a** was converted to its more stable isomer **11b**, which could then be heated in the presence of acetic acid to quantitatively give **9**. This reduced yield was therefore caused en route to **11**, most likely by polar by products formed from the self-condensation of starting material **10**.

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7. *(a) 2-Chloro-7-fluoro-4-methyl-3,4-dihydrobenzo[e][1,4]-diazepin-5-one (**2**)*: A suspension of fluketazepam (**5**) (20.80 g, 1.0 equiv., 100 mmol) and *N*,*N*-dimethyl-*p*-toluidine (38.0 ml, 2.63 equiv., 263 mmol) in toluene (200 ml) was heated to 100°C. Phosphorus oxychloride (10.20 ml, 1.1 equiv., 110 mmol) was then added dropwise over 20 min producing a slight exotherm. After 2 h at 100°C, the reaction mixture was cooled to 5–10°C and slowly poured onto ice-cold aqueous potassium carbonate (1.70 M, 200 ml). After 10 min, the mixture was filtered and the phases separated. The organic phase was washed with water (2×100 ml) and the combined aqueous phases were extracted with two portions of toluene (2×40 ml). The organic phases were combined, filtered and evaporated then dried at 35°C/15 mbar for 2 h followed by 25°C/3.0×10^{-3} mbar for 2 h. To the resultant oily solid was added diisopropylether (50 ml) with stirring at 22°C. After 30 min, *n*-hexane (20 ml) was added dropwise over 15 min. The resultant suspension was stored for a further 30 min at 22°C, then at 0–5°C for 60 min. The crystalline product was filtered under an argon atmosphere and washed portionwise with a mixture of diisopropylether (30 ml) and *n*-hexane (20 ml) and dried (3.0×10^{-3} mbar/12 h) at 22°C yielding **2** as orange crystals (19.32 g, 86%); ^{1}H NMR (250 MHz, $CDCl_3$+*N*,*N*-diisopropyl-3-pentylamine): δ 3.32 (3H, s), 4.05 (2H, s), 7.27 (2H, m), 7.69 (1H, dd, $J_{6,F}=9$ Hz, $J_{6,8}=2.5$ Hz); MS (EI): $C_{10}H_8ClFN_2O$ requires: 226.0309. Found: 226.0306.
*X-Ray data for **2***: A crystal in space group $P\bar{1}$ with cell dimensions $a=6.584(5)$, $b=8.220(5)$, $c=9.223(5)$ Å; $\alpha=97.760(5)$, $\beta=94.290(5)$, $\gamma=92.750(5)°$ and $Z=2$ was obtained from diisopropylether/hexane. All measurements were made at 173(2) K on a Siemens P4 diffractometer with graphite-monochromated Cu Kα radiation. The

structure was solved using direct methods (SHELX-93) and refined against F^2 by full matrix least squares methods using SHELX-93. The final residuals for 138 parameters (with anisotropic B-factors) without restraints refined against 1294 unique data with $I>2\sigma(I)$ were $R=0.0495$ and $R_w=0.1400$. The coordinates have been deposited at the Cambridge Crystallographic Data Centre.

(b)Ethyl-8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo-[1,5-a][1,4]benzodiazepine-3-carboxylate (flumazenil) (***11***): A solution of hexamethyldisilazane (24 ml, 2.3 equiv., 115 mmol) in tetrahydrofuran (150 ml) was cooled to −35°C with stirring. *n*-Butyl lithium in *n*-hexane (69.0 ml, 1.6 M, 2.2 equiv., 110 mmol) was added dropwise over 45 min. After a further 30 min at −35°C, a solution of (dimethylaminomethyleneamino)acetic acid ethyl ester (**3**) (15.82 g, 2.0 equiv., 100 mmol) in tetrahydrofuran (50 ml) was added dropwise over 1 h and the resulting yellow solution was stirred for 30 min at −35°C. A red-brown solution of 2-chloro-7-fluoro-4-methyl-3,4-dihydrobenzo[*e*][1,4]-diazepin-5-one (**2**) (12.02 g, 1.0 equiv., 50 mmol) and *N*,*N*-dimethyl-*p*-toluidine (2.90 ml, 0.40 equiv., 20 mmol) in tetrahydrofuran (100 ml) was added dropwise over 70 min so that the temperature of the reaction was maintained at −35 to −40°C. The reaction mixture was stirred at −35°C for 2 h. The resulting clear, red solution was adjusted at the same temperature to pH 5–6 by the dropwise addition over 20 min of a solution of acetic acid (15.0 ml, 5.2 equiv., ~260 mmol) in tetrahydrofuran (10 ml). The reaction mixture was then warmed to room temperature and stirred for 12 h. A further portion of acetic acid (5.0 ml, 1.74 equiv., 87 mmol) was added thereby lowering the pH from 6–7 to 5–6 and the solution was heated to reflux for 6 h. The resultant light brown suspension was cooled to room temperature, concentrated and dried (35°C/15 mbar) for 2 h. *n*-Heptane (100 ml) was added, the mixture again concentrated and a further portion of *n*-heptane (100 ml) was added. The mixture was stirred at 35°C for 30 min, cooled to 0–5°C for 12 h and the resultant crystalline precipitate was filtered, washed with cold (0–5°C) *n*-heptane (100 ml) and then distributed between a mixture of dichloromethane (150 ml) and 5% aqueous sodium hydrogen carbonate solution (100 ml). After stirring for 5 min at room temperature, the phases were separated and the organic phase was washed with water (2×100 ml). The combined aqueous phases were back-extracted with two portions of dichloromethane (2× 30 ml). The organic phases were combined, evaporated and dried under reduced pressure (35°C/20 mbar) for 16 h. Beige crystals were collected by filtration, crushed and then suspended in ethanol (170 ml). The mixture was refluxed until a red-brown solution was produced which was filtered hot and cooled slowly to room temperature. On further cooling to 0°C for 4 h and −20°C for 2 h, the product crystallised. The precipitate was filtered, washed with one cold portion of ethanol (50 ml) and then dried (40°C/20 mbar) for 16 h furnishing (**1**) as white needles (14.73 g, 98%, HPLC 100% with ISTD, mp 201–202°C (lit.[1a] 201–203°C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.45 (3H, t, $J=7.25$ Hz), 3.25 (3H, s), 4.45 (2H, q, $J=7.25$ Hz), 4.40 and 5.20 (2H, bd, $J=16.0$ Hz), 7.36 (1H, ddd, $J_{9,F}=7$ Hz, $J_{9,10}=8.75$ Hz, $J_{9,7}=2.75$ Hz), 7.45 (1H, dd, $J_{10,F}=4.5$ Hz, $J_{10,9}=8.75$ Hz), 7.79 (1H, dd, $J_{7,F}=8.75$ Hz, $J_{7,9}=2.75$ Hz), 7.88 (1H, s); IR (KBr): 1723 and 1651 cm^{-1}; MS (CI): 326.3 ($M+NH^+$), 304.3 ($M+H^+$). Anal. calcd for $C_{15}H_{14}FN_3O_3$: C, 59.40; H, 4.65; N, 13.85. Found: C, 59.40; H, 4.71; N, 13.81%.