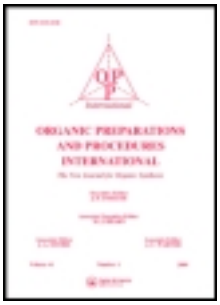

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A NEW SYNTHESIS OF FLUMAZENEL SUITABLE FOR FLUORINE-18 LABELING

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OPPI BRIEFS

A NEW SYNTHESIS OF FLUMAZENIL SUITABLE FOR FLUORINE-18 LABELING

Submitted by (05/15/03)

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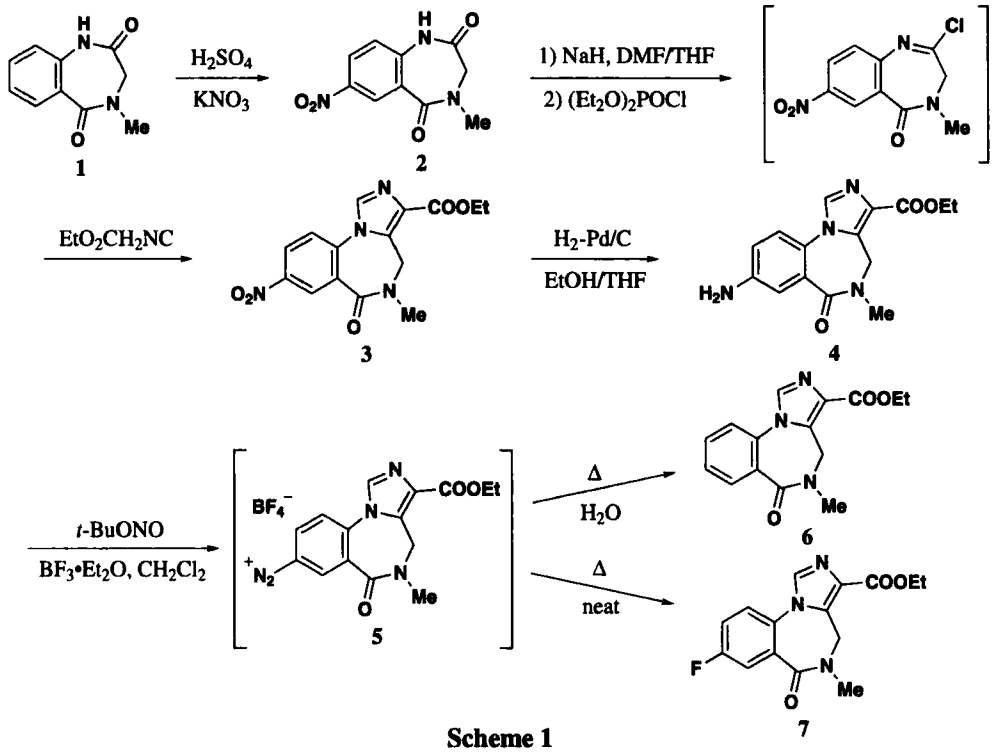
In recent years, fluorinated organic compounds have assumed an increasing importance in the biomedical area owing to the concomitance of various factors such as (*i*) the great stability of the carbon-fluorine bond, particularly in terms of thermal and oxidative degradation (*ii*) the similar steric requirements of the fluorine and hydrogen atoms which allows similar metabolic pathways and (*iii*) the enhanced lipophilicity which leads to improved diffusion into animal tissues of fluorinated compounds in comparison to the corresponding hydrogenated analogues.[1] Furthermore, ^{18}F-labeled substrates behave as tracers in the positron emission tomography (PET), which constitutes a useful tool for both pharmacokinetic *in vivo* studies and non-invasive clinical diagnoses.[2] However, due to the half-life (110 min) of the fluorine-18 nuclide, one can achieve and manipulate ^{18}F-labeled substrates, provided that the fluorine atom is incorporated in the last step of the synthetic sequence. Unfortunately, this is not the case in most of the syntheses of organic fluoro derivatives.

In the context of a cooperative program with pharmacologists, we desired to obtain new entries to the antidepressant flumazenil **7**[3] and its triazolo analogue **10** suitable for eventual fluo-

rine-18 labeling. The literature syntheses of **7**[4] and **10**[5] start from 5-fluoroisatoic anhydride or 5-fluoroanthranilic acid.

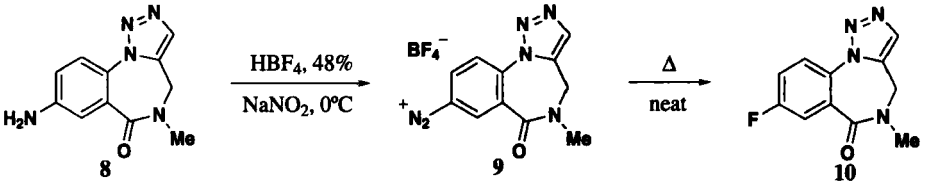
With the Balz-Schiemann[6] reaction in mind as a promising methodology to introduce the fluorine atom in our cases, we first decided to synthesize the amino derivatives **4** and **8** from which the fluoro derivatives **7** and **10** could be obtained, respectively. As illustrated in *Scheme 1*, compound **4** was prepared through *a*) nitration of 4-methyl-1,4-benzodiazepine-2,5-dione (**1**) as described in the literature,[7] *b*) conversion of the amido group of **2** in the imidoyl chloride, cyclo-condensation of the latter with ethyl isocyanoacetate to give **3** *c*) and finally reduction of the nitro group. Compound **8** was accessible by the reaction sequence previously reported.[5]



Scheme 1

At this point, we subjected compounds **4** and **8** to the Balz-Schiemann reaction. In both cases, somewhat unexpectedly, the diazonium tetrafluoborates **5** and **9** showed a pronounced solubility in water, which precluded their spontaneous crystallization. An attempt to decompose **5** in aqueous solution led to a complex mixture where the reduced product **6** was the major component and the desired fluoro derivative **7** was absent. Fortunately, compound **9** precipitated as a solid upon addition of THF, while this was not the case for compound **5**. Although the thermal decomposition of **9** in toluene at reflux furnished **10** in good yield, the reaction required 48 hours, a reaction time unsuitable for eventual ^{18}F-labeling. However, heating neat **9** at 140°C without solvent effected its complete decomposition in 30 minutes, providing **10** in 75% yield (*Scheme 2*).The drawback of the solubility of **5** in water was circumvented by diazotization of **4**

in a non-aqueous medium such as methylene chloride with *t*-butyl nitrite in the presence of BF_3•Et_2O. Under these conditions, compound **5** precipitated and its decomposition in the solid state at 130°C was complete in 40 minutes affording flumazenil **7** in 80% yield.



Scheme 2

EXPERIMENTAL SECTION

Mps were measured on a Büchi apparatus and are uncorrected. IR spectra were acquired on a Perkin-Elmer 1725X FT spectrophotometer. NMR spectra were recorded on an AVANCE 400 Bruker; chemical shifts are reported in δ from TMS. Mass spectra were measured on a WG-70EQ instrument.

5-Methyl-8-nitro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6(5*H*)-one (3).- To a solution of compound **2**[7] (4.00 g, 17.0 mmol) in DMF (34 mL)/THF (51 mL) at 0°C was added sodium hydride (0.51 g, 21.3 mmol); then diethyl chlorophosphate (3.64 mL, 25.0 mmol) was added dropwise. After stirring for 30 m at 0°C, a solution of ethyl isocyanoacetate (2.2 mL, 20.0 mmol) and NaH (0.60 g, 25.0 mmol) in DMF (20 mL) was added. The mixture was stirred for 18 h and, after addition of AcOH (0.5 mL), the mixture was poured into water (80 mL) and extracted with AcOEt. The crude oil obtained after evaporation of the solvent was chromatographed on a silica gel column (eluent: AcOEt) to afford **3** (1.79 g, 32%) as white crystals, mp. 210-212°C. IR (nujol) 1725, 1640 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.47 (t, J = 7.4 Hz, 3H), 3.14 (s, 3H), 4.50 (q, J = 7.4 Hz, 2H), 5.20 (br s, 2H), 7.60 (d, J = 8.7 Hz, 1H), 7.90 (s, 1H), 8.47 (dd, J = 2.5, 8.7 Hz, 1H), 8.95 (d, J = 2.5 Hz, 1H). MS *m/z* 330 (M^+).

Anal. Calcd for $C_{15}H_{14}N_4O_5$: C, 54.55; H, 4.27; N, 16.96. Found: C, 54.71; H, 4.09; N, 17.04.

8-Amino-5-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6(5*H*)-one (4).- A solution of **3** (0.40 g, 1.2 mmol) in THF (16.5 mL) and EtOH (16.5 mL) was treated with 10% Pd/C (0.34 g) and stirred under H_2 for 2 h. After filtration through Celite, the solvent was evaporated to give **4** (0.35 g, 97%), colorless oil. IR (nujol) 3480, 3360, 1720, 1640 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.46 (t, J = 7.4 Hz, 3H), 3.20 (s, 3H), 3.71 (q, J = 7.4 Hz, 2H), 4.40 (overlapping, 3H, 1H after deuteriation), 5.15 (br s, 1H), 6.85 (dd, J = 1.8, 6.8 Hz, 1H), 7.17 (d, J = 6.8 Hz, 1H), 7.27 (d, J = 1.8 Hz, 1H), 7.81 (s, 1H). MS *m/z* 300 (M^+).

Anal. Calcd for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66. Found: C, 60.10; H, 5.18; N, 18.53.

5-Methyl-4H-imidazo[1,5-a][1,4]benzodiazepin-6(5H)-one (6).- To a solution of **4** (100 mg, 0.33 mmol) in 50% HBF_4 (2.5 mL), cooled at 0°C, was added a 2 M aqueous solution (1 mL) of $NaNO_2$ dropwise. After stirring at room temperature for 15 m, the solution was heated at reflux

for 30 m. The complex crude mixture was chromatographed on a silica gel column (eluent: AcOEt/light petroleum 1:1) to give **6**[7] (14 mg, 15%) as a colorless solid, mp. 203-204°C.

Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.28; H, 5.09; N, 14.91

Procedure for the Preparation of 7 from 4.- A solution of **4** (200 mg, 0.66 mmol) in CH_2Cl_2 (3 mL) was added to a solution of BF_3•Et_2O (140 mg, 1.0 mmol) in CH_2Cl_2 (1.5 mL), cooled to –15°C. To this mixture *t*-butyl nitrite (85 mg, 0.82 mmol) in CH_2Cl_2 (1 mL) was added. The mixture was stirred at 5°C for 15 minutes, then the precipitate was collected and heated at 130°C for 40 minutes. The crude product was extracted with 99:1 mixture of $CHCl_3$/TEA (15 mL) and the extract was washed with 12% aqueous HCl (3 mL). The organic layer was separated, dried ($MgSO_4$) and evaporated to give 160 mg (80%) of **7** as a white solid, mp. 175-176°C, pure as shown by its ^{1}H-NMR spectrum.

Anal. Calcd for $C_{15}H_{14}FN_3O_3$: C, 59.40; H, 4.65; N, 13.85: Found: C, 59.31, H, 4.49; N, 14.01

Procedure for the Preparation of 10 from 8.- To a solution of **8** (48 mg, 0.2 mmol) in 50% HBF_4 (1.25 mL), cooled at 0°C, was added a 2M aqueous solution (0.5 mL) of $NaNO_2$ dropwise. After 15 m, the addition of THF (1.5 mL) resulted in the precipitation of a solid, which was collected and dried *in vacuo*. It was then heated at 140°C for 30 minutes. The crude product was dissolved in 99:1 mixture of $CHCl_3$/TEA (10 mL) and the extract was washed with 12% aqueous HCl (3 mL). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give 35 mg (75%) of **10** as a white solid, mp. 155°C, *lit.*[5] 155-156°C, pure as shown by its ^{1}H-NMR spectrum.

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A FACILE SYNTHESIS OF DISULFIDES BY OXIDATION OF THIOLS WITH *bis*(TRICHLOROMETHYL) CARBONATE AND TRIPHENYLPHOSPHINE OXIDE

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Disulfides are useful intermediates because of their use in a variety of chemical transformations.[1,2] They are also important organic compounds in their own right being incorporated in molecules of biological interest.[3] Numerous methods have been reported for the preparation of disulfides, such as the reaction of sodium disulfide with haloalkanes,[4] the oxidation of thiols,[5] oxidation of sodium alkyl thiosulfate by hydrogen peroxide,[6] reductive coupling of sulfonyl chlorides by piperidinium tetrathiotungstate,[7] sodium cyanoborohydride,[8] aluminium triiodide,[9] etc. However, these methods are commonly used in research laboratories and cannot be applied in industry because the reagents are expensive and/or the yields are low. Triphenylphosphine is used in the stoichiometric amount on an industrial scale in the Wittig reaction to prepare compounds such as vitamin A, and is thus oxidized to triphenylphosphine oxide. Since the extremely stable triphenylphosphine oxide has only few uses, and can be disposed of only with difficulty, there have been numerous attempts to reduce it to triphenylphosphine. Direct reduction using strong reducing agents such as alanates and silanes is too costly. Although chlorination of triphenylphosphine oxide with the less costly phosgene[10] gives triphenylphosphine dichloride, it is still an economically unsatisfactory process. In addition, phosgene is a highly toxic and dangerous gas and thus its transportation and storage pose considerable dangers.