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DEVELOPMENT OF METHODOLOGY FOR THE RAPID INCORPORATION OF CARBON-13 into 1,2,4-TRIAZOLO SYSTEMS FROM CARBON DIOXIDE

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ABSTRACT: An in situ production of C-13 acetyl chloride and subsequent reaction with amidrazones affords anxiolytic 1,2,4-triazolobenzodiazepines in reaction times suitable for labelling with carbon-11 ($t_{1/2}$=20.4 min).

The development of novel methods to label biologically active molecules with short lived isotopes (e.g. ^{11}C $t_{1/2}$=20.4 min, ^{18}F $t_{1/2}$ = 110 min) for in vivo positron emission tomographic studies is an area of great interest in radiopharmaceutical chemistry[1]. Indeed, several benzodiazepine receptor agonists or antagonists (e.g. flunitrazepam and flumazenil) have been labelled, and studied in vivo; however, all suffer from the placement of the isotopic label at a metabolically unstable position[2,3]. In light of this, we became interested in the synthesis of a carbon-11 benzodiazepine receptor probe that would be free from the complications of circulating metabolites, namely incorporation of the label into a biologically stable position. This paper describes a rapid synthesis of 8-chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine 3 (alprazolam) from carbon-13 carbon dioxide whereby the enriched center was incorporated into the heteroaromatic 1,2,4 triazolo-system.

Triazolobenzodiazepines (e.g. alprazolam) have been prepared using a variety of methods[4]. Indeed several acylating agents based on the acetate fragment were screened, in the course of this work, to determine the optimal two carbon agent to carry the isotopic label in synthesis times of

less than 3-4 half-lives of carbon-11. To the best of our knowledge, acetylchloride has not been reported for the synthesis of the 1-methyl-6-phenyl-triazolobenzodiazepine alprazolam 3. Contrary to several one pot reactions screened[5], the two pot in-situ production of acetyl chloride offered the advantage of its volatility for a facile distillation into reagent 1. This two-pot system was necessary since a one pot reaction required a time consuming purification of the intermediate 2 prior to cyclization.

In particular we wish to report a rapid production of the carbon-13 enriched 1-methyl-6-phenyl triazolobenzodiazepine 3 starting from amidrazone 1 and in-situ produced carbon-13 acetylchloride via a simple, high yield process potentially suitable for an automated ^{11}C-alprazolam (3) synthesis. The process involves in order (scheme): i) carbonation of methylmagnesium bromide (0.6 mmol in ether) with carbon-13 carbon dioxide at room temperature (2 min); ii) production[6] and nitrogen gas assisted codistillation of carbon-13 acetylchloride and THF from (i) by the action of phthalolyl dichloride (3.5 mmol) and dimethyl formamide (3.5 mmol) at 84^{o}C (12-13 min); iii) trapping of acetyl chloride (0.6 mmol) by 1 and Hunigs (0.6 mmol) base at 0^{o}C; iv) evaporation and thermal cyclization (T>200^{o}C) (12-15 min). Thus, the above sequence allowed the incorporation of carbon-13 into the 1,2,4-triazolo system of 3 in approximately 30 min, permitting time for further modifications. Thus required labelled triazolobenzodiazepine 3 was obtained in four steps from the known amidrazone[4] 1 by treatment with enriched acetyl chloride[6] produced from enriched carbon dioxide followed by thermal cyclization (84% overall yield)[7]. The percent enrichment was determined by the integral ratio method and found to be 94.3%[8,9].

The above mentioned method should prove applicable to 1-substituted 1,2,4 triazoles which can be derived from the appropriate amidrazone and volatile acid chloride. Carbon-11 studies have been undertaken and will be reported with the above experimental details elsewhere.

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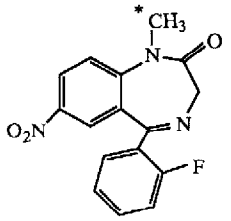
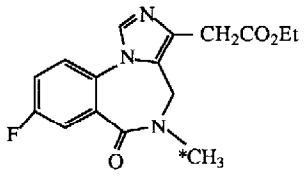
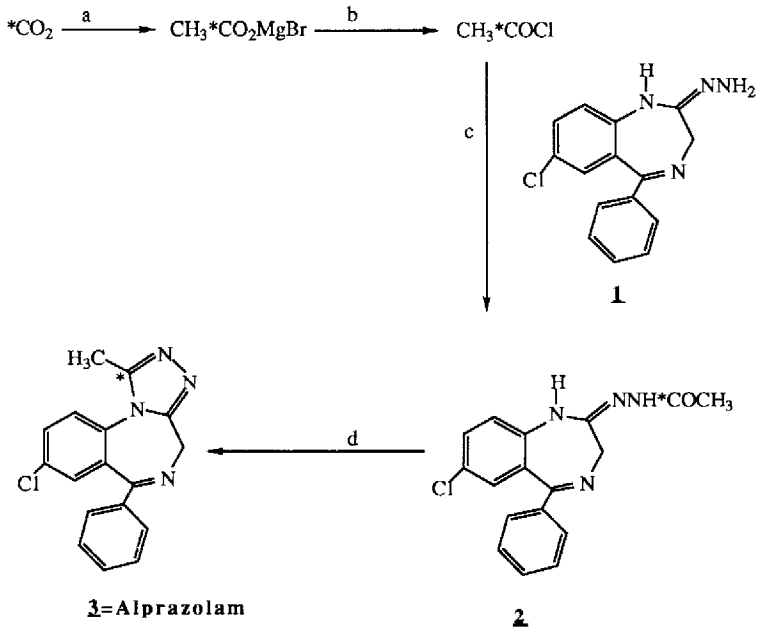


Flunitrazepam



Flumazenil

Scheme



* Denotes enriched center

Reagents: a) CH_3MgBr/Et_2O, rt; b) pthalolyl dichloride, dimethyl formamide, THF, 84 °C; c) NNN-diisopropylethylamine, 0 °C; d) t > 200 °C, 2 mm Hg

References and Notes.

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3. C. Halldin, S. Stone-Elander, J. Thorell, A. Persson, G. Sedvall, J. Nucl. Med. **(1988)**, 29 (5) 931.
4. K. Meguro, H. Tawada, H. Miyano, Y. Sato, Y. Kuwada, Chem. Pharm. Bull. (Tokyo), **(1973)**, 21 2382.
5. Among several two carbon species used for the acylation were s-phenylthioacetate, triethylorthoacetate, sodium acetate/isobutyl-chloroformate, sodium acetate/1,1'-(carbonyldioxy)-dibenzotriazole, and ethylacetimidate.
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7. Yield reflects isolated and purified product.
8. R.S.P. Hsi, W.T. Stolle, J. Labelled Compd. Radiopharm. **(1981)**, 18 (6) 881.
9. M.p. 223-225°C. ^{1}H-nmr (300 MHz) ($CDCl_3$) δ2.65 (d, 3H, $J_{^{13}C-H}$=7.3 Hz, CH_3), 4.10 (d, 1H J=12.9 Hz C_4-H), 5.50 (d, 1H, J=12.9 Hz, C_4-H). ^{13}C-nmr (300 MHz) ($CDCl_3$) δ 149.87 (enriched center) M.S. (EI 70ev) 309 (m^+).

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