NOTE

SYNTHESIS OF CARBON-14 AND CARBON-13 LABELED 3-METHYL-6-[3-(TRIFLUOROMETHYL)PHENYL]-1,2,4-TRIAZOLO[4,3-b]PYRIDAZINE

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SUMMARY

3-Methyl-6-[3-(trifluoromethyl)phenyl]-1,2,4-triazolo[4,3-b] pyridazine (4), currently being evaluated as a potential anxiolytic agent was synthesized, labeled with carbon-14 in the 3-position of the triazolo nucleus. The product was obtained in 67% radiochemical yield with specific activity of 13.5 mCi/mmol and radiopurity of greater than 99%. The carbon-13 labeled compound was also synthesized for absorption and metabolism studies.

Key Words: 3-Methyl-6-[3-(trifluoromethyl)phenyl]-1,2,4-triazolo[4,3-b] pyridazine, Anxiolytic Agent, Carbon-14, Carbon-13

INTRODUCTION

Initial screening has indicated that 3-Methyl-6-[3(trifluoromethyl)-phenyl]-1,2,4-triazolo[4,3-b]pyridazine (4) is a promising anxiolytic agent.[1] Considerable interest has been generated due to the greater separation between the therapeutic dose and the dose inducing neurological deficit (ataxia and motor incoordination) with 4 as compared to benzodiazipine reference agents.[2] In order to facilitate the studies on body distribution and metabolic pathways, the synthesis of a labeled drug was required. This was achieved by introduction of a labeled carbon in the triazolo nucleus of the molecule.

RESULTS AND DISCUSSION

Several routes toward the synthesis of 3-methyl-6-[3-trifluoromethyl)-phenyl]-1,2,4-triazolo[4,3-b]pyridazine (4) have been reported.[3] These methods require an excess of acethydrazide which would not be readily applicable to this

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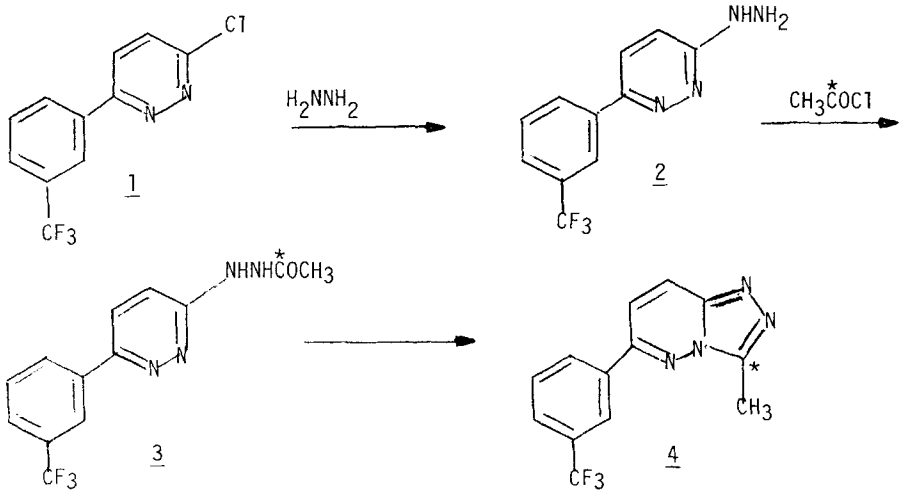
isotopic preparation. Conditions were established which facilitated optimum use of acetyl-1-^{14}C-chloride to prepare the labeled intermediate (3). Yields obtained by these modified procedures represent a two-fold improvement over reported procedures. In addition to improved yield, elimination of unnecessary reagents allowed for a simplification of method and reduction in overall cost.

The synthesis is a straightforward two-step procedure starting with 3-chloro-6-[3-(trifluoromethyl)phenyl]pyridazine[4], (1). The 3-hydrazino-6-[3-(trifluoromethyl)-phenyl]pyridazine[3], (2), was obtained in 84% yield from the reaction of 1 with hydrazine hydrate.

The label was introduced in the last step by the reaction of acetyl-1-^{14}C chloride with an excess of 2 to give the labeled product 4 in 67% radiochemical yield. The specific activity was 48.4 μCi/mg (13.5 mCi/mmol) with a radiochemical purity of greater than 99% as determined by thin layer chromatography.

The carbon-13 analog was prepared in an identical manner.

SYNTHETIC SCHEME



EXPERIMENTAL

Melting points were determined on a Mel-Temp Capillary melting point apparatus and are uncorrected. The NMR spectrum was obtained with a Varian Model HA-100 spectrometer. TLC's were run two dimensionally on Brinkman F254 silica gel precoated plates. The plates were developed using ethyl acetate-methanol

(9:1) for one development and toluene-methanol (7:3) orthogonally for the second development. Radioactivity was visualized by radioautography and the radioactive areas were scraped and counted in 1 cm segments using a Beckman LS-250 Liquid Scintillation Spectrometer.

3-Hydrazino-6-[3-(trifluoromethyl)phenyl]pyridazine (2)

To a rapidly stirring suspension of 17.7 g (68.4 mmol) of 3-chloro-6-[3-(trifluoromethyl)phenyl]pyridazine in 190 mL of n-butanol was added dropwise 34 mL (690 mmol) of 95% hydrazine hydrate. On completion of the addition, the reaction mixture was heated at reflux with stirring for 18 h. On cooling, the solvent was removed in vacuo and the gelatinous residue suspended in 900 mL of water and stirred vigorously for 0.5 h. The solid was filtered and allowed to air dry. The resulting solid was treated with petroleum ether in a Soxhlet apparatus for three days. The extraction gave 14.7 g (84.3%) of tan solid, m.p. 171°-174°;[5] IR (KBr) 6.22μ; ^{1}HNMR (DMSO-d_6) δ 3.56 (broad, H_2O), 4.46 (broad,3H), 7.20 (d,1H; J = 8Hz), 7.66 (m, 2H), 8.02 (d, 1H, J = 8Hz), 8.38 (m, 2H).

Anal. Calcd. $C_{11}H_9N_4F$ .1/4 H_2O: C, 51.07%; H, 3.60%; N, 21.66%, F, 22.03%

Found: C, 51.05%; H, 3.87%; N, 21.20%; F, 22.18%

(KF=1.01%)

3-Methyl-6-[3-(trifluoromethyl)phenyl]-1,2,4-triazolo[4,3-b]pyridazine-3-^{14}C (4)

To a stirred suspension containing 5.68 g (22.3 mmol) of anhydrous 3-hydrazino-6-[3-(trifluoromethyl)phenyl]pyridazine (2) in 135 mL dioxane was added dropwise a solution containing 871.5 mg (11.15 mmol) of acetyl-1-^{14}C-chloride (New England Nuclear, specific activity 13.5 mCi/mmol) in 20 mL dioxane over 0.5 h. The reaction mixture was heated at reflux for 8 h, cooled and the 3-hydrazino-6-[3-(trifluoromethyl)phenyl]pyridazine hydrochloride filtered from the mixture. The filtrate was evaporated to dryness in vacuo to a light brown solid. Recrystallization from isopropanol gave 2.0666 g (66.6%) of 4 as a light brown solid, m.p. 190.5°-191.2°[6]. The specific activity was 48.4 μCi/mg. Chemical and radiochemical purity by two dimensional thin layer chromatography showed only a single spot and radiopurity was found to be greater than 99%.

3-Methyl-6-[3-(trifluoromethyl)phenyl]-1,2,4-triazolo[4,3-b]pyridazine-3-^{13}C (4)

To a stirred suspension containing 6.48 g (25.5 mmol) of 2 in 140 mL dioxane was added dropwise a solution containing 1.00 g (12.7 mmol) of acetyl-1-^{13}C-chloride (Merck and Co., 90 atom % ^{13}C) in 20 mL dioxane over 0.5 h. The reaction mixture was heated at reflux for 8 h, cooled and the 3-hydrazino-6-[3-(trifluoromethyl)phenyl]pyridazine hydrochloride was filtered from the mixture. The filtrate was evaporated to dryness *in vacuo* to give a light brown solid. Recrystallization from isopropanol gave 2.59 g (73.1%) of gold crystals, m.p. 194.4°-195.0°[6]; m/e 279 (M^+): IR (KBr) 6.45μ; ^{1}HNMR (DMSO-d_6/CCl_4) δ 2.80 (m, 3H,) 7.96 (m, 3H), 8.42 (m, 3H). ^{13}CNMR shows an intense peak at 146.5δ.

Anal. Calcd. $C_{13}H_9N_4F_3$: C, 56.13%; H, 3.26%; N, 20.14%; F, 20.49%

Found: C, 55.82%; H, 3.37%; N, 20.18%; F, 20.50%

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5. Albright et al, ref. 3 give m.p. 160-164°C for the crude compound. The compound was used without purification and no analytical data were reported.

6. Albright et al ref. 3 give m.p. 193-194°C for the unlabeled compound.

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