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A FACILE SYNTHESIS OF MUSCIMOL

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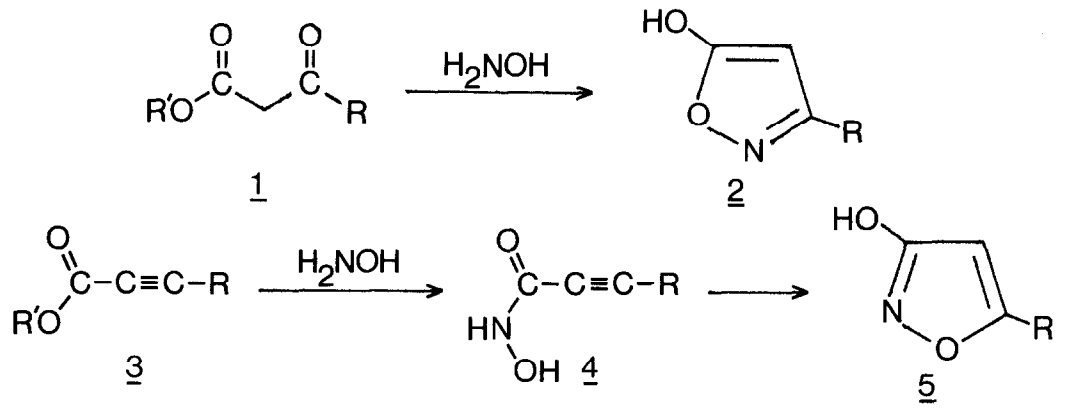
Abstract. The psychoactive isoxazole muscimol 10 has been synthesized in three steps from propargyl chloride.

We wish to report a facile, three-step synthesis of muscimol 10, a potent agonist of the neurotransmitter γ-aminobutyric acid[1]. Because of its high affinity for the receptor for γ-aminobutyric acid in the brain, muscimol 10 has proved invaluable for investigations into various aspects of the neurochemistry of γ-aminobutyric acid[1]. As part of a program to develop a series of "pro-drugs" based on muscimol we required gram quantities of this isoxazole and, thus, sought an efficient method for its preparation. Following the isolation of muscimol from Amanita muscaria[2], a number of syntheses have been reported[3]. A survey of the existing methods showed most required either a moderate number of steps or starting materials not readily available. Unable to reproduce the yields reported in a particular synthesis, we sought to develop a new, short synthesis of muscimol using inexpensive starting materials. The synthesis outlined below will be useful to those undertaking biological studies which may otherwise be precluded by the current exorbitant cost of this compound.[4]

The construction of the 5-alkyl-3-hydroxyisoxazole nucleus 5 of muscimol presents unusual problems in isoxazole synthesis that have led to a variety of solutions.[3] A common approach to isoxazoles, involving the reaction of hydroxylamine with β-dicarbonyl compounds, in this case a β-keto ester 1, yields instead of the desired isoxazole 5 its structural isomer 2 as a result of the initial attack of hydroxylamine at the more electrophilic ketone carbonyl. We felt that an efficient approach to the isoxazole nucleus 5 would involve the cyclization of an α,β-acetylenic hydroxamic acid 4, derived from the corresponding ester 3, according to the ring closure rules developed by Baldwin[5]. Indeed, Iwai and Nakamura[6] have reported that α,β-acetylenic esters 3 react with hydroxylamine under basic conditions and cyclize to 3-hydroxy-5-substituted isoxazoles.

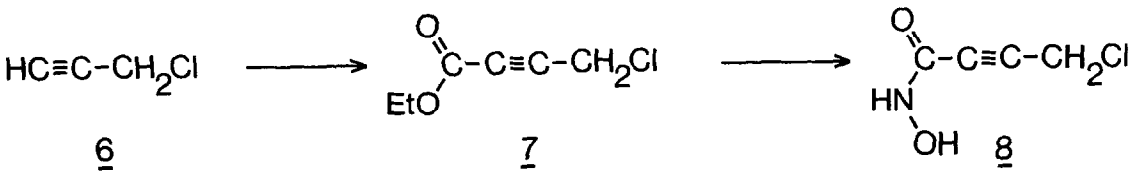
The lithium acetylide of propargyl chloride[7] 6 in ether at -40° was treated with a 2-fold excess of ethyl chloroformate to afford ethyl 4-chlorotetrolate 7 as a colorless liquid in 70% yield after distillation[8] (bp, 84°C/10mm; lit.[9], 86°C/5mm). While the method



of Iwai and Nakamura[6] led to the conversion of ethyl tetrolate 4 (R=CH_3) into 3-hydroxy-5-methylisoxazole 5 (R=CH_3) in 80% yield in our hands, no isoxazole product could be isolated when the reactive 4-chlorotetrolate 7 was treated under identical conditions. However, the desired 5-chloromethyl-3-hydroxyisoxazole 9 was isolated in a 41% yield as a white solid (mp 97-100°C; lit. [3a], 97-100°C) by adding the chlorotetrolate 7 to an aqueous methanolic solution of basic hydroxylamine at -35°, followed 15 min later by a pH 7, aqueous buffer so as to give a final pH between 8.5 and 9. After 10 hours at room temperature the chloromethylisoxazole 9 was isolated and recrystallized from hexane. The hydroxamic acid 8,[10] while not normally isolated, was prepared by quenching the above reaction with 6N HCl instead of a pH 7 buffer. The subsequent cyclization of the pure hydroxamic acid 8 at various pH values showed that at pHs greater than 10.5 or less than 6.5 none of the isoxazole 9 could be detected by tlc with the concomitant formation of a variety of polar or non-polar side-products, respectively. The yield of isoxazole 9 maximized between pH 8.5 and 9.0, in the region of the pK_a expected for such a hydroxamic acid[11].

The conversion to muscimol 10 was accomplished by heating the chloromethylisoxazole 9 in a solution of methanol saturated (at 0°) with anhydrous ammonia to 50° for 5 hours in a sealed flask. Two successive chromatographies of the reaction product on Dowex-1x8 (with elution of the first column by 2M HOAc and the second by a 0-2M linear HOAc gradient) afforded muscimol 10 as a white solid in 65% yield (mp 170-172°C (dec.), lit,[3d,e] mp 170-172°C (dec.), 172-174°C (dec.)). This substance was shown to be identical (NMR, IR, MS, tlc) with an authentic sample[12]. A side-product (mp 190-194°C) isolated in 5-10% yield, was shown to be the bisisoxazole 11[13]. The aminolysis conditions (methanolic NH_4OH, 100°, 10 hours), reported [3c] to afford muscimol in a high yield from the same chloromethylisoxazole 9 led, in our hands, to poor yields of the desired product.

In a parallel approach to muscimol, we sought to prepare the phthalimide ester 13. However, all attempts to prepare this ester either via (a) the carboethoxylation of N-propargylphthalimide 12 (mp 152-153°C, lit.,[14] 147°C) using a variety of reagents and conditions or (b) the treatment of the chlorotetrolate 7 with potassium phthalimide failed to afford the desired ester 13. In conclusion, using the procedures described here, we have prepared muscimol 10 in gram quantities in an overall yield of 18.7% starting from propargyl chloride 6.



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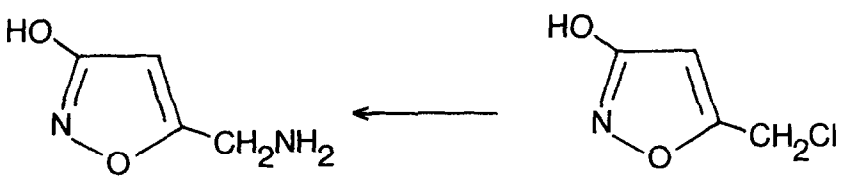

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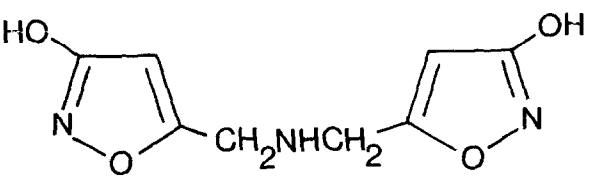

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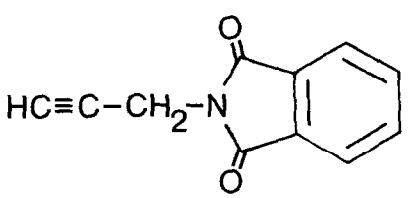

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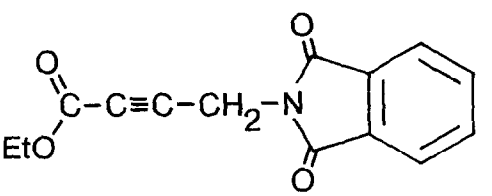

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10. All compounds showed spectral data consistent with their structures. The hydroxamic acid 8 showed the following data: anal. calc: C, 35.98; H, 3.02; N, 10.49; Cℓ, 26.55; found: C, 36.34; H, 3.12; N, 10.81; Cℓ 26.28; mp 100-102°C; IR(KBr): 3300-2600, 2270, 2230, 1650, 1625, 1575 cm^{-1}; MS (70eV): 135, 133, 119, 117, 103, 101, 75, 73, 66.

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12. We wish to thank Dr. Neville Finch, Ciba-Geigy Corp., Summit, N.J., U.S.A. for generously providing us with an authentic sample of muscimol.

13. NMR: identical to muscimol, IR: almost identical to muscimol, MS: 211(M^+), 127, 113, 98.

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