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Synthesis of Cyclohexane Carboxylic acid 1-(phenyl amino)-methyl ester: intermediate important in the production of carfentanil

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A B S T R A C T

In this process synthesis of Cyclohexane Carboxylic acid, 1-(phenyl amino) - methyl ester *is described. These intermediate* important *can be utilized in the production of commercial synthetic analgesics carfentanil*. In summary, we have developed an efficient and original procedure for the synthesis of carfentanil and remifentanil using the trichlorocarbinols reaction. This strategy in mild conditions is suitable for the synthesis of novel structurally varied l-opioid agonists and should prove valuable in library synthesis.

Keywords: Carfentanil, Cyclohexane Carboxylic acid 1-(phenyl amino) - methyl ester

A R T I C L E I N F O

CONTENTS

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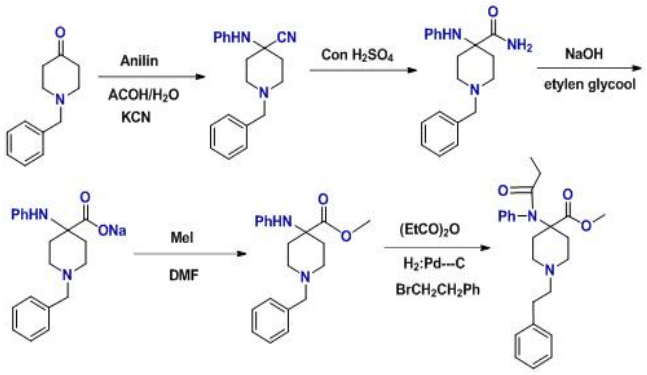
1. Introduction

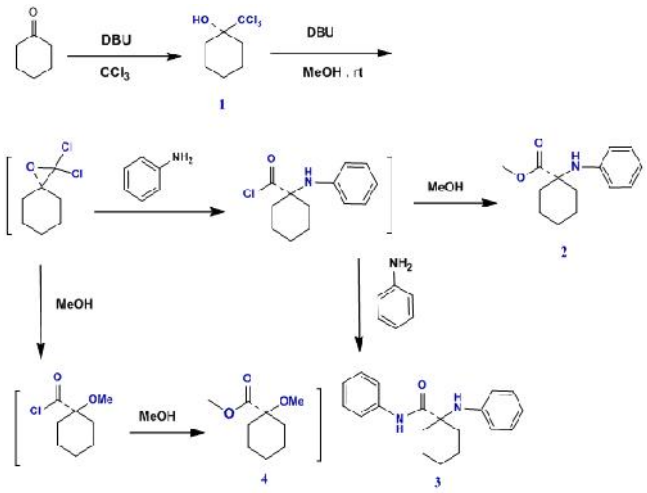
Carfentanil or carfentanyl is an analogue of the popular synthetic opioid analgesic fentanyl, and is one of the most potent opioids known [1-2]. Carfentanil was first synthesized in 1974 by a team of chemists at Janssen Pharmaceutica which included Paul Janssen [3]. It is marketed under the trade name Wildnil as a general anaesthetic agent for large animals such as rhinoceros or elephents [4]. The standard synthesis of these drugs consists of eight steps among which is the preparation of a key α-aminonitrile via Strecker reaction [5] .This α-substituted nitrile must be hydrated and the obtained amide hydrolyzed, the aniline acylated and finally the acylaminoacid must be methylated. This reaction sequence is not very powerful

because α-substituted nitriles are known to be resistant to hydration [6] (Scheme 1).



Scheme 1: The standard synthesis of carfentanil via Strecker reaction

In this Letter we used DBU with CHCl3 without solvent provided a quantitative yield of the trichlorocarbinol 1. By adding DBU in methonol gem-dichlorooxirane is probably formed and is then attacked in an SN2 fashion by aniline to give an amino acyl chloride intermediate which reacts with methanol to give the Cyclohexane Carboxylic acid, 1-(phenyl amino)- methyl ester 2 (modified Corey–Link reaction) (Scheme 2) .



Scheme 2: Synthesis of Cyclohexane Carboxylic acid, 1-(phenyl amino) - methyl ester via the Corey−Link Reaction

Reaction of 1 with aniline and DBU in methanol successfully gave 2 along with varying amounts of the amide 3 and the methoxy ester 4. Under optimized conditions (1.5 equive of aniline, 1 ml ethanol) the isolated yield of 2 was about 85% and the byproducts, mostly 3 and 4 were removed in subsequent processing. Trichloro methyl carbinols 1 are useful synthetic intermediates [7] with many applications and are most commonly prepared by the base-promoted addition of chloroform to aldehydes and ketones but to date relatively strong bases have been employed [8]. Using 1 equiv of DBU or DBN with a slight excess of $CHCl_3$ without solvent provided a quantitative yield of the trichlorocarbinol 1. Using a larger excess of chloroform resulted in longer reaction times, but similar yields could be achieved Catalytic amounts of DBU were much less effective, suggesting that some decomposition of the amidine had occurred.

2. Experimental

All chemicals were purchased from Merck and Sigma-Aldrich companies and used without any further purification. Melting points were recorded on a Buchi B-540 apparatus. Infrared (IR) spectra were recorded on an ABB Bomem model FTLA200-100 instrument. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300 and 75 MHz using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported relative to TMS, and coupling constants (J) are reported in hertz (Hz).

2.1. Preparation of 1- (Trichloromethyl) cyclohexanol (1) :

To a mixture of cyclohexane (200 µL, 1.97 mmol) and chloroform (310 µL, 3.94 mmol) was added dropwise under nitrogen 1 equiv of DBU (300 µL, 1.97 mmol). The reaction was stirred for 24 h and then diluted with chloroform (20 mL) and washed with 2 N HCl (3×10mL) to remove the catalyst. The organic phase was then dried (Na_2SO_4) and evaporated to yield the trichlorocarbinol(78% yield).

2.2. Preparation of Cyclohexane Carboxylic acid 1-(phenyl amino) - methyl ester (2)

To a suspension of 1 (157 mg, 0.51 mmol) and aniline (100 mg, 1.5 mmol) in EtOH (1 mL) 1, 8 diazabicyclo [5.4.0] undec-7-ene (DBU) (0.4 mL, 2.63 mmol) was added and the resulting reaction mixture was stirred overnight. Diethyl ether was added (8 mL) followed by saturated aqueous ammonium chloride solution (4 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to yield a crude mixture that was purified by flash chromatography (hexane/EtOAc; 4:1) (130 mg, 89% yield).

^{1}H NMR (400 MHz, CDCl3): δ = 1.30-1.51 (m, 6H), 1.55-2.12 (4H, m), 4.50 (br s, 1H), 3.65 (s, 3H), 7.01 (t, J = 7.1 Hz, 1H), 7.14 (d, J = 8.1 Hz, 2H), 7.17 (t, J = 8.1 Hz, 2H).

^{13}C NMR (100 MHz, CDCl3): δ=19.8, 26.6, 26.1, 63, 53, 118.4, 118.5, 130.1, 146.7, 173.

3. Results and Discussion

The reaction protocol for formation of the trichlorocarbinols is exceptionally simple: reactions are conducted at ambient temperature and pressure, and in the absence of solvent. Washing with water removes the amidine and gives the product in high yield, which in many cases is pure by $^{1}H/^{13}C$ NMR. This probably

represents the simplest and best method to date to prepare these useful compounds. In summary, we have developed an efficient and original procedure for the synthesis of carfentanil and remifentanil using the trichlorocarbinols reaction. This strategy in mild conditions is suitable for the synthesis of novel structurally varied l-opioid agonists and should prove valuable in library synthesis. As well, being straightforward, rapid and efficient it could be used for the synthesis of radio labeled fluoroalkyl derivatives of carfentanil/ remifentanil.

4. Acknowledgment

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