Convenient Procedures for Synthesis of Ciproxifan, a Histamine H_3-Receptor Antagonist

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Summary

Cyclopropyl 4-(3-(1*H*-imidazol-4-yl)propyloxy)phenyl methanone (ciproxifan) is a novel reference antagonist for the histamine H_3 receptor. Despite the former Mitsunobu reaction the actual key reaction for preparation based on S_NAr for acylated fluoroaromatics with an additional cyclization in a one-pot procedure needs no chromatographic purification steps and results in good yields.

Ciproxifan (cyclopropyl 4-(3-(1*H*-imidazol-4-yl)propyloxy)phenyl methanone) is a novel reference histamine H_3-receptor antagonist with high potency and selectivity [1]. This compound was obtained by Mitsunobu reaction of imidazolyl trityl-protected 3-(1*H*-imidazol-4-yl)propanol prepared in four steps from urocanic acid with cyclopropyl 4-hydroxyphenyl methanone and following acidic deprotection (Figure 1) [2,3]. Although this reaction sequence could be performed in total yield of about 80% the phenol precursor had to be prepared by Friedel-Crafts-alkylation of phenol or by ether cleavage of the corresponding commercially available 4-methoxyphenyl methanone. Not counting the high costs of the educts including the coupling reagents, the reaction needed two separate chromatographic separations that made this procedure work consuming and unattractive for industrial synthesis. Alternative methods like Williamson synthesis with 4-(3-chloropropyl)-1*H*-imidazole failed because of intramolecular cyclization [4].

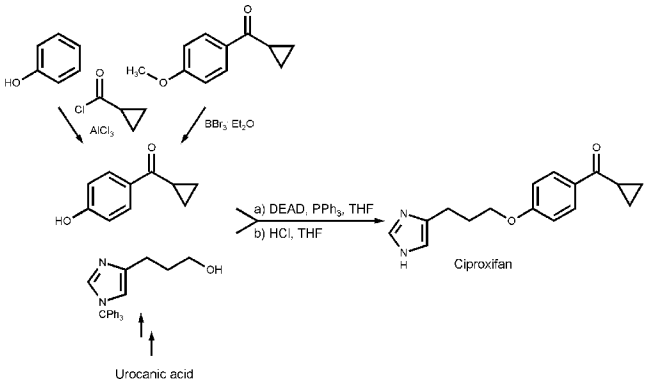

Figure 1. Synthesis of ciproxifan given in the literature [3].

In a first attempt nucleophilic exchange reaction was performed with trityl-protected 3-(1*H*-imidazol-4-yl)propanolate and cyclopropyl 4-fluorophenyl methanone in toluene. Work up by extraction, detritylation, and additional extraction resulted in a 40% overall yield of the desired product (Figure 2, I). Despite the reduced yields total costs and work expenditure of this procedure were much lower than that of the Mitsunobu way strategy.

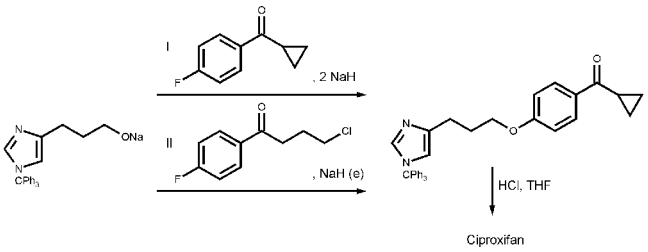

Figure 2. Improved synthesis procedures for ciproxifan.

Further improvement was performed with the introduction of 4-chloro-4′-fluorobutyrophenone, a versatile, moderately priced synthon well known in the synthesis of neuroleptics, e.g., haloperidol [5]. Reacting this synthon with the alcoholate in an excess of sodium hydride resulted in the same intermediate as described before in the same yield (Figure 2, II). A similar work-up procedure also resulted in 40% overall yields. In this one-pot synthesis the nucleophilic exchange reaction and the formation of the cyclopropyl moiety [6] took place simultaneously. The cyclopropyl ketone moiety proved to be stable under both basic and acidic conditions applied. With larger batches (20–200 mmol) only traces of the corresponding 4-oxobutanol derivative were identified [7].

The improved synthesis procedure for ciproxifan using 4-chlor-4′-fluorobutyrophenone under basic conditions of S_NAr reactions is a simple cost-effective procedure, which can be carried out also in scaling up for industrial synthesis of larger amounts [8].

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Preparation Procedure

Freshly prepared sodium 3-(1-triphenylmethyl-1*H*-imidazol-4-yl)-propanolate (5 mmol) was heated with NaH (25 mmol, 60% suspension in mineral oil) and 4-chloro-4′-fluorobutyrophenone (10 mmol) in toluene (40 ml) for 48 h under reflux. The mixture was evaporated to dryness, 2N HCl (30 ml) was carefully added as well as THF (10 ml), and heating at

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70 °C was continued for 2 h. This mixture was concentrated under reduced pressure, triphenyl methanol filtered off, and the residue extracted with Et_2O (3×20 ml). The aqueous phase was basified with potassium carbonate and extracted with CH_2Cl_2 (3×20 ml). The combined organic extracts were dried (Na_2SO_4), evaporated, transformed into hydrogen maleates and crystallized from Et_2O/EtOH.

The reaction of sodium 3-(1-triphenylmethyl-1*H*-imidazol-4-yl)propanolate (5 mmol) with cyclopropyl 4-fluorophenyl methanone (7.5 mmol) was performed as described above with NaH (10 mmol) being added in two portions.

The analytical data of the compounds obtained (mp, ^{1}H NMR, EI-MS, IR, TLC-R_f) are in agreement with those of ciproxifan prepared as described in literature [3].

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