A New Chemoselective Synthesis of Brombuterol

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Abstract: A practical method for the synthesis of brombuterol [1-(4-amino-3,5-dibromophenyl)-2-(tet-butylamino)ethanol] in high overall yield is described starting from 4'-aminoacetophenone using a new chemoselective route.

Key words: β-agonists, chemoselective, bromination, brombuterol, clembuterol

Clembuterol (1) is licensed as a bronchodilator in veterinary and human medicine (Figure 1).1,2 However, this substance increases muscle mass in cattle,1 suggesting increased protein synthesis or decreased protein degradation or that both biochemical processes operate. A significant reduction in the spontaneous ingestion of food and water in the animals evaluated has also been noted.3 High doses can result, however, in the accumulation of this drug in various organs in animals, which can result in cases of poisoning in humans as a result of the ingestion of liver and other contaminated parts from animals treated with clembuterol.3 The clinical symptoms observed were tremors, headache, tachicardia, diarrhea, and, in some cases, heart failure.4

Figure 1

Legislation from health organizations in the USA and the European Union banned the indiscriminate use of clembuterol in matrixes for human consumption. However, in cases of fraud, meat producers resort to the use of the less easily detected brombuterol (2), a structural analogue of clembuterol (1), which is not commercially available, but can be obtained illegally in various countries (Figure 1). Currently, various analytical methods of high specificity and sensitivity for the detection of these and other β-agonists5 are available. A number of approaches to the synthesis of aminodihalophenylethylamines, including clembuterol and brombuterol, can be found in the literature, notably the papers by Keck and co-workers.6

In view of the legal and public health problems related to meat exports described and the fact that many South American countries are currently major meat producers, brombuterol (2) seemed an attractive synthetic challenge. The purpose would be to facilitate access to this illegal substance through a low-cost, direct synthesis approach, allowing laboratories involved in residue analysis easy preparation of brombuterol (2) as an analytical standard. Subsequent analysis through conventional gas chromatography–mass spectrometry would then afford facile detection and/or quantification of the compound in different biological matrixes. A synthetic scheme starting from 4'-aminoacetophenone (3) employing reaction methods well established in the literature with the aim of preparing brombuterol (2) in a limited number of steps was planned, involving, initially, bromination of 4'-aminoacetophenone (3).

Many methods for the α-bromination of aliphatic ketones are described in the literature.7 Three of these were evaluated in this work for the bromination of 4'-aminoacetophenone (3): molecular bromine,7 copper(II) bromide,8 and trimethylphenylammonium tribromide.9 Bromination reactions of 4'-aminoacetophenone (3) utilizing 3.0 equivalents of molecular bromine in acetic acid, dioxane, or chloroform as the solvent, or copper(II) bromide in ethyl acetate, yielded, on isolation, a complex mixture of products with the starting material predominating.

The best yields for our purposes were obtained with trimethylphenylammonium tribromide (Scheme 1). 4'-Aminoacetophenone (3) was reacted with three equivalents of trimethylphenylammonium tribromide in tetrahydrofuran using ethylene glycol to promote the formation of the ketal function of the aromatic ketone, with the aim of avoiding formation of adducts dibrominated at the position α to the ketonic carbonyl. After acidifying the medium with 2 M hydrochloric acid, two main products were obtained: 4'-amino-2,3,5'-tribromoacetophenone (5) and 4'-amino-3',5'-dibromo-2-chloroacetophenone (6) in 79% yield and 1:1 ratio by NMR. This fact can be rationalized by a nucleophilic substitution reaction of the bromine atom by the chloride ion during hydrolysis of the intermediate bromo ketal 4. The two α-haloacetophenones 5 and 6 have similar chromatographic behavior and could not be separated.

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and they were used as a mixture in subsequent chemical reactions.

We investigated the use of 3 M hydrobromic acid in the ketal hydrolysis in an attempt to avoid the formation of 6, however, this drastically decreased the yields of the desired product.

The ketones 5 and 6 were reduced with sodium borohydride\(^{10}\) in methanol affording the bromohydrin 7 and chlorohydrin 8 in a 1:1 ratio in quantitative yield. Treatment of the halohydrins 7 and 8 with excess tert-butylamine in methanol under reflux yielded the desired brombuterol (2) in 98% yield.

It is interesting to note that the results obtained with chemoselective bromination reactions of 4’-aminoacetophenone (3) in the presence of ethylene glycol with tetrahydrofuran as solvent, employing 1.0 equivalents of trimethylphenylammonium tribromide. Under such conditions 4’-amino-3’-bromoacetophenone (9) was formed exclusively in 93% yield (Scheme 2). The same reaction utilizing 2.0 equivalents of trimethylphenylammonium tribromide produced 4’-amino-3’,5’-dibromoacetophenone (10) in 95% yield. Such results show the greater reactivity of the aromatic ring in 4’-aminoacetophenone compared to the enol function formed in the process of the formation of α-haloacetophenones. This hypothesis was supported by deactivation of the aniline. When 4’-(pivaloylamo)acetophenone (11) was submitted to 1.0 equivalents of trimethylphenylammonium tribromide under reaction conditions similar to those described previously in this work for the chemoselective brominations, 2-bromo-4’-(pivaloylamo)acetophenone (13) was obtained in 95% yield using 3 M hydrobromic acid to open the bromo ketal intermediate 12 (Scheme 3).

In this work, brombuterol (2) was synthesized in better yields compared to other methods described in literature.\(^{6}\)

This illegal substance is not commercially available and, using our approach, health analytical laboratories for the control of toxic substances can detect brombuterol (2) in different types of biological matrixes using gas chromatography–mass spectrum techniques.
Melting points were determined using in a Melt-Temp apparatus. 

\(^1H\) and \(^{13}C\) NMR spectra were obtained in GEMINI-200 MHz spectrometer with TMS (δ = 0.00) as internal standard using as solvents CDCl₃, or MeOD. LR-MS were obtained in an Auto Specq, in EI mode at 70 eV and HRMS using a Varian MAT-CH7 instrument at 70 eV. All chemicals commercially available were purchased from Aldrich Co. (USA) or TermoVida (Rio de Janeiro, Brazil).

**Bromination with Trimethylphenylammonium Tribromide; General Procedure**

To a soln composed of 3 (0.405 g, 0.003 mol) or 11 (0.657 g, 0.003 mol), THF (30 mL) and ethylene glycol (15 mL), a soln of Me₆PHNBr₃ (3.0 equiv for the preparation of 5 and 6; 1.0 equiv for the preparation of 9; 2.0 equiv for the preparation of 10; 1.0 equiv for the preparation of 13) in THF (15 mL) was added via a cannula, with agitation, under an inert atmosphere and in an ice bath at 0 °C. The reaction of the progress was followed by TLC, until the starting material had been totally consumed. After 18–20 h, the mixture was acidified with 3 M HCl or 3 M HBr, until pH ~1, and agitation was continued for an additional 1 h. The mixture was then partitioned with EtOAc–hexane (2:1, 0.375 L), and the mixture kept under reflux for 22 h. The mixture was then partitioned with cyclohexane (2:1, 0.375 L), and the residue obtained was submitted to purification by flash column chromatography (30% EtOAc–hexane) to give a mixture of 7 and 8 (1:1) as a white powder; yield: 1.407 g (100%).

\[\text{HRMS (CI): calculated for C}_{13}H_{16}BrNO: 366.1071; found: 366.1321.}\]
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