An Improved Synthesis of (+)-2-Tropinone

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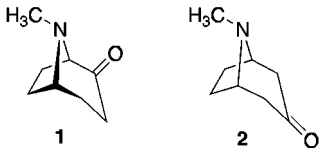
The tropane ring system (8-methyl-8-azabicyclo[3.2.1]-octane) is an important substructure in a number of natural products and synthetic compounds of biological and medicinal importance. As a result of the significance of the tropane ring system, the development of new synthetic methodology for the preparation of useful tropane precursors for the construction of more complex molecules continues to be an important field of study.[1−11]

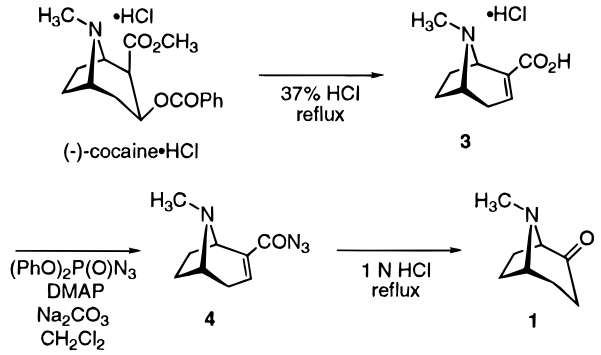
(+)-2-Tropinone (**1**) has long been recognized as a useful precursor in the preparation of many compounds of potential and actual biological interest.[12,13] Unfortunately, **1** is not as readily available as the *meso*-derivative 3-tropinone (**2**).[10,14−17] (+)-2-Tropinone (**1**) has classically been prepared by the degradation of (−)-cocaine.[15] However, the degradation process can be tedious and only affords a moderate overall yield of **1**. Alternatively, multigram quantities of the racemic compound (±-**1**) can be prepared by a variety of methods.[9,10,15,16]



As part of an ongoing program aimed at the synthesis of several enantiopure substituted tropanes, it became necessary to develop a practical route to (+)-2-tropinone (**1**). Herein we wish to report our improved two-step synthesis of **1** from (−)-cocaine.

As illustrated in Scheme 1, treatment of confiscated grade (−)-cocaine hydrochloride with concentrated hydrochloric acid under reflux afforded (−)-anhydroecgonine (**3**) in almost quantitative yield.[18] The acid **3** was then

Scheme 1



dried thoroughly under vacuum and ground into a fine powder. A suspension of the acid **3** in dichloromethane was treated with diphenylphosphoryl azide (DPPA) in the presence of 2.5 mol % of DMAP at room temperature for 2 days. This afforded the corresponding acyl azide **4**.[19] Since the acylation reaction was a heterogeneous mixture, grinding the acid **3** into a fine powder was found to facilitate complete conversion of the acid into the acyl azide **4**. In addition, when the reaction was performed without DMAP, the overall yield of the reaction was considerably lower.

The acyl azide **4** was not isolated or purified but was converted directly into the desired (+)-2-tropinone (**1**) *via* a Curtius rearrangement in refluxing acid.[19] Pure **1** was obtained in 65−84% overall yield from (−)-cocaine by distillation under high vacuum. Purification of the crude material by distillation was found to be preferable to that of column chromatography since **1** was usually obtained in a higher state of purity and as a result could be stored for longer periods of time without decomposition.

The variance in the overall yield of the sequence seemed to be dependent upon the quality of the confiscated (−)-cocaine. There was little variance in yield when the reaction sequence was performed on samples from the same batch of the confiscated material, while different batches of confiscated material gave varied yields of **1**. Presumably, this was due to the different concentrations of impurities and degradation products present in the confiscated material. However, this range in yield did not warrant purification of the confiscated (−)-cocaine prior to use, since some of the degradation products are useful intermediates in the conversion of (−)-cocaine into **1**.

In summary, the synthetic procedure described above is a direct method for the conversion of (−)-cocaine into (+)-2-tropinone (**1**) and avoids the isolation and purification intermediates. In addition, this method is amenable to both small-scale (1 g) and large-scale (10 g) preparation of **1** and provides material in a state of exceptional purity.

Experimental Section

All chemicals and reagents not otherwise noted were purchased from Aldrich Chemical Co. Dichloromethane was dried by distillation from CaH_2. Confiscated grade (−)-cocaine hydrochloride was provided by NIDA Drug Supply System, Research Technology Branch, National Institute on Drug Abuse.

(−)-Anhydroecgonine Hydrochloride (3). A solution of (−)-cocaine hydrochloride (34.0 g, 100 mmol) in concentrated

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hydrochloric acid (276 mL) was refluxed for 24 h. After the mixture was cooled to room temperature, it was diluted with H_2O (255 mL) and extracted with Et_2O (2 × 255 mL) to remove benzoic acid. The aqueous phase was then evaporated under vacuum to dryness. The white solid was further dried under vacuum at 100 °C for 24 h. This afforded crude **3** (20.0 g, 98%) which without further purification was used in the next step. An analytical sample was obtained by recrystallization from EtOH, mp 239−244 °C (lit. mp,[18] 240−244 °C). $[\alpha]^{21}_D = (-)-50.7°$ (*c* 2.0, H_2O).

(+)-2-Tropinone (1). To finely powdered **3** (20.0 g, 98.2 mmol) in a 2 L round bottom flask were added Na_2CO_3 (25.4 g, 240 mmol) and DMAP (305 mg, 2.50 mmol), and the vessel was sealed under an atmosphere of nitrogen. Dried CH_2Cl_2 (366 mL) was added to the flask followed by addition of DPPA (25.9 mL, 0.12 mol). The reaction mixture was stirred vigorously for 48 h. The solvent was removed under vacuum, and the resulting residue was then dissolved in H_2O (106 mL) followed by the careful addition of 1 N HCl (604 mL). The solution was then heated in a preheated oil bath (120 °C) for 35 min (until the carbon dioxide and nitrogen evolution ceased). The aqueous HCl was removed under vacuum, and the residue was made basic (pH 9.5−10.0) with a saturated solution of Na_2CO_3. The aqueous solution was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent was removed under vacuum. The resulting liquid was purified by vacuum bulb-to-bulb distillation (Kugelrohr). This afforded **1** (10.6 g, 78% yield) as a colorless liquid. The NMR and IR spectra of **1** were identical with those previously reported for (±)-2-tropinone.[9] $[\alpha]^{21}_D = (+)-23.3°$ (*c* 1.5, H_2O).

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