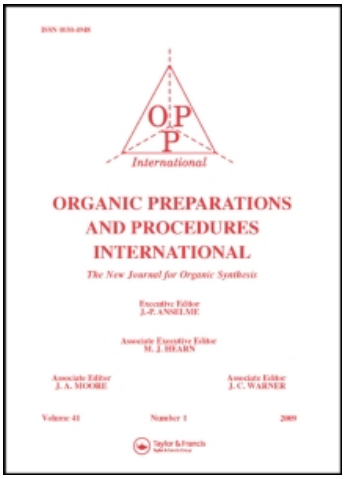

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A Simple and Convenient Synthesis of Triprolidine

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A Simple and Convenient Synthesis of Triprolidine

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Triprolidine (**3**)[1] is an anti-histamine drug belonging to 1,1-diaryl-2-propyleneamine class[1] having trade names *Actidil*™ and *Myodil*™. It is a very popular first-generation anti-histamine used for coughs and colds. In combination with *pseudo*-ephedrine, it is being sold under the brand name *Actifed*™. Recently Bolser,[2] Pratter, and Abouzgheib[3] reported that for coughs associated with the common cold, first-generation anti-histamine decongestants would be more effective than newer nonsedative antihistamines. This observation together with continuous demand for first-generation anti-histamines prompted us to search for nonhazardous commercially viable alternate synthesis of triprolidine.

The carbon-carbon double bond in propyleneamines such as *Acrivastine*,[4–7] *Pyrrobutamine*,[8,9] *Triprolidine*, *Zimeldine*[10] have been built by dehydration of corresponding alcohols[11–14] or by the Wittig method.[15] *n*-Butyllithium has been employed in both the Wittig condensation and in the preparation of the tertiary alcohol (*Scheme 1*) at around −70°C. However, large-scale preparations of these compounds employ the dehydration method rather than the Wittig method because no efficient method was available for preparation of the intermediates such as 2-(*N,N*-dialkylaminoethyl)triphenylphosphonium bromides and 2-aroylpyridines. Having developed commercially viable methods for the preparation of 2-(p-toloyl)pyridine (**1**)[16] and 2-(*N*-pyrrolidinoethyl)triphenylphosphonium bromide (**2**)[17] we now report the preparation of triprolidine (**3**) without the use of *n*-butyllithium.

The existing industrial scale preparation of triprolidine[11–14] involves the condensation of 2-bromopyridine with β-pyrrolidino-4-methylpropiophenone using alkyllithium at around −70°C followed by dehydration using sulfuric acid between 140

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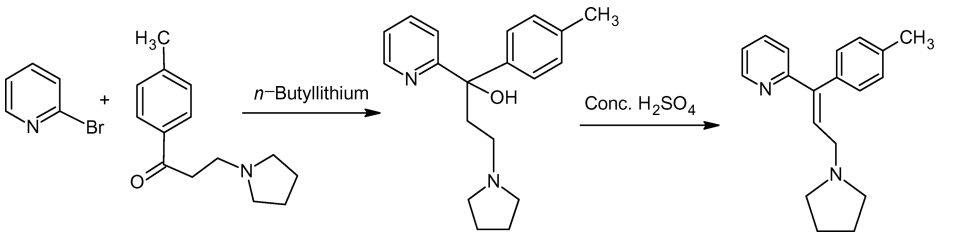
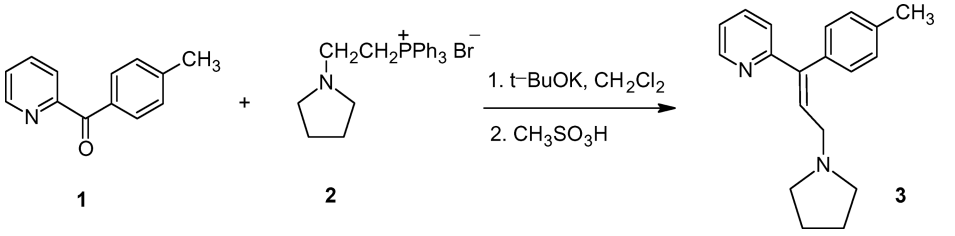


Scheme 1

and 160°C to give thermally more stable E-isomer. The disadvantages of this method are poor yields (about 30% overall yield from bromopyridine), use of alkyllithium at low temperatures (−70°C) and the use of large amounts of sulfuric acid (five volumes). The present method for the preparation of triprolidine involves the Wittig condensation of compound **1** with compound **2** using potassium *t*-butoxide in methylene dichloride (MDC) at around 10°C followed by isomerisation with methanesulfonic acid (*Scheme 2*). The Wittig condensation of compounds **1** and **2** had been performed using bases such as t-BuOK, sodium hydride, and sodamide in various solvents such as hexane, toluene, dimethylformamide, dichloromethane, etc. (*Table 1*). Combinations such as t-BuOK and MDC, NaH and DMF gave better results while all other combinations result in formation of either traces of product or no product at all. However, the relative ease of handling t-BuOK compared to NaH prompted us to use the first combination for the scale-up.



Scheme 2

The Wittig condensation led to a mixture of *E*,*Z*-isomers in a 1:2 ratio and simple heating of this mixture at 200°C for several hours did not alter the isomeric ratio. The existing dehydration and isomerization step using sulfuric acid is temperature-sensitive and gave inconsistent results. In contrast, replacement of sulfuric acid with methanesulfonic acid in the isomerization step did not affect the yield of the product or its purity even at a temperature of about 200°C. The crude *E*-isomer thus obtained was purified as its oxalate and then converted into triprolidine hydrochloride using a saturated solution of HCl gas in isopropanol.

In conclusion, we have developed a new, simple, and cost-effective route for the preparation of triprolidine using intermediates **1** and **2**. These intermediates are in turn prepared using cheaper and commercially available raw materials. Thus this method is not only commercially viable but also eliminates the use of hazardous *n*-butyllithium. We

Table 1
Wittig Condensation of **1** and **2** under Different Conditions

S. No	Base	Solvent	Yield of Product	E/Z Ratio
1	Sodamide	THF, Toluene	Nil	—
2	t-BuOK	DMF	Nil	—
3	t-BuOK	THF, Toluene	Traces	—
4	t-BuOK	MDC	71%	1:2
5	NaH	THF, Toluene	Traces	—
6	NaH	DMF	70%	1:2

believe that this method would also be useful for the preparation of compounds related to triprolidine.

Experimental Section

All chemicals and solvents are LR grade and were used as obtained. Crystallizations were performed in 2-butanone and ethyl acetate. The melting point was determined on Acro melting point apparatus and are uncorrected. The IR Spectrum was recorded on a Thermo Nicolet FT-IR instrument in KBr discs. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 200 MHz instrument. Chemical shifts are reported in δ units downfield from TMS as an internal standard in the case of $CDCl_3$ and DSS in the case of D_2O. Mass spectrum was recorded on a Q-TOF micro^{TM} instrument with AMPS MAX 10/6A system. The HPLC analysis was performed using a Shimadzu CLASS VP using column conditions: RP18 column, 5 microns, 250 × 0.46 mm; mobile phase-acetonitrile: 0.1 M phosphate buffer of pH 3.0 (7:3); detection 210 nm; flow rate 1 mL/min.

Preparation of 1-(4-Methylphenyl)-1-(2-pyridyl)-3-pyrrolidino-prop-1-ene E/Z Mixture

To a stirred solution of **1** (40 g, 0.2 mol) and **2** (104 g, 0.23 mol) in CH_2Cl_2 (400 mL) at 10°C was added potassium t-butoxide as a solid (52 g, 0.46 mol) over a period of 1 hour. After the complete addition of t-BuOK, the reaction mixture was stirred using a magnetic stirrer at room temperature for 2 hours and then quenched in 500 mL of water. The layers were separated and the product from the organic layer was extracted into aqueous oxalic acid solution (25 g, in 250 mL of water), which was basified to pH 9.0 using 10% aqueous NaOH solution and re-extracted into toluene (2 × 100 mL). The toluene layer was then dried over anhydrous Na_2SO_4 and evaporated to give a reddish brown oil (40 g, 71% yield) consisting of about two parts of *Z* and one part of *E* isomers of compound **3**.

Isomerization of E and Z Mixture of 1-(4-Methylphenyl)-1-(2-pyridyl)-3-pyrrolidino-prop-1-ene into Triprolidine (3)

The isomeric mixture of compound **3** (40 g) was heated with methanesulfonic acid (80 mL) at 190°C for 6 hours. The reaction mass was cooled to 10°C and the pH adjusted to 8.0 using

conc. ammonia solution. The solid product was extracted into hexane (3 × 150 mL) and the hexane layer was dried over anhydrous sodium sulfate and evaporated to afford triprolidine (35 g, 87% yield). The free base thus obtained was dissolved in 175 mL of 2-butanone, 12 g of oxalic acid was added and then the mixture was stirred at room temperature for 2 hours. The solid product obtained was collected and dried to yield the *E*-isomer (99% pure by HPLC, 38.0 g, 75% yield). The pure *E*-isomer of triprolidine oxalate was dissolved in 100 mL of water and 7 mL of conc. ammonia was added to yield triprolidine free base as a solid (28 g). The solid obtained was dissolved in 150 mL of ethyl acetate, and 10% gaseous HCl in isopropanol (37 mL) was added to afford triprolidine hydrochloride (29.0 g, 67% yield) as a white solid, mp. 117–118°C, lit.[18] mp.116–118°C.

IR(KBr): 3402, 3251, 2885, 2611, 2499, 1631, 1581, 1512, 1461, 1427, 991 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 2.05 (brs, 4 H), 2.43 (s, 3 H), 3.34 (brs, 4 H), 3.97 (d, 2 H, J = 7.2 Hz), 6.55 (t, 1 H, J = 7.2 Hz), 7.13 (d, 2 H, J = 7.8 Hz), 7.25 (d, 1 H, J = 7.8 Hz), 7.37 (d, 2 H, J = 7.8 Hz), 7.43 (m, 1 H), 7.80 (t, 1 H, J = 7.8 Hz), 8.53 (d, 1 H, J = 4.4 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 23.3, 52.3, 119.0, 123.0, 129.1, 129.6, 133.1, 136.5, 138.3, 148.1, 149.2, 156.2; TOF-MS (ES+) m/z: 279$(M+H)^+$, 208 (100%).

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