A SIMPLE, CONVENIENT AND EFFECTIVE METHOD FOR THE SYNTHESIS OF DIBENZ(B,F) 1,4-OXAZEPINES(CR); A NEW GENERATION RIOT CONTROL AGENT AND ITS ANALOGUES

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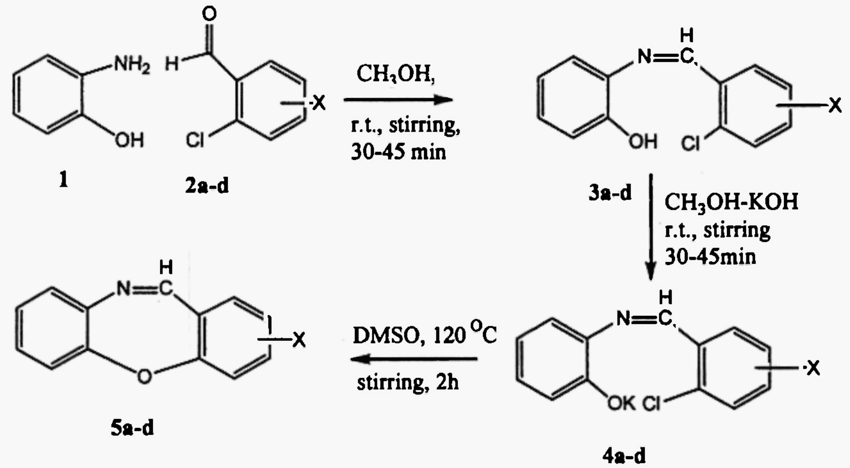
Abstract : A new synthetic route has been developed for the synthesis of seven membered heterocyclic ring dibenz (b, f) 1,4-oxazepine (CR) starting with condensation of *o*-aminophenol and *o*-chlorobenzaldehyde followed by salt formation and cyclisation in DMSO at 120^{0}C. The method has been extended for the preparation of other substituted dibenzoxazepines.

Keywords : Dibenz(b,f)1,4-oxazepine, CR, O-aminophenol, O-chlorobenzaldehyde, Schiff's base

Introduction

Seven membered three ring heterocyclic compounds are of potential biological and pharmacological interest. Major interest in this area has been centered on the heterocyclic rings with potential purotropic and psychotropic activity.[1,2] Most of the derivatives of these systems are used as antidepressants, protoglands ion antagonistic, tranquilizers and sedatives. Dibenz (b,f) 1,4-oxazapine (CR) is a strong irritant to both the eyes and skin of mammals. It is more potent and less toxic than widely used riot control agents namely, *o*-chlorobenzylidene malononitrile (CS) and *ω*-chloroacetophenone (CN). Methods for detection, identification and quantitative determination of riot control agents [3-5] are required during their use for prohibited activities.[6] The availability of identification data of these compounds would facilitate the verification in case of alleged use of these chemicals. The biological and pharmacological evaluation of Dibenz(b,f)1,4-oxazepines showed that its powerful skin irritant properties are associated with very low mammalian toxicity.[7,8] Following the discovery of skin irritating properties of dibenzoxazepines co-opted with its low mammalian toxicity, it is an important and safe chemical to be used as riot control agent in civil unrest. There has been a considerable interest in the synthesis of these seven membered tricyclic systems, wherein central seven member ring is flanked by two aromatic rings. Various synthetic routes for the preparation of Dibenz(b,f)1,4-oxazepines have been reported in the literature. It has been prepared from 1-chloro-2-nitrobenzene and sodium phenoxide.[9] CR has also been synthesized from 2-aminodiphenyl ether by cyclisation with *n*-butyllithium[10]and third method involves cyclization of salicylaldehyde with *o*-chloronitrobenzene followed by reduction of nitro to amino group.[11] However majority of these methods are associated with limitations like the accessibility of the starting materials, multi-step procedures, formation of side products and comparatively low yields.[9-11] Our aim in undertaking this work was to overcome the limitations and drawbacks of the reported methods. (Scheme-1)



Scheme-I Synthesis of dibenz (b,f)1,4-oxazepines

Experimental

(a) ***Step-I: Preparation of Schiff's base (3a):*** A 500ml two neck round bottom flask, equipped with condenser and mechanical stirrer, was charged with *o*-aminophenol (10.9g, 0.1mol) and methanol 250ml. The mixture was stirred to form yellow slurry. To this *o*-chlorobenzaldehyde (15.4g, 1.1 mol) was added slowly in 10min. The solid first dissolved into the solution and reappeared after stirring for 10 minutes at room temperature. Stirring was continued for 10 minutes to complete the reaction. The yellow mass so obtained was filtered through Buckner funnel and washed with pet. ether (40-60°C). The filtrate along with washings was further chilled to recover more products. Yield 22.1g (96%). M.P.91°C

(b) ***Step-II: Preparation of potassium salt (4a):*** Potassium hydroxide (4.6g, 0.082mol) dissolved in methanol (90ml) was added slowly over 15 minutes to a suspension of Schiff's base (17.3g, .075mol) in methanol (100ml) at room temperature with constant stirring. After completion of the addition all the solids dissolved into the solution. The reaction mixture was then stirred at room temperature for 20 minutes and cooled to 5°C. After 10 minutes the product was precipitated from the solution. Stirring was continued for another 15min followed by addition of diethyl ether (175ml). The solids so obtained were filtered off and washed with pet. ether (40-60°C) and dried in air. Yield 18.6g (92%).

(c) ***Step-III: Preparation of dibenz(b,f)1,4-oxazepine (CR) (5a):*** A one-liter three neck round bottom flask, equipped with mechanical stirrer, thermometer and condenser was charged with DMSO (200ml) and heated on an oil bath till the temperature reached 120°C. The bath temperature was maintained at 150-160°C. Potassium salt of Schiff's base (4a) (13.5g, .05 mol) dissolved in DMSO (30ml), was added to the pre heated DMSO. The temperature of the reaction mixture was maintained at 120°C for 2h and then cooled to 20°C. Distilled water and pet. ether (40-60°C, 125ml each) were added to the reaction mixture and heated on a water bath for

10minutes. The yellow upper layer formed was separated. The process was repeated at least five times. The combined petroleum ether extracts were dried over anhydrous sodium sulfate. Solvent distilled off to reduce the volume to about 50ml and transferred to a drying tray and left at room temperature for 30 minutes to give the title compound as yellow crystals. Yield 8.0g (82%) m.p. 72^{o}C. Over all yield 72 %.

Result and Discussion

Herein, we report an efficient, economic and easy to scale-up method [12,13] for the effective synthesis of dibenz(b,f)1,4-oxazepine and substituted dibenzoxazepines by condensation of commercially available *o*-aminophenol with corresponding substituted *o*-chlorobenzaldehyde in methanol at room temperature to give Schiff's base followed by salt formation of the Schiff's base in methanolic KOH at room temperature and finally cyclisation in DMSO at 120^{0}C to give the title compounds with 68—72% yield (scheme-1). The method has also been extended for the synthesis of substituted dibenz (b,f)1,4-oxazepines (Table-1).

Table -1 : Preparation of dibenz (b,f) 1,4-oxazepines

Entry	**X**	**Yield (%)**	**M.P.(^{0}C)**	**IR, KBr(cm^{-1})**	**^{1}H NMR^b (ppm)**
5a	H	72	72	1609(C=N),1447(C=C), 1032(C-O-C)	6.95-7.62 (m,8H,) 8.52(s, 1H, imine)
5b	6-Cl	70	112	1620 (C=N),1480 (C=C), 1200 (C-O-C)	7.13-7.85(m,7H,) 8.64(s, 1H, imine)
5c	8-Cl	70	120	1630(C=N), 1600, 1447(C=C),1200 (C-O-C)	7.05-7.74 (m,7H,) 8.51(s, 1H, imine)
5d	7-NO_2	68	230	1630(C=N),1525, 1320 (NO_2)1440(C=C), 1200, 1220 (C-O-C)	7.32-7.54 (m,5H,) 8.36-8.62 (d, 2H) 9.32 (s, 1H, imine)

[a] Isolated yield of products starting from o-aminophenol

[b] ^{1}H NMR spectra were recorded in $CDCl_3$ using 400MHz instrument.

The purity of all the compounds were checked with GC and gave satisfactory elemental analysis GC-MS data

The important advantage of this method is that it involves less number of steps and most of the steps (two out of three steps) operate at room temperature circumventing the tedious synthetic steps such as reduction required in earlier reported method.[11] Another advantage is that the final product formed with an over all 68-72% yield starting from *o*-amino phenol which is far better than any of the reported methods. We also studied the reproducibility and scale-up feasibility of the developed protocol. To prove the concept we carried the reaction at 1- 5mol levels which was subsequently extended to a pilot plant scale upto 10 kg batch with an overall yield of 65-70%.

All the compounds are unpleasant with strong irritant properties for skin and mucus membrane. The toxicological and pharmacological properties of these compounds are published elsewhere[14]. Precautionary measures must be taken to avoid the contact of the dibenz(b,f)1,4-oxazepines as they are severely irritating to both eyes and skins. Final step must be carried out in a fume hood. Irritancy increases further on contact with water.

Conclusion

We have reported an effective method for the convenient synthesis of seven membered three ring heterocyclic compounds dibenz (b,f) (1,4) Oxazepine and their substituted derivatives starting from commercially available o-aminophenol and o-chlorobenzaldehyde under mild conditions with improved yield.

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