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Synthesis of N-Substituted Tetrahydrocarbazoles for Anticonvuslant Activity

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Abstract

Thrust in the preparation of new heterocyclic molecules is increasing due to their proven significant biological activities. The paramount importance of heterocycles such as indoles and their derivatives in natural product chemistry and pharmacology constantly drives the search for the new procedures for their construction and also for the preparation of variety of their derivatives to exploit their useful biological activities. A tetrahydrocarbazole had been synthesized by reacting cyclohexanones with substituted hydrazine hydrochlorides in the presence of glacial acetic acid to produce N-(1,2,3,4-tetrahydrocarbazole) which later used to synthesize compounds with different heterocyclic new rings containing, sulfur and nitrogen in structures i.e., substituted-N-(1,2,3,4-tetrahydrocarbazole) which were characterized by IR, ^{1}H and ^{13}C NMR spectral studies and these structures were investigated for analgesic and anti inflammatory activity.

Keywords: Cyclisation, phenyl hydrazine, cyclohexanone, Tetrahydrocarbazole

Contents

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1. Introduction

The tetrahydrocarbazole ring system has been the structural subunit of many naturally occurring alkaloids, biologically active molecules and medicinal important synthetic analogues. tetrahydrocarbazoles condensed with indole, furan, pyrimidine, pyrazoline, and thiophene, moieties have been known to processes wide spectrum biological activities. There has been many methods of synthesis .In general the carbazoles synthesis is carried out by multistep Fisher reaction which requires the usage of organic solvents with very meager product yields. Hence a simple and efficient method for the synthesis of these pharmaceutically important class of compounds is highly desirable precluding the usage of organic solvents. Initially Substituted phenyl Hydrazine's were used to optimize the reaction conditions such as different acids, solvents, and reaction temperature. Among, several Acids were tested, finally we found that glacial acetic acid given excellent yields. In presence of CH_3COOH, $ZnCl_2$ and HCl lesser amount of the desired product was obtained. The effect of solvents was also investigated and the highest yield

was observed in glacial acetic acid, When the reaction was conducted at lower temperatures lower yields were obtained. Ideal temperature for the reaction was found to be 90°C. In the presence of electron releasing groups present in the Para position of phenyl Hydrazine's observed more yield comparatively presence of electron withdrawing groups. To the best of our knowledge this is a first report for the efficient and economic synthesis of carbazoles using readily available laboratory reagents with short reaction times.

2. Materials and Method

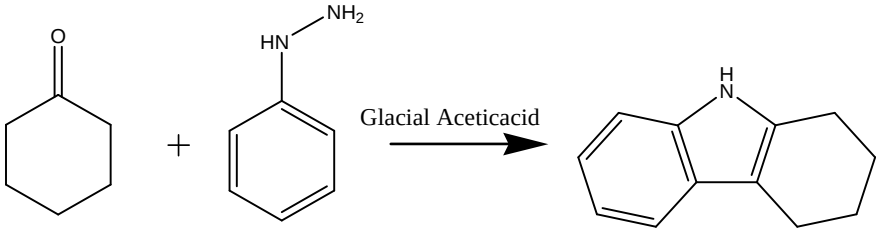
Melting points were taken in open capillaries and are uncorrected. FTIR spectra were recorded on Shimadzu FTIR 8400 spectrophotometer as KBr disc. The 1H-NMR and 13C-NMR spectra were recorded on a make Bruker model ultrashield 300MHz NMR at the university of Jordan DMSO-d6 was used as solvent and TMS as internal reference. U.V. spectra were recorded on Shimadzu UV-Vis recorder.

Chemicals: Starting chemical compounds were obtained from S.D fine Chemicals.

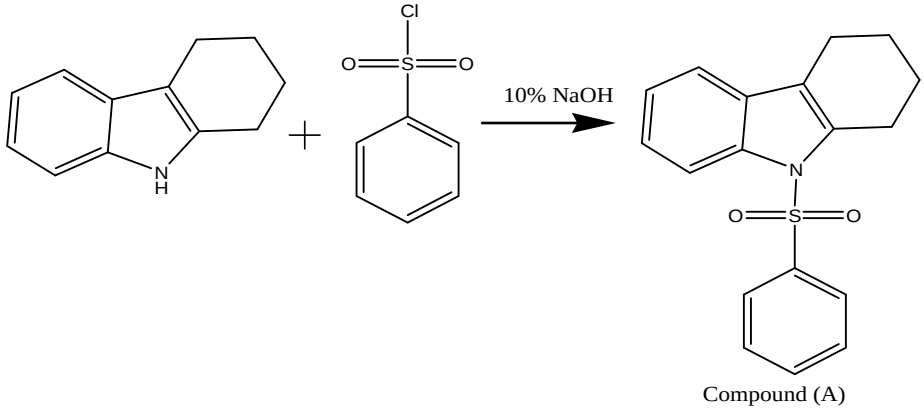
Methodology:

Synthetic scheme:

Step 1: **Preparation of tetrahydrocarbazole:**



Step 2: ***Synthesis of (N –Substituted -amino benzene sulphonyl) 1, 2, 3, 4-tetrahydrocarbazole:***



Compound (A)

Step I: Synthesis of 1,2,3,4 tetrahydrocarbazole:

(The Fischer's indolisation reaction)

The Fischer indolisation reaction occurs when the phenyl hydrazones of a suitable aldehyde or ketone undergoes Cyclisation with loss of ammonia, under the influence of various reagents, such as zinc chloride, ethanolic hydrogen chloride or acetic acid.

Experimental Procedure:

Dissolve calculated quantity of cyclohexanone (9.8 gm,0.1mol) in (34.65 gm,0.6 mol) of glacial acetic acid, add calculated . (10.8 gm,0.1mol) of phenyl hydrazine and boiled the solution under reflux for 10 minutes. Cooled the solution, where the tetrahydrocarbazoles was crystallized out, filtered at the pump, drained well and recrystallise from aqueous ethanol. The recrystallized was performed rapidly, since tetrahydrocarbazoles under goes atmospheric oxidation in hot solution. which has melting point of 146^0c. The purity of the compound was confirmed by melting point, TLC and IR Spectroscopy.

Step II:

1, 2, 3, 4-Tetrahydrocarbazole (1 gm,5.78 m.mol) was added to 10% NaOH solution in a well cooled conical flask and then add 2ml of acid chloride, with constant shaking and cooled in water Shaken vigorously for 10 minutes until the odour of the benzoyl chloride was disappeared filtered off the solid N-substituted derivative, washed with a little cold water and recrystallise it from ethanol.

Characterization

The synthesized compounds were purified by recrystallisation. and conformation by M.P&TLC will be subjected to elemental analysis, spectral characterization, U.V-visible,IR-spectroscopy and NMR spectroscopy if necessary will be recorded and conformation of synthesized compound will be established.

Evaluation of Anticonvulsant activity

Anticonvulsant activity was performed by MES (maximal electroshock method)**.** In the MES method, adult male and female Albino rats (Wistar strain) weighing 100-200 g were used. The animals were divided into three groups (control, standard and test) and each group comprising of three rats. The test compound was suspended in 1% aqueous CMC suspension and were injected i.p. in doses ranging from 15, 30 and 60 mg/kg body weight. Phenytoin sodium was used as a standard drug which was given in the dose of 30 mg/kg by I.P. which was observed to protect 100% against the induced convulsions.

The control group received only 1% aqueous CMC suspension.The seizures were induced by electroconvulsiometer. The animals were subjected to electroshock by delivering the current of 150 mA through the corneal electrodes for a period of 0.2 seconds. The animals were observed for 30 min convulsive responses. Different stages of convulsions i.e. the tonic flexion (towards the upper extremities), tonic extensor phase (extension of the lower extremities), clonic convulsions (intermediate jerking of limbs), stupor (unconsciousness) and recovery or death were observed for each animal (data as shown in Table 2). The anticonvulsant effect of newly synthesized compound was assessed by absence or reduction of hind limb tonic extensor phase. Each value represents the mean SEM (standard error mean) of three rats significantly different from standard drug phenytoin (ttab < tcal, P < 0.05) (student's *t*-test)

Table 1: Anticonvulsant activity of titled compounds

Code of compounds	30 mg/kg (Dose)				
	Flexion (mean± SEM)	**Extensor (mean±SEM)**	**Clonus (mean± SEM)**	**Stupor (mean±SEM)**	**Recovery/Death**
Compound	4.1±0.4	7.4±0.9	10.1±0.7	110.4±0.4	R
Control	4.2±0.9	9.6±0.4	11.8±0.2	114.1±0.4	R
Phenytoin Sodium	Absent	5.6±0.2	2.4±0.1	104.2±0.2	R

3. Results and Discussion

Anticonvulsant activity of the compound was performed using the maximal electroshock-induced seizure (MES) method in albino rats (Wistar strain) of either sex. This method claimed to detect compounds possessing activity against generalized tonic clonic (grandmal) seizures. The MES test is a measure of an anticonvulsant drug to abolish or reduce the time of the tonic extensor component of the hind limb in the maximal seizure pattern induced by 150 mA of current delivered for 0.2 seconds. In the primary MES screening compound **(A)** afforded protection against seizures confirming their potential utility as prototypic molecules. The anticonvulsant activity data revealed that the compound **(A)** showed remarkable reduction of hind limb tonic extensor phase when given in the dose of 30 mg/kg i.p. phenytoin used as standard anticonvulsant drug.

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