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AN EFFICIENT SYNTHESIS OF 2-ARYLQUINOXALINES FROM α,α-DIBROMOACETOPHENONES AND *O*-PHENYLENEDIAMINE

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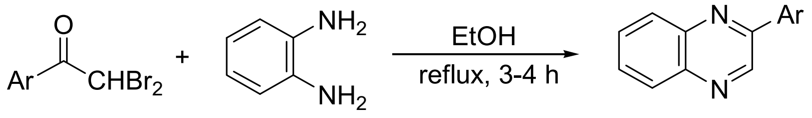
ABSTRACT An efficient synthesis of 2-arylquinoxaline derivatives (**3a-f**) has been developed from the reaction of α,α-dibromoacetophenones (**1a-f**) and *o*-phenylenediamine (**2**) under mild reaction conditions.



1 **2** **3**

KEYWORDS 2-Arylquinoxalines, α,α-dibromoacetophenones, *o*-phenylenediamine, one-step procedure.

INTRODUCTION

Nitrogen containing heterocyclic compounds are indispensable structural units for both chemist and biochemist. Among the various classes of heterocyclic compounds, quinoxalines form an important component of pharmacologically active compounds. Quinoxaline ring is a part of various antibiotics such as Hinonycin, Levomycin and Actinoleutic[1,2] that are known to inhibit growth of gram-positive bacteria and are active against various transplantable tumors.[3] In addition, quinoxaline derivatives are also associated with a wide spectrum of biological activities ranging from anthelmintic and anticancer to antimicrobial, antifungal, antidepressants, antibacterial and anti-inflammatory activities.[4-8] In view of above mentioned findings, we tried to synthesize quinoxaline derivatives by easier method that may be value in designing new, potent and selective biological agents.

Though the synthetic utility of α-halocarbonyl compounds in heterocyclic chemistry is well known for more than a century and they have been widely used as versatile intermediates [9-15] for the synthesis of variety of heterocyclic systems, these compounds suffer with serious handling problems due to highly lachrymatory properties associated with them. Therefore, there has been considerable interest in developing alternative approaches in synthetic chemistry.

Recently, α,α-dihalocarbonyl compounds are found to be important intermediates in the synthesis of pharmaceutically important heteroaromatics, unsaturated acids and ynol esters.[16-18] They have been used as synthetic equivalents[19-22] to the corresponding á-halocarbonyl compounds in many nucleophilic reactions and they possess high reactivity in most of the reactions. Being non-lachrymatory, generally solid at room temperature and soluble in commonly used reaction

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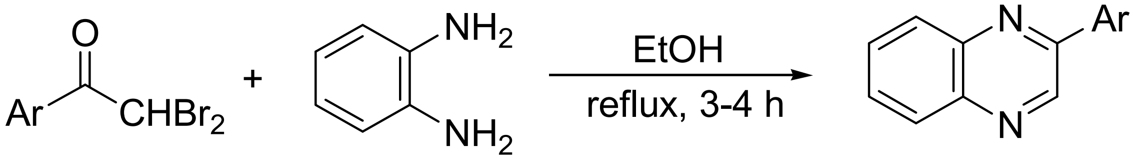
solvents, these compounds can be handled easily.[23-26] In the present communication, α,α-dibromocarbonyl compounds are treated with *o*-phenylenediamine with the aim i) to compare their reactivity pattern with the corresponding á-bromocarbonyl compounds and ii) to develop an alternative and efficient route for the synthesis of 2-arylquinoxalines.

RESULTS AND DISCUSSION

Initially, α,α-dibromoacetophenone **(1a)** was treated with *o*-phenylenediamine (**2**) at room temperature in ethanol as well as in acetonitrile. The reaction, however, did not give any fruitful result as it led to the formation of gummy material containing mixture of several compounds including starting material. In order to optimize the conditions for the completion of reaction, several experiments were performed and finally it was found that on refluxing the mixture of α,α-dibromoacetophenone with two equivalents of *o*-phenylenediamine in ethanol for about 3 h, the reaction gave a crystalline solid with m.p. 67-68°C. This product was identified as 2-phenylquinoxaline (**3a**), on the basis of its lit. m.p. and spectral data. This method was found to be of general use as variously substituted α,α-dibromacetophenones (**1b-f**) reacted with **2** under similar reaction conditions thereby affording the corresponding quinoxaline derivatives (**3b-f**) in good yields (**Scheme 1**, **Table 1**).



1 **2** **3**

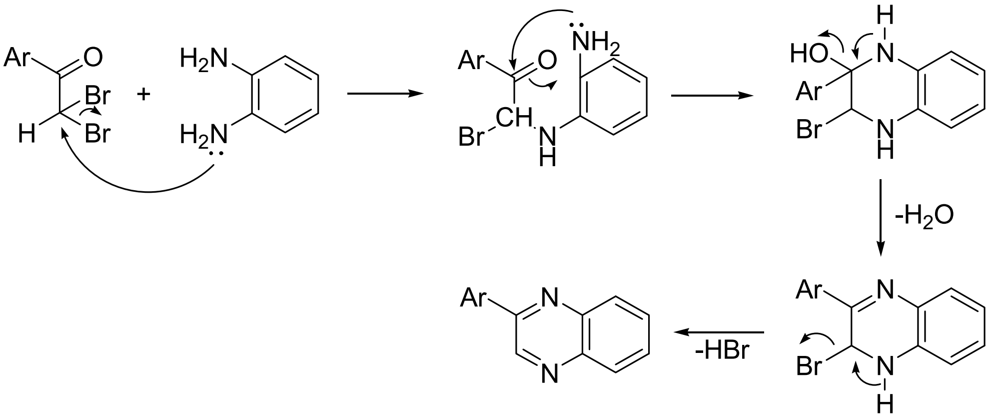
Scheme 1

Table 1: Physical and spectral data of 2-Arylquinoxalines (3a-f)

Compd	Ar	Mp (°C)	Lit Mp (°C)	Yield (%)	^{1}H NMR (, $CDCl_3$, 300 MHz)
3a	C_6H_5	67-68	76-77[27]	77	7.55-8.30 (*m*, 9H, Ar-H), 9.40 (*s*, 1H, C_3-H)
3b*	4-$CH_3C_6H_4$	81-82	-	79	2.40 (*s*, 3H, CH_3), 7.56-8.31 (*m*, 8H, Ar-H), 9.38 (*s*, 1H, C_3-H)
3c	4-ClC_6H_4	122-23	120-22[28]	83	7.55-8.20 (*m*, 8H, Ar-H), 9.34 (*s*, 1H, C_3-H)
3d	4-BrC_6H_4	130-32	136-37[27]	81	7.58-8.18 (*m*, 8H, Ar-H), 9.35 (*s*, 1H, C_3-H)
3e	4-FC_6H_4	108-09	120[29]	76	7.55-8.20 (*m*, 8H, Ar-H), 9.34 (*s*, 1H, C_3-H)
3f	4-$NO_2C_6H_4$	176-78	187-88[27]	84	7.55-7.80 (*m*, 4H, Ar-H), 8.31 (*d*, 2H, *J* 8.9 Hz, Ar-H), 8.68 (*d*, 2H, *J* 8.9 Hz, Ar-H), 9.34 (*s*, 1H, C_3-H)

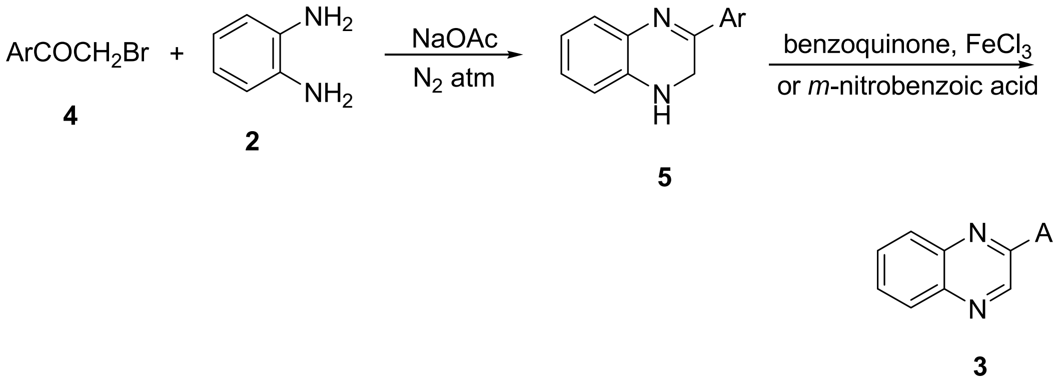
* Analysis calculated for $C_{15}H_{12}N_2$: C, 81.82; H, 5.45; N, 12.73. Found: C, 81.50; H, 5.15; N, 12.46.

Although mechanism of this reaction is not certain, a plausible pathway is outlined in **Scheme 2**.



Scheme 2

It is worthwhile to mention here that some 2-arylquinoxaline derivatives have been reported in literature[27] by the two-step procedure starting from α-bromocarbonyl compounds **4** as shown in eq. 1.



(eq. 1)

EXPERIMENTAL SECTION

Melting points were taken in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument using TMS as an internal standard. IR spectra were recorded on a Buck Scientific IR M-500 spectrophotometer. Physical and spectral properties of the prepared compounds are summarized in **Table 1**. The α,α-dibromoacetophenones were synthesized according to literature procedure[30] and were confirmed by comparison with literature melting points.

Synthesis of 2-Arylquinoxalines (3a-f) from α,α-dibromoacetophenones and *o*-Phenylenediamine General Procedure

To a solution of appropriate α,α-dibromoacetophenone (**1**, 1.5 mmol) in ethanol (20 ml) was added *o*-phenylenediamine (**2**, 0.32 g, 3 mmol) and the reaction mixture was heated under reflux for 3-4 h. About half of the solvent was removed under *vacuum* and the reaction mixture was cooled to room temperature. The solid, which was separated out of the solution, was filtered and recrystallized from ethanol to give pure product **3**. The physical and spectral data of the pure products are listed in **Table 1**.

CONCLUSIONS

1. The study offers a superior approach for the synthesis of 2-arylquinoxalines (**3a-f**) as it is easier to prepare and handle α,α-dibromoacetophenones as compared to α-bromoacetophenones.
2. The method developed in the present study is very convenient as this reaction occurs in single step. The procedure involves simple experimentation with mild conditions.

3. Comparing the results of present study with reported synthesis of **3** involving α-bromoacetophenones, it is evident that α-bromoacetophenones and α,α-dibromoacetophenones behave differently in their reactions with *o*-phenylenediamine. Further work dealing with mechanisitic pathways of such reactions is underway.

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