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α,α-DIBROMOKETONES AS USEFUL PRECURSORS IN ORGANIC SYNTHESIS: A SIMPLE AND EFFICIENT SYNTHESIS OF 2,4-DIARYL-1,2,3-TRIAZOLES VIA OXIDATIVE CYCLIZATION OF BISPHENYLHYDRAZONES

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ABSTRACT : α,α-Dibromoacetophenones (**1a-1f**) on [illegible] drazine afford corresponding arylglyoxal bisphenylhydrazones (**2a-2f**). [illegible] zones **2a-2f** by using copper(II) chloride in acetic acid leads to intramolec[illegible] ormation of 2,4-diaryl-1,2,3-triazoles (**3a-3f**). The method for the conversion 1 → 3 has been simplified by developing one-pot procedure without isolation of intermediates **2**.

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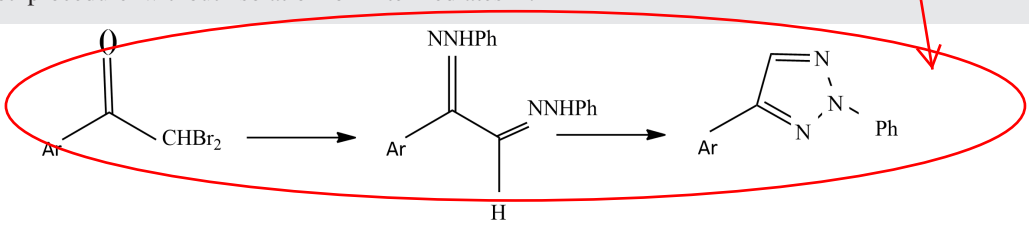

KEYWORDS : α,α-Dibromoacetophenones, Arylglyoxal bisphenylhydrazones, Oxidation, Copper(II) chloride, 2,4-Diaryl-1,2,3-triazoles

INTRODUCTION

1,2,3-Triazole has become one of the most important heterocycles in current chemistry research[1-4] because its large number of derivatives are used as agrochemicals and pharmaceuticals, especially in biological science,[5,6] material chemistry,[7] and medicinal chemistry.[8-10] 1,2,3-Triazole and its analogues find applications as antimicrobial,[11] anti-AIDS,[12] anti-hypertensive agents[13], potassium channel activators[14], etc.

One of the most attractive strategies for the synthesis of 1H-1,2,3-triazoles, involves thermal 1,3-dipolar cycloaddition of various azides with alkynes or activated methylene compounds.[15-17] However, only a few synthetic routes are available in literature for the synthesis of 2,4-diaryl-1,2,3-triazoles and the most common one is the oxidative intramolecular cyclization of bishydrazones. The bishydrazones needed in this procedure are prepared by the condensation of 1,2-dicarbonyl compounds with hydrazines.[18-20] The requisite dicarbonyl compounds

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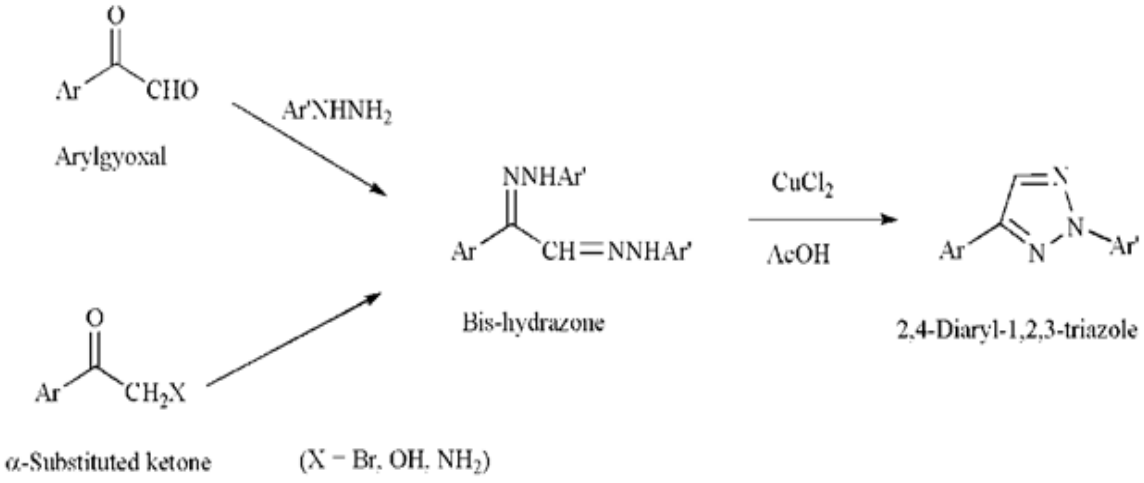
such as arylglyoxals are prepared by the oxidation of aryl alkyl ketones such as acetophenones with selenium dioxide. In a most recent development, α-substituted ketones[21-23] such as α-hydroxyacetophenones,[21] α-aminoacetophenones[22] and α-bromoacetophenones[23] have been offered as a superior replacement for arylglyoxals in the synthesis of **3** via bishydrazones **(Scheme 1)**.



Scheme 1

α,α-Dibromoketones (DBKs)[24] have attracted increasing attention because of their high reactivity and easy handling as compared to α-bromoketones (BKs)[25] which are versatile precursors in organic synthesis. α-Bromoketones are associated with highly lachrymatory property, whereas α,α-dibromoketones are devoid of lachrymatory property. It has recently been reported that the DBKs in their reactions with soft nucleophiles, such as thiols and thioureas behave analogous to BKs.[26-30] These studies have demonstrated the possibility of offering a superior alternative to BKs by using DBKs.

On the other hand, nitrogen containing nucleophiles such as hydroxylamine, amines and hydrazines, follow different course and overall results obtained in several cases are similar to α-ketoaldehydes.[24,31]

Prompted by above mentioned observations on α,α-dibromoketones, it was planned to synthesize triazoles **3** using α,α-dibromoacetophenones as precursors with a view to develop a simpler and superior alternative to the existing syntheses of **3** involving BKs or arylglyoxals.

RESULTS AND DISCUSSION

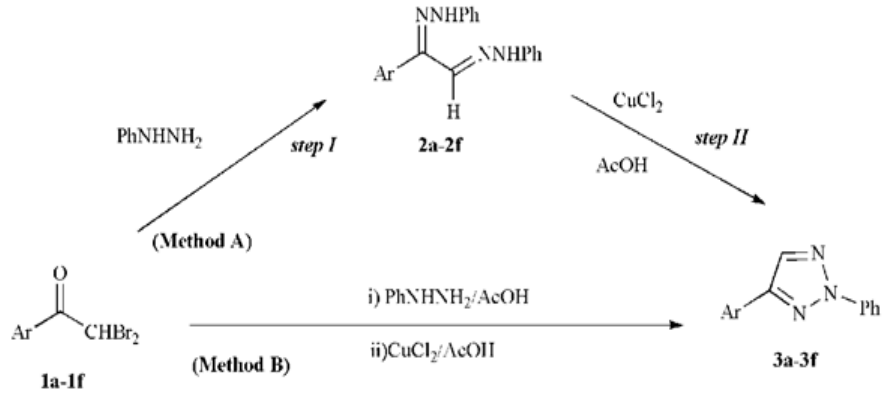
Based on the presumption that α,α-dibromoketones can be used as synthetic equivalent to corresponding α-ketoaldehydes in their reactions with nitrogen nucleophiles,[24,31] we first investigated the reaction of α,α-dibromoacetophenone (**1a**) with one equivalent of phenylhydrazine in ethanol by stirring at room temperature. The reaction, however, resulted in the formation of gummy product containing mixture of several compounds including starting material. After conducting a series of experiments by changing the reaction conditions, it was found that refluxing a mixture of **1a** and two equivalents of phenylhydrazine in ethanol for about 3 h gives a crystalline solid, identified as arylglyoxal bisphenylhydrazone **2a** on the basis of lit. mp and spectral analysis.

The formation of bishydrazone from this reaction is an encouraging observation because such bishydrazones are important precursors for the synthesis of 2,4-diaryl-1,2,3-triazoles. So, it was considered worthwhile to assess the generality of this approach for the synthesis of variously substituted bishydrazones. Accordingly, these substituted α,α-dibromoacetophenones **(1b-1f)** were treated with two equivalents of phenylhydrazine under

the same reaction conditions. The reaction occurred in a similar manner thereby affording bishydrazones **2b-2f** in moderate to good yields (**Scheme 2, step I, Method A, Table 1**).

These bishydrazones were subjected to oxidative cyclization by using copper(II) chloride in acetic acid to afford the corresponding 2-phenyl-4-aryltriazoles (**Scheme 2, *step II*, Method A**). The physical data of thus obtained products **3a-3f** is summarized in **Table 1**.

In order to simplify the procedure, we attempted the conversion of **1** into **3** in one-pot without isolating bishydrazones. Although thin layer chromatography of the reaction mixture indicated formation of the desired triazole **3**, the results obtained from such experiment using ethanol as a solvent were not satisfactory because of the formation of some side products along with recovery of the significant amount of unreacted starting material. Interestingly, the reaction proceeded according to the expectation giving good yield of the triazoles **3a-3f**, when acetic acid was used as a solvent in place of ethanol. Thus, acetic acid is a solvent of choice for the smooth conversion of **1a-1f** to **2a-2f**, and then **2a-2f** to **3a-3f** in one-pot (**Scheme 2, Method B, Table 1**).



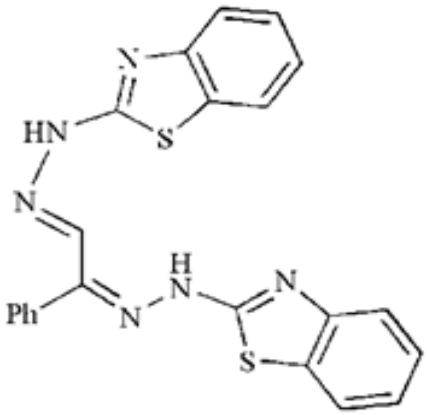
Scheme 2

Table 1: Physical data of Bishydrazones 2 and Triazoles 3

Product	Ar	Mp (lit.mp)[21,22] °C	Yield[a] (%)	Product	Ar (lit.mp)[23] °C	Mp	Yield (%)
2a	C_6H_5	145-146[e] (148)	63	**3a**	C_6H_5	38-39[e] (39-40)	48[b] (51)[c]
2b	4-$CH_3C_6H_4$ (136)	132-134[e]	71	**3b**	4-$CH_3C_6H_4$	60[e] (64-66)	48[b] (53)[c]
2c	4-ClC_6H_4	165-167[e] (169)	71	**3c**	4-$C_1C_6H_4$	98-99[e] (98-100)	67[a] (70)[b]
2d	4-BrC_6H_4	174-175[e] (180)	81	**3d**	4-BrC_6H_4	110-111[e] (111-112)	68[a] (70)[b]
2e	4-FC_6H_4	137-140[d]	73	**3e**	4-FC_6H_4	103-104[e] (104-105)	65[a] (63)[b]
2f	4-$OMeC_6H_4$	145-146[e] (188)	69	**3f**	4-$OMeC_6H_4$	90-92[e] (90-92)	63[a] (65)[b]

[a] Yield of the isolated pure product **2** with respect to the quantity of **1**.
[b] Overall yield of the isolated pure product **3** with respect to the quantity of **1** by **Method A**.
[c] Yield of the isolated pure product **3** with respect to the quantity of **1** by **Method B**.
[d] A new compound which was fully characterized by spectral and analytical data.
[e] These are known compounds and showed satisfactory spectral data (IR and ^{1}H NMR).

To extend the scope of this approach to some new 2-heteroarytriazoles, we were particularly interested in the synthesis of 2-(2-benzothiazolyl)-4-aryl-1,2,3-triazoles for the purpose of their biological screening. Initially, we carried out reaction of DBK **1a** with 2-benzothiazolylhydrazine in stepwise manner



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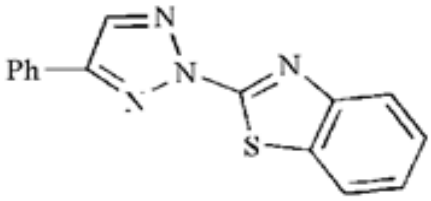

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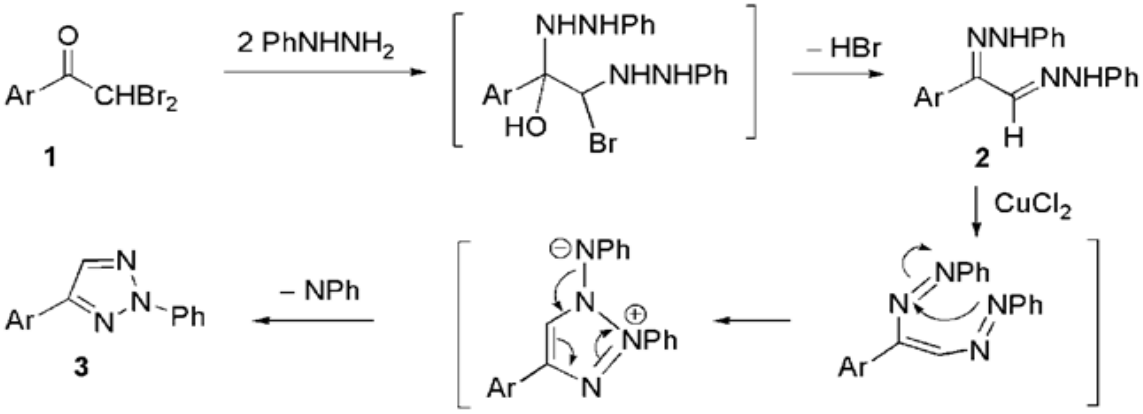
and the approach worked efficiently to give corresponding bishydrazone **4** and triazole **5**. Further work in this connection is still under progress and will be published elsewhere along with fuller details of chemistry and biological activity.

The plausible mechanistic pathways for the ***step I*** and ***step II*** are outlined in **Scheme 3**. Two simultaneous nucleophilic attacks of phenylhydrazine on carbonyl and C-Br followed by elimination of one molecule of water and two molecules of HBr probably complete the first step. The mechanism for the oxidative cyclization of bishydrazones to triazoles (***step II***) has earlier been suggested through involvement of elimination of a nitrene molecule,[21,22] though there is no experimental support. More work is needed to determine the mechanistic course of this conversion.



Scheme 3

EXPERIMENTAL SECTION

Melting points were taken in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker 300 MHz instrument using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer 1800 IR spectrophotometer.

Most of the common chemicals such as acetophenones, phenylhydrazine, and bromine were purchased from commercial suppliers and were used without further purification. α,α-Dibromoacetophenones

(1a-1f) were prepared by bromination of acetophenones using bromine in chloroform according to literature conditions [26,32] and identified by comparison of their mps and ^{1}H NMR data with those reported in literature.

Preparation of 2,4-diaryl-1,2,3-triazoles (3)

Method A (via isolation of intermediate bishydrazones)

Step I: **Arylglyoxal bisphenylhydrazones (2a-2f) General Procedure**

To a solution of appropriate a,a-dibromoacetophenone (**1**, 2 mmol) in ethanol (25 mL) was added phenylhydrazine (4 mmol) and the reaction mixture was heated under reflux for 3 h. About half of the solvent was removed under *vacuum* and the reaction mixture was cooled to room temperature. The yellow colored solid product, which was separated out of the solution, was filtered and recrystallized from ethanol to give pure **2**.

4-Fluorophenylglyoxal bisphenylhydrazone (2e)
IR (ν_{max}., KBr): 1599 cm^{-1} (C=N str.), 3291 cm^{-1} (-NH str.);
^{1}H NMR ($CDCl_3$, 300 MHz, δ): 6.97-7.71 (m, 14H, Ar-H), 7.92 (s, 1H, -CH=), 12.62 (s, 1H, -NH);
Analysis calculated for $C_{20}H_{17}N_4F$: C, 72.29; H, 5.12; N, 16.87. Found: C, 72.00; H, 4.98; N, 16.72.

Step II: **4-Aryl-2-phenyl-1,2,3-triazoles (3a-f)**

General Procedure

Bishydrazone (**2**, 1 mmol) and cupric chloride (1 mmol) were added to acetic acid (20 mL). The mixture was refluxed for about 2 h, cooled to room temperature and filtered. The filtrate was diluted with water (50 mL) and then extracted with dichloromethane (2 x 10 mL) The combined organic phase was washed with a saturated solution of sodium bicarbonate (10 mL) followed by water (10 mL) and then dried over anhydrous sodium sulfate. The dried organic phase was concentrated by distilling off solvent, and purified by column chromatography on silica gel using petroleum ether-ethyl acetate (30 : 1).

Method B (one-pot procedure for 3)

To a solution of α,α-dibromoacetophenone (**1**, 2 mmol) in acetic acid (25 mL) was added phenylhydrazine (4 mmol) and the reaction mixture was heated under reflux for 2 h and then cupric chloride (2 mmol) was added. The resulting mixture was refluxed for 1 h, cooled to room temperature and filtered. The filtrate was diluted with water (100 mL) and then extracted with dichloromethane (2 x 20 mL). The combined organic phase was washed with a saturated solution of sodium bicarbonate (20 mL) followed by water (20 mL) and then dried over anhydrous sodium sulfate. The dried organic phase was concentrated by distilling off solvent, and purified by column chromatography on silica gel using petroleum ether-ethyl acetate (30 : 1).

CONCLUSION

The results obtained from the present study offer an easy and ecofriendly approach for the synthesis of 4-aryl-2-phenyl-1,2,3-triazoles (3a-f). These results reveal that α,α-dibromoacetophenones can be used as synthetic equivalent to corresponding α-arylglyoxals in their reactions with phenylhydrazine. The most remarkable feature of this approach is that it avoids the use of highly lachrymatory BKs. Further studies on the scope and mechanistic considerations of reactions of DBKs with various nucleophiles are desirable.

LIST OF ABBREVIATIONS

AIDS = Acquired Immuno Deficiency Syndrome
BKs = α-Bromoketones
DBKs = α,α-Dibromoketones

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