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Organoiodine(III)-Mediated Efficient Synthesis of New 3,9-Diaryl-bis-1,2,4-triazolo[4,3-*a*][4,3-*c*]pyrimidines

Om Prakash, Rajesh Kumar, Deepak Sharma, Rajesh Naithani, and Ravi Kumar

Department of Chemistry, Kurukshetra University, Kurukshetra 136119, India

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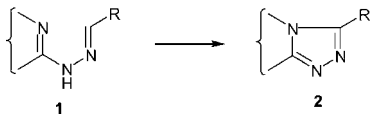
ABSTRACT: *Oxidation of bis-2,4-pyrimidinylhydrazones of various araldehydes with two equivalents of iodobenzene diacetate in dichloromethane provides an efficient and easy method for the synthesis of eight new 3,9-diaryl-bis-1,2,4-triazolo[4,3-a][4,3-c]pyrimidines*. © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:653–655, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20250

INTRODUCTION

In recent years, organohypervalent iodine reagents [1] have emerged as reagents of choice for various synthetically useful transformations due to their low toxicity, ready availability, and ease of handling. As part of our ongoing program directed toward the unique applications of organohypervalent iodine reagents in organic synthesis, we have shown that organoiodine(III) reagents such as iodobenzene diacetate (IBD) [2] and [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's reagent) [3] are excellent reagents for the oxidation of phenolic compounds [4], α-functionalization of carbonyl compounds [5], and synthesis of a wide variety of heterocyclic compounds [6], including biologically active compounds [7]. In continuation of these encouraging reports, we have developed an efficient and easy method for the synthesis of new 3,9-diaryl-bis-1,2,4-triazolo[4,3-*a*][4,3-*c*]pyrimidines **4** as potential antibacterial agents. The results of this useful synthesis involving oxidation of bis-hydrazones **3** with IBD are reported herein.

Oxidative cyclization of hydrazones of general formula **1** using various reagents is a viable route for the synthesis of fused triazolo heterocyclic systems of the type **2** [8].



1 **2** (1)

Based on synthetic route given in Eq. (1), it was anticipitated that oxidation of bis-hydrazones **3** with two equivalents of IBD might afford the desired bis-triazoles **4**. Accordingly, a solution of bis-hydrazone **3a** in dichloromethane was treated with two equivalents of IBD at room temperature. A rapid reaction occurred to afford the product **4a** as crystalline solid in 60% yield. Encouraged by the feasibility of our strategy for **4a**, we studied oxidative cyclization of a wide range of substituted hydrazones **4b–h** with IBD under similar conditions. The method, indeed, worked efficiently for the synthesis of aryl derivatives **4b–h** (Scheme 1, Table 1).

Correspondence to: Om Prakash; e-mail: dromprakash50@rediffmail.com.
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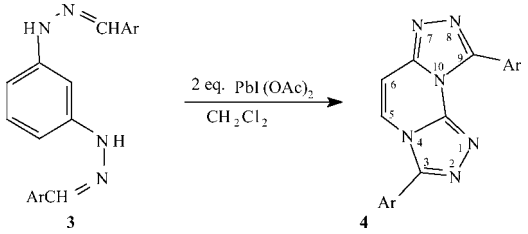
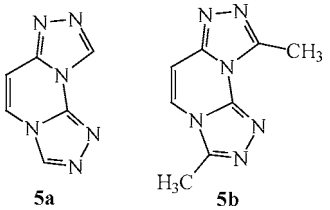


SCHEME 1

The mechanism of this transformation is not certain, and a probable mechanism is outlined in Scheme 2. The first step involves the electrophilic attack of IBD on **3** to form an organoiodine(III) intermediate **A**. Subsequently, **A** generates another intermediate, a bis-nitrile amide **B** along with expulsion of two molecules of iodobenzene and acetic acid each. The nitrile amide **B** undergoes cyclization to give the product **4**.

It should be noted that synthesis of parent bis-1,2,4-triazolo[4,3-*a*][4,3-*c*]pyrimidine **5a** and its 3,9-dimethyl derivative **5b** has been reported earlier [9], whereas no example of 3,9-diaryl derivative of the type **4** is known yet.

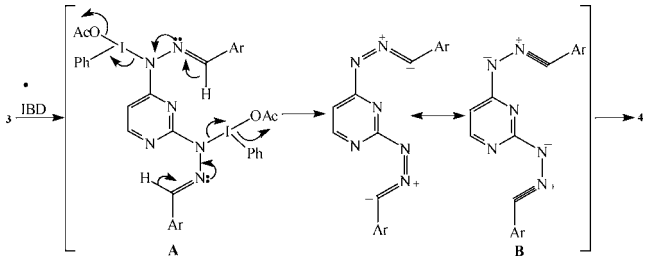


The reported synthetic route to **5a** and **5b** involves the reaction of 2,4-dihyrazinopyrimidine **6** with formic acid and triethyl orthoacetate, respectively. In an analogous manner, we attempted the preparation of **4a** by the reaction of **6** with benzoic acid/benzoyl chloride under various conditions [10]. Although we were successful in obtaining dibenzoylamino derivative **7**, the cyclization of the latter did not give any acceptable result to obtain the desired product **4a** (Scheme 3).

Finally, the present study offers an easy access to new bis-triazolopyrimidines **4**, which are potential antibacterial agents [11]. The method for oxidative cyclization of hydrazones **3** to triazolo heterocyclic compounds **4** involves mild conditions.

EXPERIMENTAL

Melting points were determined in open capillaries in electrical melting point apparatus and are

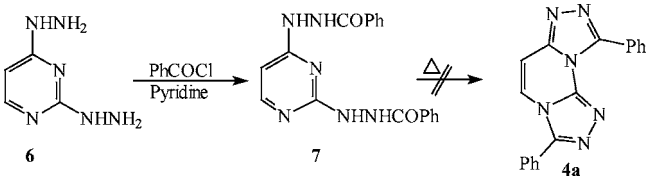


SCHEME 2

TABLE 1 3,9-Diaryl-bis-1,2,4-triazolo[4,3-*a*][4,3-*c*]pyrimidines **4** Prepared According to Scheme 1

Product[a]	*Ar*	*M.p. (°C)*	*Yield*[b] *(%)*	*^{1}H NMR ($CDCl_3$)* δ
4a	C_6H_5	82–85	60	7.81 (d, 1H, *J* = 8.1 Hz), 7.31 (d, 1H, *J* = 8.1 Hz), 7.2–7.55 (m, 6H), 7.95–8.10 (m, 4H)
4b	4-$CH_3C_6H_4$	98–102	62	2.50 (s, 6H, CH_3), 7.86 (d, 1H, *J* = 8.1 Hz), 7.25 (d, 1H, *J* = 8.1 Hz), 8.18 (d, 2H, *J* = 8.4 Hz), 7.68 (d, 2H, *J* = 8.4 Hz) 7.40–7.45 (m, 4H)
4c	4-$CH_3OC_6H_4$	121–123	57	3.83 (s, 6H, OCH_3), 7.9 (d, 1H, *J* = 8.1 Hz), 7.62 (d, 1H, *J* = 8.1 Hz), 8.17 (d, 2H, *J* = 8.7 Hz), 7.61 (d, 2H, *J* = 8.7 Hz), 7.02–7.05 (m, 2H), 6.90–6.94 (m, 2H)
4d	2,5-$(MeO)_2C_6H_3$	92–96	67	3.85 (s, 12H, OCH_3), 7.62 (d, 1H, *J* = 8.1 Hz), 7.28 (d, 1H, *J* = 8.1 Hz), 7.12–7.23 (m, 6H)
4e	4-FC_6H_4	192–195	59	7.90 (d, 1H, *J* = 8.1 Hz), 7.36 (d, 1H, *J* = 8.1 Hz), 8.38–8.45 (m, 2H), 8.24–8.29 (m, 2H), 7.18–23 (m, 4H)
4f	4-ClC_6H_4	202–206	67	7.85 (d, 1H, *J* = 8.1 Hz), 7.62 (d, 1H, *J* = 8.1 Hz), 8.35 (d, 2H, *J* = 8.7 Hz), 8.20 (d, 2H, *J* = 8.7 Hz), 7.51–7.56 (m, 4H)
4g	4-BrC_6H_4	150–153	62	7.94 (d, 1H, *J* = 8.1 Hz), 7.64 (d, 1H, *J* = 8.1 Hz), 8.30 (d, 2H, *J* = 8.7 Hz), 8.14 (d, 2H, *J* = 8.7 Hz), 7.68–7.75 (m, 4H)
4h	4-$O_2NC_6H_4$	183–185	68	8.16 (d, 1H, *J* = 8.1 Hz), 8.02 (d, 1H, *J* = 8.1 Hz), 8.4–8.5 (m, 4H), 8.11–8.25 (m, 4H)

[a]The elemental analyses (C, H, N) of all the products were found within the ±0.4% of their calculated values.
[b]The yields of the isolated pure products **4** with respect to **3** under the optimized conditions.



SCHEME 3

uncorrected. The IR (KBr) and ^{1}H NMR spectra were recorded on Buck Scientific IR M-500 and Bruker (300 MHz) spectrophotometers, respectively. Bis-2,4-pyrimidinylhydrazones **3** were synthesized by refluxing 2,4-dihydrazinopyrimidine **6** and araldehydes in ethanol with a trace of glacial acetic acid on water bath for about 2–3 h [12,13].

3,9-Diaryl-bis-1,2,4-triazolo[4,3-a][4,3-c]pyrimidines **4**

General Procedure. To a stirred solution of hydrazones **3** (0.01 mol) in dichloromethane (25 mL) at room temperature, IBD (0.02 mol) was added in four to five portions during 5 min. The solvent was evaporated on a steam bath and the residual mass containing product and iodobenzene triturated with petroleum ether to give solid product, which was recrystallized from methanol to yield pure bis-triazolopyrimidines **4**.

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