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Short communication

Hypervalent iodine mediated synthesis of 1-aryl/hetryl-1,2,4-triazolo[4,3-*a*] pyridines and 1-aryl/hetryl 5-methyl-1,2,4-triazolo[4,3-*a*]quinolines as antibacterial agents

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Abstract

Oxidation of 2-pyridyl and 2-quinylhydrazones with iodobenzene diacetate (IBD) in dichloromethane yield 1-aryl/hetryl-1,2,4-trizolo-[4,3-*a*] pyridines (**3a**–**f**) and 1-aryl/hetryl-5-methyl-1,2,4-triazolo[4,3-*a*] quinolines (**6a**–**f**). Seven compounds were tested in vitro for their antibacterial activity. 1-(5′-Nitro-2-furyl)-5-methyl-1,2,4-triazolo[4,3-*a*]quinoline (**6e**) was associated with substantially higher antibacterial activity than some commercial antibiotics against *Salmonella typhi* at MIC i.e. 10 μg mL^{-1}.

Keywords: Iodobenzenediacetate; Brigeheadtriazoles; Triazolopyridines; Triazoloquinolines; Antibacterial activity

1. Introduction

As part of our on going studies dealing with the use of hypervalent iodine reagents in the synthesis of various types of heterocycles [1], [2] and bridgehead heterocycles [3], we have extended the scope of our recently developed hypervalent iodine mediated synthesis of bridgehead triazoles [4] to the synthesis of 1,2,4-triazolo [4,3-*a*]pyridines (**3a**–**f**) and 1,2,4-triazolo[4,3-*a*]quinolines (**6a**–**f**) as antibacterial agents [5].

2. Chemistry

Treatment of benzaldehyde 2-pyridylhydrazone (**2a**) with iodobenzenediacetate (IBD) in dichloromethane for about 1 h at room temperature resulted in the formation of a single product, which was identified as 1-phenyl-1,2,4-triazolo[4,3-*a*]pyridine (**3a**). The generality of this facile transformation was established by converting other 2-pyridylhydrazones (**2b**–**f**) and 4-methyl-2-quinolinylhydrazones (**5a**–**f**) to the corresponding 1-aryl/hetryl-1,2,4-triazolopyridines (**3b**–**f**) and 1-aryl/hetryl-5-methyl-1,2,4-triazoloquinolines (**6a**–**f**) in good yields (Scheme 1).

It should be noted that triazolopyridines **3a**–**e** have been synthesized by previously oxidation of 2-pyridylhydrazones (**2a**–**e**) with nitrobenzene [6], or lead–tetracetate [5,7,8]. Synthesis of triazoloquinolines **6a**,**c** and **d** has been reported by microwave irradiation of 2-quinolinylhydrazones (**5a**–**f**) in acetic anhydride [9].

The structures of the known compounds were confirmed by comparison of their m.p.s with literature m.p.s and spectral data (IR, ^{1}H-NMR). The new products were fully characterized by elemental analysis, IR, ^{1}H-NMR and mass spectra. A comparison of the literature m.p.s and spectral data of known compounds **3a**–**e** with ours indicate that data of compounds **3a**–**e** was identical with those reported in literature. However, the m.p.s of **6a** (196–98 °C) and **6c** (150–152 °C) [9] are different from our products (**6a**, 152–53 °C and **6c**, 201–202 °C). Therefore, it became essential to synthesize authentic sample of **6a** and **6c** by using reported

Abbreviations: IBD, iodobenzene diacetate; MIC, minimum inhibitory concentration; DMF, dimethylformamide; NA, nutrient agar.

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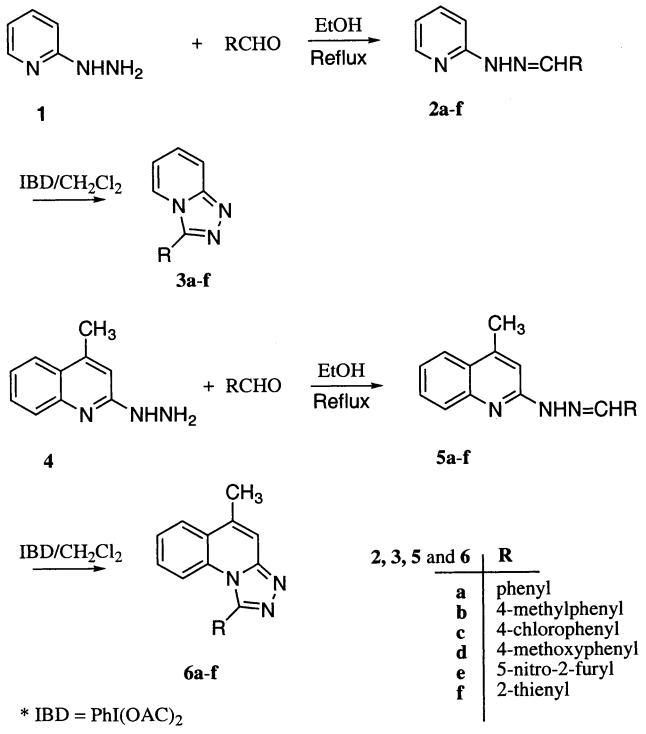

Scheme 1.

procedure [9]. Since m.p.s, TLC and spectral data of the compounds prepared by known procedure [9] were identical to those obtained by hypervalentiodine approach, the reported data might be in error.

3. Biological investigation and results

Compounds **3b**–**f**, **6c** and **6e** were tested in vitro for their antibacterial activity against *Bacillus subtilis*, *Lactobacillus bulgaricus* and *Salmonella typhi*. 1-(5′-Nitro-2-furyl)-5-methyl-1,2,4-triazoloquinoline (**6e**) was associated with higher antibacterial activity than the reported triazolopyridine **3e** [5] against selected bacterial strains. Its activity was also compared with the commercial antibiotics and **6e** was found to be more potent against *S. typhi* at MIC i.e. 10 μg mL^{-1} (Table I).

4. Experimental

4.1. Chemical synthesis

Melting points were determined in open capillaries in electrical melting point apparatus and are uncorrected. IR (nujol) and ^{1}H-NMR were recorded on Buck and Bruker (300 MHz) spectrometers, respectively. Mass spectra were measured on a Kratos MS-50 mass spectrometer. All the new compounds gave satisfactory analytical results (within ±0.4 of the theoretical values).

4.1.1. Hydrazones *2a–f* and *5a–f*

Hydrazones **2a**–**f** and **5a**–**f** were prepared according to the literature procedure [6,8,10]. The characterization of the new hydrazones are given.

2f: m.p. 173–75 °C, yield 90%. IR cm^{-1} 3410 N–H str.; ^{1}H-NMR δ 7.95 (s, 1H, =C–H), 6.74–8.13 (m, 7H, Ar–H), 9.32 (s, 1H, –N–H exchangeable with D_2O).

5b: m.p. 155–56 °C, yield 88%. IR cm^{-1} 3437 N–H str.; ^{1}H-NMR δ 2.36 (s, 3H, C_4'–CH_3), 2.67 (s, 3H, C_4–CH_3), 7.63 (s, 1H, N–H, exchangeable with D_2O), 7.16–7.73 (m, 12H, Ar–H) and 7.97 (s, 1H, –CH=N–).

5e: m.p. 225–26 °C, yield 95%. IR cm^{-1} 3430 N–H str.; ^{1}H-NMR δ 2.63 (s, 3H, C_4–CH_3), 7.03–7.94 (m, 8H, Ar–H) 7.97 (s, 1H, –CH=N–) and 9.30 (s, 1H, N–H, exchangeable with D_2O).

5f: m.p. 171–72 °C, yield 87%. IR cm^{-1} 3430 N–H str.; ^{1}H-NMR δ 2.67 (s, 3H, C_4–CH_3), 6.67–7.84 (m, 7H, Ar–H), 7.83(s, 1H, –CH=N–) and 9.30 (s, 1H, N–H, exchangeable with D_2O).

4.1.2. 1-Aryl-1,2,4-triazolo[4,3-a] pyridines (*3a–f*) and 6-methyl-1,2,4-triazolo[4,3-a]quinolines (*6a–f*)

4.1.2.1. General procedure. Hydrazone **2** (0.005 mol) was dissolved in 20 mL of dichloromethane. IBD (0.005 mol) was added and the reaction mixture was stirred at room temperature (r.t.) for about 1 h. The excess solvent was evaporated in vaccuo and the resulting mass was crystallized from ethanol or benzene/pet-ether to afford the product **3**.

3a: m.p./lit. [8]; m.p. 173–75/176 C, yield 70%.

3b: m.p./lit. [6]; m.p. 154–55/151 C, yield 68%.

3c: m.p./lit. [6]; m.p. 190–91/192 °C, yield 78%.

3d: m.p./lit. [6]; m.p. 124–26/127 °C, yield 82%.

3e: m.p./lit. [5]; m.p. 254–56/255–57 °C, yield 50%.

3f: m.p. 162–63 °C, yield 71%

^{1}H-NMR δ 6.93–6.96 (m, 1H, C_4'–H), 7.22–7.33 (m, 2H, C_5–H, C_6–H), 7.55–7.56 (d, 1H, C_3'–H, $J = 3$ Hz), 7.64–7.65 (d, 1H, C_5'–H, $J = 3$ Hz), 7.83–7.86 (d, 1H, C_4–H, $J = 8$ Hz), 8.37–8.40 (d, 1H, C_7–H, $J = 8$ Hz). *m/z* M^+ 201.

6a: m.p./lit. [9]; m.p. 152–53/196–98 °C, yield 75%. ^{1}H-NMR δ 2.65 (s, 3H, C_5–CH_3), 7.35–7.90 (m, 9H, Ar–H). *m/z* M^+ 259.

6b: m.p. 213–214 °C, yield 67%. ^{1}H-NMR δ 2.50 (s, 3H, C_4'–CH_3), 2.64 (s, 3H, C_5–CH_3), 7.14–8.23 (m, 9H, Ar–H). *m/z* M^+ 273.

6c: m.p./lit. [9]; m.p. 201–202/150–52 °C, yield 77%. ^{1}H-NMR δ 2.64 (s, 3H, C_5–CH_3), 7.38–7.94 (m, 9H, Ar–H). *m/z* M^+ 293/295.

6d: m.p./lit. [9]; m.p. 162–63/172–74 °C, yield 73%. ^{1}H-NMR δ 2.64 (s, 3H, C_5–CH_3), 3.93(s, 3H, C_4'–OCH_3), 7.08–7.91(m, 9H, Ar–H). *m/z* M^+ 289.

6e: m.p. 182–83 °C, yield 71%. ^{1}H-NMR δ 2.66 (s, 3H, C_5–CH_3), 7.30–7.99 (m, 7H, Ar–H). *m/z* M^+ 294.

Table I
In vitro antibacterial activity

Compound	Conc. (μg mL^{-1})	% Age inhibition		
		Bacillus	*Lactobacillus bulgaricus*	*Salmonella typhi*
3b	500	43.6	25.69	35.4
	100	15.0	11.25	12.0
	50	Nil	Nil	Nil
3c	500	29.4	19.3	30.0
	100	Nil	Nil	Nil
	50	Nil	Nil	Nil
3d	500	Nil	Nil	Nil
3e	500	100.00	100.00	100
	100	100.00	100.00	100
	50	98.25	97.50	100
	10	76.20	75.80	100
3f	500	Nil	Nil	Nil
6c	500	18.75	12.2	46.8
	100	8.74	9.7	11.2
	50	Nil	Nil	Nil
6e	500	100.00	100.00	100.00
	100	100.00	100.00	100.00
	50	100.00	100.00	100.00
	10	100.00	94.52	90.01
Ciprofloxacin	500	–	–	100.00
	10	–	–	Nil
Chloroamphenicol	500	–	–	75.8
	10	–	–	Nil
Ofloxacin	500	–	–	99.2
	10	–	–	Nil

6f: m.p. 164–65 °C, yield 82%. ^{1}H-NMR δ 2.64 (s, 3H, C_5–CH_3), 7.27–7.93 (m, 8H, Ar–H). *M*/*z* M^+ 265.

All the compounds were crystallized in ethanol except **3e** and **6e**, which were crystallized in $CHCl_3$–ethylacetate.

5. In vitro antibacterial assays

The stock solution (1 μg mL^{-1}) of the test chemical was prepared by dissolving 10 μg of the chemical in 10 mL of DMF. The stock solution was suitably diluted with sterilized distilled water to get dilutions of 500, 100 and 50 μg mL^{-1}. Control for each dilution was prepared by diluting 10 mL of DMF instead of stock solution, with sterilized distilled water.

Spread-plate method was used for *B. subtilis* and *L. bulgaricus*. For this 24-h-old broth cultures were diluted up to 10^{-3}. Fifty microliters of the test chemical of required dilution and 50 μL of culture broth of 10^{-3} dilution were mixed to make a total volume of 0.1 mL. It was then spread on the surface of nutrient agar (NA) plates. For control, 50 μL of respective dilution of DMF was added instead of the dilution of test chemical. Plates were incubated overnight at 30 °C and the colonies in the test and control plates were counted.

Pour-plate method was used for *S. typhi* (as it is motile). Twenty-four-hour-old broth culture of *S. typhi* was diluted to 10^{-3}. To the petri plates, was added 500 μL of the test chemical of the required dilution and 500 μL of culture of 10^{-3} dilution to make a total volume of 1 mL. Sufficiently cooled NA medium was poured to the petri plates and rotated them to mix the contents. For control, 500 μL of respective dilution of DMF was added in place of the dilution of test chemical. Plates were incubated overnight at 30 °C and the colonies in the test and control plates were counted to get percent inhibition by the test chemical.

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