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Short communication

Molecular iodine: A highly efficient catalyst for the synthesis of 7-arylbenzopyrano[1,3]diazepines in non-protic solvents

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Abstract

A simple and facile synthesis of 7-arylbenzopyrano[1,3]diazepines has been accomplished by treatment of 4-hydroxycoumarin, cyanoguanidine with aromatic or heteroaromatic aldehydes using molecular iodine in non-protic solvent under reflux. This method not only provide an excellent complement for 7-arylbenzopyrano[1,3]diazepines but also avoids the multistep and harsh reaction conditions.

Keywords: 7-Arylbenzopyrano[1,3]diazepines; Molecular iodine; Non-protic solvents; 4-Hydroxycoumarin; Aromatic or heteroaromatic aldehydes

The prevalence of diazepines [1] in natural product and pharmacological active compounds has resulted in a number of synthetic approaches to these heterocycles [2]. 1,4-Diazepines are well known for their pharmaceutical properties. The discovery of diazepam followed by many other psychotropic agents sharing 1,4-benzodiazepines skeleton has also promoted the studies of the isomeric 1,5- and 1,3-benzodiazepines ring system [3]. In contrast, 1,3-diazepines are relatively little known [4]. Some 1,3-diazepine-2-ones and other cyclic ureas have received considerable attention recently as potential anti-AIDS drug [5]. There are several methods have been reported in the literature for the synthesis of annelated diazepines. One of this method involves the use of azirinium ylides in the synthesis of fluorinated 4*H*-1,3-diazepines via 1,3-dipolar cycloaddition [6]. Unlike fused 1,3-diazepines [7], monocyclic 1,3-diazepines are poorly studied, however, some perhydroderivatives have received considerable attention. Literature methods for non-fused 1,3-diazepines reported are photolytic ring expansion of 2-azido or tetrazolopyridines [8], reaction of 2*H*-azirines with 1,2,4-triazines or 1,3-oxazines [9] derivatives and reaction of diazirines with cyclobutadienes [10]. Further 1,3-diazepines-2-one can also be synthesised from palladium catalysed cycloaddition of 2-vinylpyrrolidines with aryl isocyanates [11].

Although most of these procedures suffers with many drawbacks like lengthy, multistep, requires expensive, commercially non-available reagents and hazardous catalyst with an out come of poor yields. Therefore, it was thought worthwhile to develop a simple, efficient, inexpensive, nontoxic, eco-friendly and convenient procedure for title compounds.

Owing to unique catalytic properties of molecular iodine, it has been extensively used for plethora of organic reactions [12]. Recently, molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations, affording the corresponding products with high selectivity in excellent yields. The mild Lewis [13] acidity associated with iodine enhanced its usage in organic synthesis to give several organic transformation using stoichiometric levels to catalytic amounts. Owing to advantages associated with this eco-friendly catalyst [14], molecular iodine has been explored as a powerful catalyst for various organic transformations.

As a part of our continuing effort in the laboratory toward the development of new methods [15] for expeditious synthesis of bioactive heterocycles compounds [16] and usage of iodine for organic transformation [17], we here in report a novel and efficient method for benzopyrano[1,3]diazepines scaffold using molecular iodine as a catalyst. This is a simple, rapid, one port and eco-friendly protocol for synthesis of annelated diazepines.

An initial study was performed by the treatment of 4-hydroxycoumarin **1**, cyanoguanidine **2** and benzaldehyde **3a** in acetonitrile in the presence of catalytic amount of I_2 (10 mol%)

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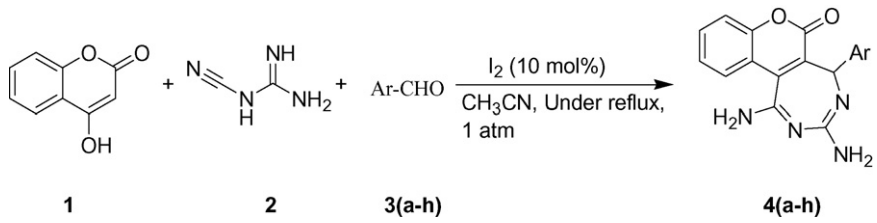
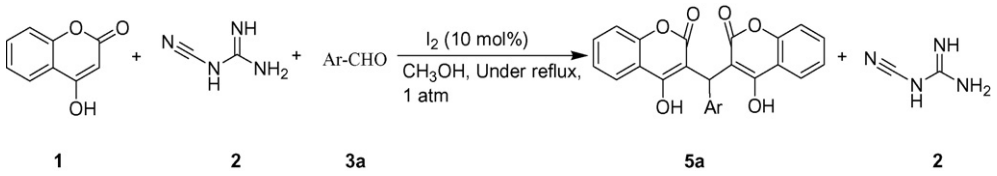


Scheme 1. Iodine catalysed synthesis of 7-arylbenzopyrano[1,3]diazepines.



Scheme 2. Synthesis of 3,3′-phenylmethylenebis-(4-hydroxycoumarin) in protic solvent.

Table 1
Catalytic activity evaluation for 7-arylbenzopyrano[1,3]diazepines[a] synthesis

Entry	Iodine (mol%)	Time (h)	Yield (%)[b]
1	0	48	0
2	10	3.2	89
3	20	2.9	91
4	30	2.5	92
5	50	2.2	95

[a] Reaction conditions: benzaldehyde (1 mmol); 4-hydroxycoumarin (1 mmol); cyanoguanidine (1 mmol); solvent CH_3CN; under reflux; 1 atm.
[b] Isolated and unoptimized yields.

Table 3
Effect of solvent on the synthesis of 7-arylbenzopyrano[1,3]diazepines[a]

Entry	Solvents	Product	Time (h)	Yield (%)[b]
1	Methanol	**5a**	3.5	48
2	Ethanol	**5a**	3.0	51
3	Dichloromethane	**4a**	2.9	92
4	Tetrahydrofuran	**4a**	4.6	85
5	Acetonitrile	**4a**	3.2	89

[a] Reaction conditions: benzaldehyde (1 mmol); 4-hydroxycoumarin (1 mmol); cyanoguanidine (1 mmol); I_2 (10 mol%); under reflux; 1 atm.
[b] Isolated and unoptimized yields.

at room temperature. To our delight, we observed the formation of benzopyrano[1,3]diazepines **4a** in 84% yields after 12 h (Scheme 1). Where as in the absence of catalyst, the reaction did not yield any product even after long reaction times. With these encouraging results in hand, further investigations were carried out for best reaction conditions. The increase in the amount of iodine upto 50 mol% not only enchances the product yield, but also reduces the reaction times as depicted in Table 1. Faster reaction also occurred on increasing the temperature (Table 2). Thus, we proceed further with 10 mol% of molecular iodine under reflux conditions, so that only catalytic amount is used.

The surprising results were obtained when the same reaction was tried with different solvents. In protic polar solvents like methanol, ethanol the condensation of 4-hydroxycoumarin with benzaldehyde facilitates bis adduct 3,3′-phenylmethanebis-(4-hydroxycoumarin) **5a** (Scheme 2). However, same reactions in non-protic solvents like dichloromethane and tetrahydrofuran leads to the formation of benzopyrano[1,3]diazepines with excellent yields (Table 3). Thus, it is concluded that formation of benzopyrano[1,3]diazepines are favoured only in the non-protic solvents. However, extent of polarity of solvents has not shown much effect on the formation of the desired product.

Various aldehydes (**3a**–**h**) exemplify the versatility of this simple protocol. As shown in Table 4, aromatic and heteroaromatic aldehydes (both electron withdrawing and electron donating group) reacted equally effectively and smoothly to produce a range of benzopyrano[1,3]diazepines derivatives.

Table 2
Effect of temperature on iodine catalysed 7-arylbenzopyrano[1,3]diazepines[a] synthesis

Entry	Temperature (°C)	Time (h)	Yield (%)[b]
1	Room temperature	30	68
2	45	18	74
3	60	10	83
4	75	8	89
5	Under reflux	3.2	89

[a] Reaction conditions: benzaldehyde (1 mmol); 4-hydroxycoumarin (1 mmol); cyanoguanidine (1 mmol); solvent CH_3CN; I_2 (10 mol%); 1 atm.
[b] Isolated and unoptimized yields.

Table 4
Iodine promoted synthesis of 7-arylbenzopyrano[1,3]diazepines[a]

Entry	**3**	Ar	Time (h)	Product	Yield (%)[b]
1	**3a**	$-C_6H_5$	3.2	**4a**	89
2	**3b**	4-ClC_6H_4	2.8	**4b**	91
3	**3c**	3-$NO_2C_6H_4$	3.4	**4c**	92
4	**3d**	2-HOC_6H_4	4.8	**4d**	85
5	**3e**	4-$MeOC_6H_4$	4.0	**4e**	93
6	**3f**	$-CH{=}CH-C_6H_4$	1.5	**4f**	96
7	**3g**	3,4-Piperonyl	3.7	**4g**	87
8	**3h**	2-Thiophenyl	2.5	**4h**	90

[a] Reaction conditions: 4-hydroxycoumarin (1 mmol); cyanoguanidine (1 mmol); aromatic/heteroaromatic aldehydes (1 mmol); I_2 (10 mol%); solvent CH_3CN; under reflux; 1 atm.
[b] Isolated and unoptimized yields.

Complete conversion and good to excellent isolated yields were observed for all substrate employed.

In conclusion, this is first report for the synthesis of benzopyrano[1,3]diazepines utilizing molecular iodine as a novel catalyst in a non-protic solvents. This method not only provide an excellent complement to benzopyrano[1,3]diazepines but also avoids the multistep and harsh reaction conditions. Thus, this is an environmentally benign process for the generation of desired product in good to excellent yields in less reaction times.

1. Experimental

1.1. General

Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer FTIR-1710 spectrophotometer using Nujol film. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance Spectrospin 300 (300 MHz) using TMS as internal standard and chemical shift are in δ. Elemental analysis was performed on a Horeaus CHN Rapid analyzer. Mass spectra were recorded on a Waters LCT Micromass. The temperature of the reaction mixture was measured through a infrared thermometer (model 8868). The purity of compounds was checked on aluminium plates coated with silica gel (Merck) using 20% ethylacetate in *n*-hexane as eluantand. The isolated product **4a**–**h** were further purified by column chromatography using silica gel (Aldrich 24, 217–9, 70, 35–70 mesh, 40 Å, surface area 675 m^2/g) and purified products were recrystallised.

1.2. Synthesis

General procedure for the preparation of 7-arylbenzopyrano[1,3]diazepines (**4a**–**h**).

A mixture of 4-hydroxycoumarin **1** (1 mmol), cyanoguanidine **2** (1 mmol) aromatic and heteroaromatic aldehydes **3a**–**h** (1 mmol) and iodine (10 mol%) in 15 ml of CH_3CN was stirred at 100 °C for the appropriate time mentioned in Table 3. The completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (having small amount of $Na_2S_2O_3$). The solid crude products, which separated out, were filtered, washed with water and dried. The isolated products which were single spot on TLC (silica gel coated aluminium plates, Merck) were subjected to further purification by column chromatography using silica gel with 25% ethylacetate in petroleum ether as eluent to yield 7-arylbenzopyrano[1,3]diazepines **4a**–**h**.

1.3. The spectral data of synthesized compounds are given below

*1.3.1. Compound **4a***

mp 230–232 °C; IR (cm^{-1}, Nujol): 3330, 3296, 3157, 1728, 1687, 1643, 1614 and 1456; ^{1}H NMR ($CDCl_3$; Me_4Si; 300 MHz): δ 5.5 (1H, s, CH), 7.3–7.8 (9H, m, 9× CH), 8.2 (2H, br, NH_2) and 10.1 (2H, br, NH_2); ^{13}C NMR ($CDCl_3$; Me_4Si; 75 MHz): δ 50.3, 123.4, 125.0, 125.2, 125.6, 125.7, 126.0, 127.4, 130.2, 130.4, 130.8, 138.3, 140.7, 149.9, 164.1 and 165.3; HRMS: *m*/*z* 318.08 (M^+). Anal. calcd. for $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43; N, 17.60. Found: C, 67.86; H, 4.40; N, 17.53.

*1.3.2. Compound **4b***

mp 236–240 °C; IR (cm^{-1}, Nujol): 3380, 3349, 3176, 1727, 1689, 1651, 1620 and 1456; ^{1}H NMR ($CDCl_3$; Me_4Si; 300 MHz): δ 5.5 (1H, s, CH), 7.3–7.8 (8H, m, 8× CH), 8.1 (2H, br, NH_2) and 9.9 (2H, br, NH_2); ^{13}C NMR ($CDCl_3$; Me_4Si; 75 MHz): δ 49.3, 118.7, 125.7, 125.9, 126.5, 127.6, 127.9, 128.1, 130.3, 130.9, 132.0, 132.4, 133.8, 138.4, 150.0, 168.8 and 170.2; HRMS: *m*/*z* 351.86 (M^+). Anal. calcd. for $C_{18}H_{13}N_4O_2Cl$: C, 61.28; H, 3.71; N, 15.88. Found: C, 61.34; H, 3.63; N, 15.82.

*1.3.3. Compound **4c***

mp 240–242 °C; IR (cm^{-1}, Nujol): 3428, 3326, 3140, 1729, 1691, 1648, 1624, 1527, 1459 and 1349; ^{1}H NMR ($CDCl_3$; Me_4Si; 300 MHz): δ 5.8 (1H, s, CH), 7.5–7.9 (8H, m, 8× CH), 8.3 (2H, br, NH_2) and 10.1 (2H, br, NH_2); ^{13}C NMR ($CDCl_3$; Me_4Si; 75 MHz): δ 51.3, 120.2, 120.8, 125.6, 125.7, 126.0, 126.8, 127.3, 130.0, 140.2, 145.8, 148.4, 168.8 and 170.8; HRMS: *m*/*z* 362.67 (M^+). Anal. calcd. for $C_{18}H_{13}N_5O_4$: C, 59.5; H, 3.61; N, 19.28. Found: C, 59.43; H, 3.72; N, 19.03.

*1.3.4. Compound **4d***

mp 230–234 °C; IR (cm^{-1}, Nujol): 3583, 3423, 3287, 3187, 1722, 1671, 1638 and 1458; ^{1}H NMR ($CDCl_3$; Me_4Si; 300 MHz): δ 6.1 (1H, s, CH), 7.0–7.8 (8H, m, 8× CH), 8.0 (2H, br, NH_2), 9.0 (1H, s, OH) and 10.2 (2H, br, NH_2); ^{13}C NMR ($CDCl_3$; Me_4Si; 75 MHz): δ 45.8, 118.3, 120.8, 120.9, 124.0, 125.0, 125.1, 125.2, 125.7, 130.6, 132.3, 141.4, 160.2, 164.0 and 168.3; HRMS: *m*/*z* 333.83 (M^+). Anal. calcd. for $C_{18}H_{14}N_4O_3$: C, 64.66; H, 4.22; N, 16.76. Found: C, 64.32; H, 4.28; N, 16.59.

*1.3.5. Compound **4e***

mp 216–218 °C; IR (cm^{-1}, Nujol): 3423, 3391, 3177, 1728, 1680, 1641, 1608, 1457, 1257 and 1036; ^{1}H NMR ($CDCl_3$; Me_4Si; 300 MHz): δ 3.7 (3H, s, CH_3), 5.4 (1H, s, CH), 6.9–7.9 (8H, m, 8× CH), 8.2 (2H, br, NH_2) and 10.2 (2H, br, NH_2); ^{13}C NMR ($CDCl_3$; Me_4Si; 75 MHz): δ 54.6, 55.8, 113.2, 119.1, 125.4, 125.5, 126.0, 126.4, 126.8, 128.1, 128.7, 130.2, 137.3, 148.3, 160.0, 160.9, 165.8 and 167.4; HRMS: *m*/*z* 348.22 (M^+). Anal. calcd. for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.44; H, 4.58; N, 16.15.

*1.3.6. Compound **4f***

mp 206–208 °C; IR (cm^{-1}, Nujol): 3410, 3341, 3380, 3155, 1724, 1694, 1680, 1650, 1620, 1494 and 1455; ^{1}H NMR ($CDCl_3$; Me_4Si; 300 MHz): δ 4.2 (1H, d, CH, J_{HZ} = 4.6), 6.8 (1H, d, CH, J_{HZ} = 7.2), 7.0 (1H, t, CH, J_{HZ} = 8.4), 7.2–7.9 (8H, m, 8× CH) and 8.3 (4H, br, 2× NH_2); ^{13}C NMR ($CDCl_3$; Me_4Si; 75 MHz): δ 50.4, 120.3, 125.7, 126.0, 126.1, 127.4, 127.6, 128.0, 128.1, 128.8, 130.3, 138.3, 140.8, 148.6, 161.2, 165.9 and 173.3; HRMS: *m*/*z* 343.81 (M^+). Anal. calcd. for $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.80; H, 4.61; N, 16.18.

*1.3.7. Compound **4g***

mp 244–246 °C; IR (cm^{-1}, Nujol): 3430, 3392, 3180, 1732, 1685, 1664, 1616, 1456, 1233 and 1039; ^1H NMR ($CDCl_3$; Me_4Si; 300 MHz): δ 2.4 (2H, s, CH_2), 5.4 (1H, s, CH), 7.0–7.9 (7H, m, 7× CH), 8.2 (2H, br, NH_2) and 10.1 (2H, br, NH_2); ^{13}C NMR ($CDCl_3$; Me_4Si; 75 MHz): δ 55.6, 88.9, 110.6, 112.3, 120.9, 124.9, 125.3, 128.0, 128.3, 129.1, 130.8, 140.0, 143.2, 145.5, 148.2, 148.8, 165.1, 170.3 and 170.8; HRMS: *m/z* 362.0 (M^+). Anal. calcd. for: C, 62.98; H, 3.89; N, 15.46. Found: C, 62.88; H, 3.81; N, 15.40.

*1.3.8. Compound **4h***

mp 210–212 °C; IR (cm^{-1}, Nujol): 3411, 3302, 3072, 1726, 1687, 1640, 1608 and 1454; ^1H NMR ($CDCl_3$; Me_4Si; 300 MHz): δ 5.8 (1H, s, CH), 6.5–6.8 (3H, m, 3× CH, thiophene), 7.6–7.9 (4H, m, 4× CH), 8.2 (2H, br, NH_2) and 10.0 (2H, br, NH_2); ^{13}C NMR ($CDCl_3$; Me_4Si; 75 MHz): δ 56.1, 120.2, 120.9, 124.2, 124.8, 125.0, 125.8, 126.0, 127.6, 127.8, 128.1, 138.3, 140.3, 148.5, 168.3 and 170.8; HRMS: *m/z* 324.65 (M^+). Anal. calcd. for: C, 59.25; H, 3.73; N, 17.27; S, 9.89. Found: C, 59.21; H, 3.66; N, 17.31; S, 9.79.

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