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Rapid generation of *N,N'*-diacylhydrazines by I_2 or Br_2/hydrazine hydrate: A facile route to 1,3,4-oxadiazoles

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ABSTRACT

We report the rapid preparation of symmetrical aldazines, ketazines and *N,N'*-Diacylhydrazines by $NH_2NH_2{\cdot}H_2O$ in presence of molecular iodine or bromine at 0–10ºC. This method afforded an exceedingly convenient route to the preparation of 1,3,4-Oxadiazoles. The reactions are safe, affording excellent yields of high purity products in shorter durations and the work-up procedure involves no solvent extraction, which is environmentally acceptable.

KEYWORDS

Hydrazine hydrate;
Azines;
N,N'-diacylhydrazines;
1,3,4-oxadiazoles.

INTRODUCTION

Azines have been extensively studied due to their utility in a number of interesting organic reactions and applications[1]. Azines also participate in [3 + 2] cycloadditions reactions as an ene fragment[2]. Furthermore, azines have received attention as possible non-linear optical (NLO) materials[3–5]. Derivatives of azine have been reported to possess variety of biological activities, important being the antibacterial and antifungul[6], anticonvulsant[7], antidepressant[8], anti-inflammatory[9], antiviral[10], anticancer[11], platelet inhibitors[12] and of aldose reductase[13]. Azines have also been used in the synthesis of novel organometallic compounds[14].

On the other hand, 1,3,4-oxadiazole and its derivatives have attracted a great deal of attention in pharmaceuticals, which is well documented in the literature. For example, 1,3,4-oxadiazoles act as antiemetic[15], antibacterial[16], anticonvulsant[17], hypnotic and sedative agents[18]. They also exhibit muscle relaxant[19], antimitotic[20], analgesic[15], antiinflammatory[15], anticonvulsive[15] and diuretic[15] activities. 1,3,4-oxadiazoles have also been utilized in the field of photosensitization and liquid crystals[21]. 1,3,4-oxadiazoles have also attracted significant interest in medicinal chemistry as ester bioesters in a number of biological targets including benzodiazepine receptor agonists[22], 5-HT receptor agonists[23], muscarinic agonists[24], 5-HT antagonists[25], Human NK_1 antagonists[26] and antirhinoviral compounds[27].

Methods have been developed for the preparation of azines under various conditions[28], but still have drawbacks since the most of the reported procedures do not meet the demand of simplicity, require elevated tem-

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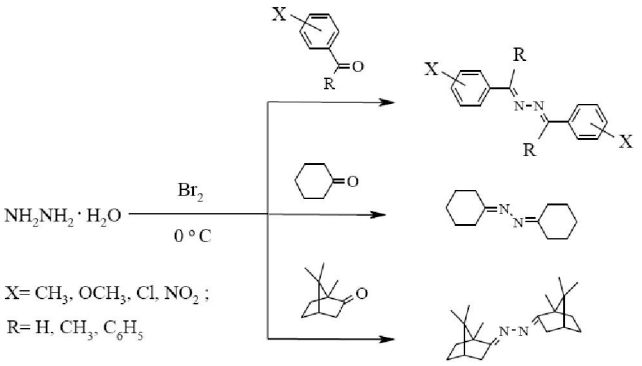
perature, complex catalysts and unstable starting materials. Due to the importance of azines in chemistry and biology, methods have been developed for the preparation of these compounds under various conditions, but none of them meet the demand of simplicity, require elevated temperature, complex catalysts and unstable starting materials.

RESULTS AND DISCUSSION

In continuation of our research on the effective utilization of hydrazine and its derivatives in presence or absence of metal catalysts, we have reported some interesting transformations[29]. Recently, we found that hydrazine hydrate in presence of iodine is an efficient and convenient system for the rapid generation of a series of symmetrical azines[30]. In this communication molecular bromine was tested instead of iodine to reproduce the same results as shown in scheme 1 (TABLE 1). The method worked well for the rapid generation of aldazines and ketazines from both aliphatic and aromatic carbonyl compounds.



Scheme 1

When benzoyl chloride was subjected to the above reaction condition, we observed the rapid formation of colorless solid and thought of getting either the corresponding hydrazide or benzalazine. Benzoyl chloride displays a strong absorption band at 1850 cm^{-1} of the IR spectrum due to C=O stretching which is shifted to 1685 cm^{-1} in the product. Also, a characteristic absorption at 3452 and 3209 cm^{-1} due to –NH stretching is observed. Further, ^1H NMR and Mass spectroscopy supported the formation of *N,N'*-Dibenzoylhydrazine.

The earlier procedures to obtain *N,N'*-Dibenzoylhydrazine involve the oxidation of hydrazides using various oxidizing agents such as lead tetra acetate[31], diacetoxy iodobenzene[32], trifluorotoluonyl sulfonyl peroxide[33] and Oxone[34], copper(II) acetate[35] and by acids such as sulfuric acid[36], phenylselenic acid[37] $NaBO_3$-AcOH[38] and Amberlyst A-26[39]. *N,N'*-diacylhydrazines have also been synthesized by the oxidation of hydrazines by benzeneselenic acid[40], Chlorine[41], aryl sulfonyl peroxides[42] and iodobenzene diacetate[43]. However, all these reported-methods require expensive reagents, drastic reaction conditions and sometimes, tedious workup procedures.

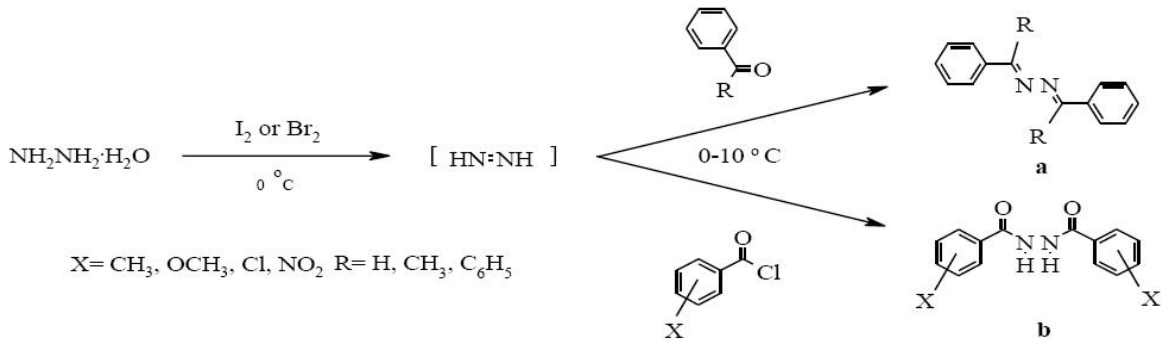
TABLE 1 : Rapid generation of azines from carbonyl compounds by $Br_2/NH_2NH_2{\cdot}H_2O$

Entry	R	X	Time (s)	Yield (%)	m.p. °C	
					Found	Reported
a1	H	H	60	98	92-93	93[1a]
a2	H	3-NO_2	60	98	197-199	196-197[1b]
a3	H	4-NO_2	60	98	299-302	297-298[1b]
a4	H	4-Cl	60	97	207-209	207[1c]
a5	H	4-CH_3	100	98	152-153	153[1a]
a6	H	4-OMe	100	97	179-181	179-180[1b]
a7	H	4-OH	100	96	265-268	268[1d]
a8	H	3,4-OMe	100	96	192-193	193[1c]
a9	CH_3	H	100	97	120-121	121-122[1a]
a10	CH_3	4-OH	120	96	222-224	222-223[1d]
a11	Ph	Ph	120	95	163-165	164[1a]
a12	Cyclohexanone		30	97	36	36[1c]
a13	Camphor		150	92	186-187	185-186[1e]
a14	Cinnamaldehyde		60	96	161-162	162[1b]
a15	Furfuraldehyde		65	93	111-112	110-111[1b]

Therefore we wanted to optimize the reaction of getting *N,N'*-diacylhydrazines and to check the suitability of the method, a series of substituted benzoyl chlorides were prepared and subjected to the above reaction conditions and get the desired *N,N'*-Dibenzoylhydrazines in excellent yields as shown in Scheme 2 and the results are summarized in TABLE 2.

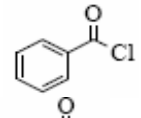
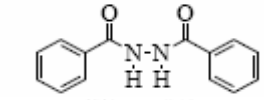
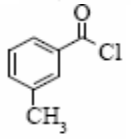
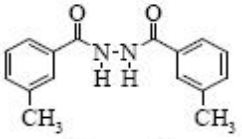
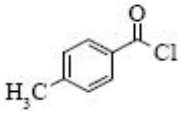
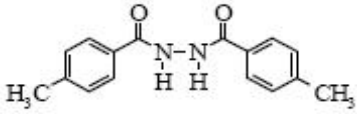
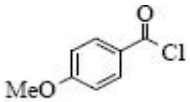
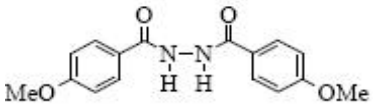
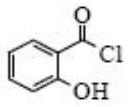
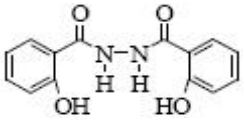
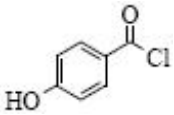
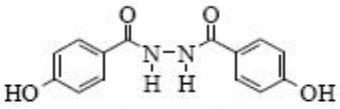
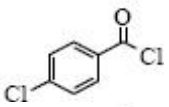
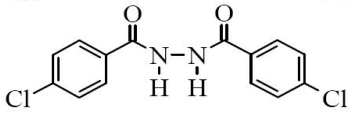
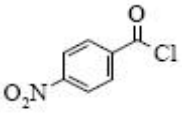
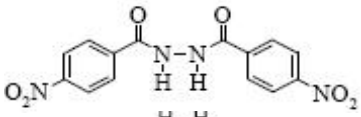
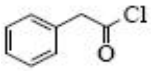
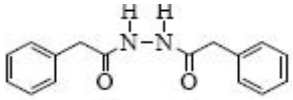
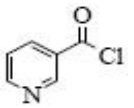
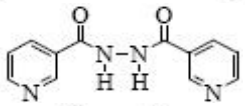
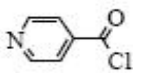
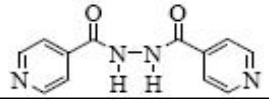
1,3,4-oxadiazoles have been reported to possess a wide spectrum bioactivities such as anti microbial, anti malarial, anti tubercular, anti inflammatory, anti convulsant and anti HIV activities and are best prepared by the cyclization of *N,N'*-diacylhydrazines under various reaction conditions including the reagents such as P_2O_5[44], $POCl_3$[45], PPh_3[46] and $SOCl_2$[47].

In view of the importance of 1,3,4-oxadiazoles and since *N,N'*-diacylhydrazines can easily be obtained by



Scheme 2

TABLE 2 : Rapid generation of *N,N'*-Diacylhydrazines from acylchlorides by hydrazine hydrate in presence of molecular iodine or bromine

Entry	Substrate	Time(min)/ Yield (%)	Product	m.p. °C	
				Found	Reported
b1		5/98		238–239	238–240[48]
b2		5/91		208–209	210[49]
b3		5/93		252–253	253–254[50]
b4		5/92		227–228	228–228.5[51]
b5		5/88		314–316	315–316[52]
b6		6/90		258–259	260[49]
b7		5/85		288–289	292[51]
b8		5/82		295–297	297–298[53]
b9		5/86		235–236	236–237[54]
b10		5/77		226–227	227–228[51]
b11		5/82		254–255	254–255[55]

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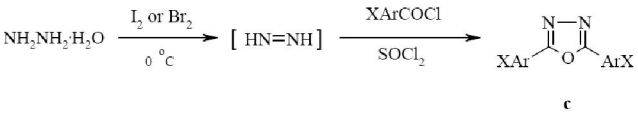
our procedure, we tried the above reagents for the cyclization of *N,N'*-diacylhydrazines and found best results with $SOCl_2$. Therefore we decided to synthesize 1,3,4-oxadiazoles directly from benzoyl chlorides without isolating *N,N'*-diacylhydrazines and succeeded in getting a series of substituted 1,3,4-oxadiazoles in excellent yields as shown in Scheme 3 and the results are summarized in TABLE 3.



X= CH_3, OCH_3, Cl, NO_2 R= H, CH_3, C_6H_5

Scheme 3

TABLE 3 : One-pot synthesis of 1,3,4-oxadiazoles

Entry	ArX	Reaction Time (h)	Yield (%)	m.p. °C	
				Found	Reported
c1	Ph	1.60	86	137–138	138[56]
c2	4-ClC_6H_4	1.60	85	240–241	242[57]
c3	4-$OMeC_6H_4$	1.60	80	159–160	162[58]
c4	2-OHC_6H_4	1.75	84	207–208	209[56]
c5	3-Pyridyl	1.75	80	186–187	188[56]
c6	4-Pyridyl	1.75	82	188–189	189[58]
c7	4-OHC_6H_4	1.65	83	347–348	350[58]
c8	4-$CH_3C_6H_4$	1.75	82	173–174	174[56]
c9	3-$CH_3C_6H_4$	1.75	80	71–72	72[59]
c10	$PhCH_2$	1.75	75	98–99	98-99.5[60]

EXPERIMENTAL

Acylhalides were prepared by standard procedures in our laboratory. Hydrazine hydrate (99%) was obtained from Aldrich Chem; Bromine and iodine (resublimed) and thionyl chloride were obtained from Aldrich chemicals. Methanol was of commercial grade and redistilled before use. TLC were performed on precoated silica gel on Aluminium plates. The compounds on TLC were detected by exposing the plates to UV light or to iodine vapour. IR and ^1H NMR spectra were recorded on NICOLET 400D FT-IR and Bruker 400 MHz spectrometer respectively.

Typical procedure for the rapid generation of azines

Molecular Bromine (480 mg, 6 mmol) in small portions was added to Hydrazine hydrate (300 mg, 6 mmol) taken in 50 mL round bottomed flask at 0°C carefully with constant stirring. (Care must be taken while adding bromine to hydrazine hydrate since the reaction is very violent which produce lots of fume, should be carried out in fume cup-board). To this resulting mixture, benzaldehyde (1.061 g, 10 mmol) was charged dropwise at 0–10ºC. Yellow solid soon separated was filtered, recrystallized from ethanol to get 1.02 g (98%) of benzalazine crystals.

Typical procedure for the preparation of *N,N'*-Dibenzoylhydrazine

Hydrazine hydrate (99–100 %, 300 mg, 6 mmol) taken in 50 mL round bottomed flask was added molecular iodine (762 mg) or bromine (480 mg) in small portions at 0°C carefully with constant stirring. To this resulting mixture, benzoyl chloride (1.405 g, 10 mmol) in methanol (5 mL) was added maintaining the temperature at 0–10 ºC, a colorless solid obtained within 5 min. The contents were poured onto 100 mL of 10% sodium hydroxide taken in 250 mL beaker to get colourless precipitate which was filtered and dried to get *N,N'*-dibenzoyl hydrazine (1.177 g) in 98% yield.

One-pot synthesis of 2,5-Diphenyl-1,3,4-oxadiazole

Hydrazine hydrate (300 mg, 6 mmol) taken in 50 mL round bottomed flask was added molecular iodine (762 mg) or bromine (480 mg) in small portions at 0°C carefully with constant stirring. To this resulting mixture, benzoyl chloride (1.405 g, 10 mmol) in methanol (5 mL) was added maintaining the temperature at 0–10ºC, a colorless solid obtained within 5 min. The contents were cooled to 0°C and thionyl chloride (1.428g, 12 mmol) was added drop wise and refluxed for 1.5 h, cooled to room temperature, poured onto crushed ice (200 g) taken in 400 mL beaker, the solid obtained was filtered off and washed with water, dried and recrystallized to afford the 2,5-disbstituted-1,3,4-oxadiazoles in 80–86% yield.

SPECTRAL DATA OF SELECTED PRODUCTS

(a1) Benzalazine

IR (KBr): ν = 3053, 3007, 2955, 2355, 1962,

1626, 1574, 1502, 1455, 1316, 1212, 1070, 1020, 964, 762, 705 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ: 7.41-7.52 (m, 6H), 7.82-7.86 (d, 4H, *J*= 9.9 Hz), 8.63 (s, 2H).

(a9) Acetophenone azine

IR (KBr): ν = 3167, 3059, 2934, 2397, 1719, 1678, 1616, 1450, 1336, 1264, 1119, 762, 700 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 2.35 (s, 3H), 6.98-7.20 (m, 10H).

(b1) N,N'-Dibenzoylhydrazine

IR (KBr): ν = 3214, 3059, 3007, 1672, 1636, 1579, 1543, 1491, 1295, 876, 695, 607, 540 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ: 7.49-7.61 (m, 6H), 7.90-7.92 (d, 4H, *J*= 6.3 Hz), 10.56 (br, 2H); LCMS: 241.4 (Exact mass = 240.2).

(b8) N,N'-bis(p-nitrobenzoyl)hydrazine

IR (KBr): ν = 3447, 3203, 3007, 1678, 1636, 1579, 1548, 1491, 1295, 700 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ: 8.07-8.09 (d, 4H, *J*= 7.4 Hz), 8.21-8.23 (d, 4H, *J*= 7.6 Hz), 10.67 (br, 2H).; LCMS: 329.1 (Exact mass = 330.26).

(c1) 2,5-Diphenyl-1,3,4-oxadiazole

IR (KBr): ν = 3073, 1667, 1557, 1287, 1024, 968, 832, 659 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ: 7.26–8.19 (m, 10H, Ar-H).

(c4) 2,5-Di-(2-hydroxyphenyl)-1,3,4-oxadiazole

IR (KBr): ν = 3093, 1556, 1254, 1033, 1022, 962, 831, 618 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ: 7.01–7.94 (m, 8H, ArH), 10.83 (s, 2H, OH).

CONCLUSIONS

In summary the procedures developed by us for the rapid generation of substituted azines, *N,N'*-diacylhydrazines and one-pot synthesis of 1,3,4-oxadiazoles are new, mild, inexpensive; requires shorter durations, affords excellent yields and are environmentally acceptable since isolation of products do not require organic solvents.

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