A simple and efficient approach for synthesis of hydrazones from carbonyl compounds and hydrazides catalyzed by meglumine

Mo Zhang[1], Ze-Ren Shang[1], Xiao-Tang Li[1], Jia-Nan Zhang[1], Yong Wang[1], Kang Li[1], Yang-Yang Li[1], Zhan-Hui Zhang[1]

[1]College of Chemistry and Material Science, Hebei Normal University, Shijiazhuang, P. R. China

CONTACT: Z.-H. Zhang, College of Chemistry and Material Science, Hebei Normal University, Shijiazhuang 050024, P. R. China. Email: zhanhui@126.com

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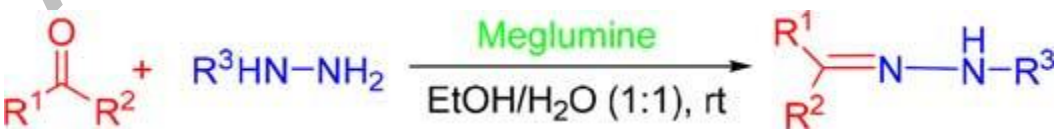
Abstract

A simple, environmentally benign protocol for synthesis of hydrazones from carbonyl compounds and hydrazides has been developed in the presence of meglumine in aqueous-ethanol media at room temperature. The salient features of the present protocol are mild reaction conditions, short reaction time, high yields, operational simplicity, metal-free, applicability toward large-scale synthesis as well as the use of biodegradable and inexpensive catalyst.

Graphical Abstract:



KEYWORDS: Hydrazones; Carbonyl compounds; Hydrazides; Meglumine; Metal-free; Green and sustainable chemistry

INTRODUCTION

Hydrazone derivatives are a class of fundamental organic molecules and they can be used as valuable building blocks for synthesis of bioactive natural products and functional materials.[1] These hydrazone-based molecules have also shown a broad range of biological properties such as monoamine oxidase inhibitory,[2] antiproliferative,[3] antiplatelet aggregation,[4] amoebicide,[5] insecticidal,[6] antimicrobial activities,[7] EGFR inhibitors,[8] antiinflammatory and analgesic agents.[9] In addition, they have been utilized as dyes,[10] fluorescent sensor,[11] and ligands in chemical synthesis[12]. Besides, the preparation of highly crystalline hydrazone derivatives has been known as a very effcient method for the characterization, isolation, and purification of carbonyl compounds.[13]

As a classical approach for the synthesis of hydrazone derivatives, condensation of carbonyl compounds and hydrazides is the most widely employed strategy, but it requires harsh dehydrating conditions.[14] Some acid catalysts such as glacial acetic acid,[15] SiO_2/H_2SO_4,[16] polystyrene sulfonic acid,[17] $Mg(ClO_4)_2$,[18] zeolites,[19] Dowex (strongly acidic cationic exchange resin) polymer,[20] choline chloride–oxalic acid[21] and $[Et_3NH][HSO_4]$,[22] have been developed to promote this reaction. This reaction has also

been performed under ultrasonic irradiation,[23] microwave irradiation,[24] or by kneading ball-milling technique.[25] Although these protocols were efficient workednicely in many cases for synthesis of hydrazone derivatives, sometimes, however, some methods suffer from one or more disadvantages such as the use of volatile organic solvents, unsatisfactory yields, overoxidization of aldehydes to the carboxylic acids, long reaction times, high temperature, difficulties in the product isolation, the lack of generality or the requirement of special apparatus. Especially, many protecting groups are deprotected easily under acidic conditions. Thus, the development of a more efficient method for synthesis of hydrazone derivatives under environmentally benign conditions is still highly desirable**.**

Recently, significant attention has been focused on using bio-based materials as solvent or catalyst in organic synthesis.[26] Meglumine is an attractive candidate as it possesses environmentally benign properties such as bio-degradablity and physiological inertness. It is an amino sugar derived from sorbitol and can be used in the formulation of pharmaceuticals as an excipient and in conjunction with iodinated compounds in contrast media due to its low toxicity. It has also important properties such as inexpensive, non-corrosive, stable to air and moisture and readily available in the market. In 2012, Gu *et al*. introduced meglumine and gluconic acid aqueous solution as a promoting medium for the reaction of β-ketosulfones and formaldehyde.[27] Very recently, meglumine has been used as an efficient catalyst for synthesis of functionalized 2-amino-4*H*-pyrans,[28]

pyranopyrazole derivatives,[29] pyrazolopyranopyrimidines,[30] dihydropyridines[31] and pyrazoles.[32] Under all these backgrounds and our research interests on the development of environmentally benign methodologies for the preparation of bioactive and fine chemicals,[33] herein, we descried the use of meglumine as a catalyst to promote the condensation of hydrazides with carbonyl compounds for synthesis of hydrazones (Scheme 1).

RESULTS AND DISCUSSION

For our initial investigation, benzaldehyde and phenylhydrazine were taken as the model substrates to optimize the reaction conditions. We explored the reaction of an equimolar of benzaldehyde and phenylhydrazine in aqueous-ethanol at room temperature in the presence of various catalysts. As shown in Table 1, in the absence of the catalyst a low yield (49%) of the expected (*E*)-1-benzylidene-2-phenylhydrazine (**3a**) was obtained (Table 1, entry 1). Although all catalysts have provided the desired product **3a** with yields ranging from 56-90%, meglumine was proven to be the most effective. In addition, the reaction could be shortened to 30 min using meglumine as a catalyst (entry 11).

Next, we found that the solvent played an important role in the success of this reaction. The reaction using EtOH and water gave the corresponding product **3a** in high yields (Table 2, entries 4 and 5). While the results with other solvents such as CH_2Cl_2, glycerin,

and PEG 400 were not much impressive. Further studies showed that aqueous-ethanol (1:1, v/v) was the best choice of solvent for this transformation (Table 2, entry 10). The effect of catalyst loading was also evaluated in the model reaction. The results showed that 15 mol% of catalyst was the best choice for the present reaction. Decreasing the amount of catalyst to 10 mol% resulted in relatively low yield (entry 11). When the reaction was conducted with increasing amounts of meglumine, the yield of **3a** could not be further increased. From the above investigations, the optimized reaction conditions were established by employing benzaldehyde (1 mmol), and phenylhydrazine (1 mmol) with meglumine (0.15 mmol) in aqueous-ethanol (1:1 v/v, 4 ml) at room temperature for 30 min.

In order to demonstrate the efficiency as well as the practical applicability of the catalytic system, a reaction of benzaldehyde with phenylhydrazine was performed at the 100 mmol scale with meglumine (15 mmol) in aqueous-ethanol (1:1, v/v) (400 mL). The corresponding product **3a** was obtained in 91% yield (Table 2, entry 13). By using these optimized conditions, this process will be useful to industries for the larger-scale production of various hydrazones.

Having identified the optimized reaction conditions, we next commenced exploring the scope and generality of this process. As evidenced in Table 3, a variety of substituted aromatic aldehydes, regardless of the presence of electron-donating or

electron-withdrawing functional groups attached to benzene rings could react with phenylhydrazine to give the desired products in high to excellent yields. It is indicated that the electron-withdrawing substitutent on aromatic rings has a positive effect on the transformation. The reaction is slightly sensitive to the steric hindrance of benzaldehyde, as 2-methoxybenzaldehyde displays lower reactivity than its *para*-substituted homologue. Furthermore, aromatic heterocyclic aldehydes such as picolinaldehyde and thiophene-2-carbaldehyde (Table 3, entries 12 and 13) could be applied as suitable starting materials for this transformation and gave the corresponding products in high yields. It is also important to note that the reactions were efficient for aliphatic and α,β-unsaturated aldehydes (entries 14-16) under similar reaction conditions. Notably, the method was found applicable for the preparation of bis-hydrazone by reaction of terephthalaldehyde with 2 equivalents of phenylhydrazine, giving the corresponding product **3q** in 89% yield (entry 17).

Encouraged by these results, we next applied this protocol to less electrophilic ketones. Without any optimization, we are pleased to find that cyclic ketones such as cyclohexanone and adamantan-2-one as well as alkyl-alkyl ketones, and aryl-alkyl ketones also underwent this conversion to afford the respective hydrazones in high yields under these conditions. Notably, silyl ethers can be cleaved under acidic conditions. It is quite exciting to find out that trimethylsilyl and triethylsilyl ethers were well tolerated in this process and no desilylated products were detected (entries 29 and 30).

Isatin and its derivatives have been shown to possess a broad spectrum of bioactivity. These interesting properties promoted us to further showcase the synthetic usefulness of the developed method for isatins. As shown in Table 3, various isatins having electron-neutral, electron-deficient, and electron-rich substituents on the aryl ring underwent this transformation affording the expected hydrazones in high yields (entries 31-33).

Subsequently, arylhydrazines bearing different functional groups were evaluated. Satisfactorily, aryhydrazines having either electron-donating or electron-withdrawing group worked well and delivered expected products in high to excellent yields. Alkyl substituted hydrazine such as *tert*-butylhydrazine was also investigated and the corresponding product **3aq** was obtained in 76% yield.

Furthermore, when phenylhydrazine was replaced by hydrazine, (1*E*,2*E*)-1,2-dibenzylidenehydrazine (**4**) was obtained in 83% yield by reaction of 2 equivalents of benzaldehyde and hydrazine (Scheme 2).

The structures of the products were determined by spectroscopic analysis, and the structure of product **3al** (CCDC 1408548) was also confirmed by single-crystal X-ray analysis (Figure 1).

CONCLUSION

In summary, we have developed a novel catalytic approach for synthesis of hydrazones from carbonyl compounds and hydrazides in the presence of meglumine in aqueous-ethanol media. This method is applicable to a wide range of aldehydes, including aromatic, aliphatic, α,β-unsaturated and heterocyclic substrates, ketones and isatins. The attractive features of this procedure are the mild reaction conditions, high conversions, wide substrate scope, and use of inexpensive and environmentally friendly catalyst, all of which make it an attractive strategy for large-scale industrial preparation of hydrazones.

EXPERIMENTAL

Melting points were determined on an X-5 digital melting point apparatus and are uncorrected. The FT-IR spectra were obtained as KBr pellets or liquid films on KBr pellets with a Thermo Fisher is50 spectrometer. NMR spectra of the products were recorded on a Bruker Avance III 500 in $CDCl_3$ using tetramethylsilane as an internal reference. The mass spectra were performed on a 3200 Qtrap instrument with an ESI source.

General Procedure For Synthesis Of Hydrazones

To a mixture of carbonyl compound (1 mmol) and hydrazine (1 mmol) in aqueous-ethanol (1:1, 4 ml) was added meglumine (0.15 mmol). The reaction mixture was stirred at room temperature and monitored by TLC. After completion of the reaction, water (5 ml) and ethyl acetate (5 ml) were added and the product was extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The crude product was then purified by column chromatography or recrystallized (petroleum ether–EtOAc).

Selected Spectral Data For (*E*)-1-(3,4-Dimethoxybenzylidene)-2-Phenylhydrazine (3d)

Yellow solid, mp 136–138 °C; IR (KBr): 3303, 3054, 1747, 1598, 1508, 1463, 1418, 1022 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 10.07 (s, 1H), 7.84 (s, 1H), 7.32 (s, 1H), 7.21 (t, J = 8.0 Hz, 2H), 7.11-7.09 (m, 3H), 6.91 (d, J = 8.0 Hz, 1H), 6.72 (t, J = 7.0 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 161.5, 149.6, 149.5, 145.9, 137.4, 129.5, 129.2, 119.9, 119.0, 112.4, 112.0, 108.3, 55.8, 55.7; ESI-MS: m/z = 283 $(M+1)^+$; Anal. calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.08; H, 6.68; N, 10.15%.

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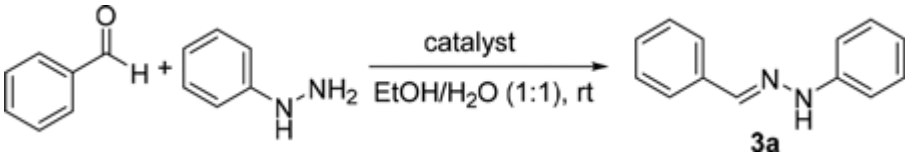
Table 1. Screening catalysts for the reaction of benzaldehyde and phenylhydrazine[a]



Entry	Catalyst	Time (min)	Yield (%)
1	no	60	49
2	TsOH	60	71
3	L-(-)-Proline	60	61
4	Betaine HCl	60	75
5	Et_3N	60	80
6	Piperidine	60	74
7	Na_2CO_3	60	56
8	Chitosan	60	78
9	Mannitol	60	72
10	1,3-Dimethylurea	60	73
11	Meglumine	30	90

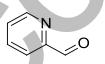
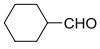
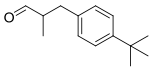
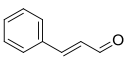
[a] Experimental conditions: benzaldehyde (1 mmol), phenylhydrazine (1 mmol), catalyst (0.15 mmol), EtOH: H_2O (1:1, 4 ml), room temperature.

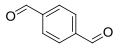
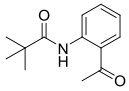
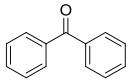
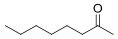
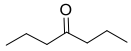
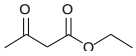
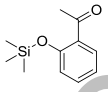
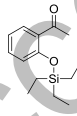
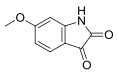
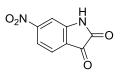
Table 2. Optimization of reaction conditions[a]

Entry	Solvent	Catalyst loading (mol%)	Time (min)	Yield (%)
1	CH_2Cl_2	15	60	62
2	CH_3CN	15	60	68
3	MeOH	15	60	70
4	EtOH	15	60	72
5	H_2O	15	60	80
6	Glycerin	15	60	56
7	PEG 400	15	60	53
8	Glycerin/H_2O (1:1)	15	60	73
9	PEG 400/H_2O (1:1)	15	60	70
10	EtOH/H_2O (1:1)	15	30	90
11	EtOH/H_2O (1:1)	10	60	82
12	EtOH/H_2O (1:1)	20	30	90
13[b]	EtOH/H_2O (1:1)	15	40	91

[a] Experimental conditions: benzaldehyde (1 mmol), phenylhydrazine (1 mmol), solvent (4 ml), room temperature.[b]100 mmol scale.

Table 3. Scope of reaction of carbonyl compounds and hydrazides catalyzed by meglumine

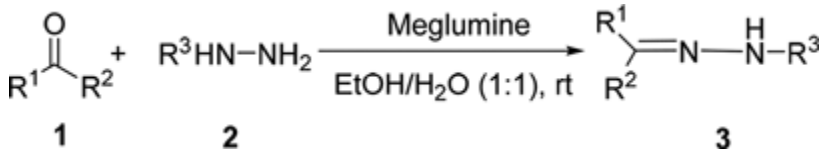
Entry	Carbonyl compounds	R^3	Product	Time (min)	Yield (%)[a]
1	PhCHO	Ph	**3a**	30	90
2	2-$OMeC_6H_4CHO$	Ph	**3b**	65	80
3	4-$OMeC_6H_4CHO$	Ph	**3c**	55	84
4	3,4-$(OMe)_2C_6H_3CHO$	Ph	**3d**	65	79
5	2,3,4-$(OMe)_3C_6H_2CHO$	Ph	**3e**	70	75
6	4-FC_6H_4CHO	Ph	**3f**	25	95
7	4-ClC_6H_4CHO	Ph	**3g**	25	95
8	4-BrC_6H_4CHO	Ph	**3h**	25	96
9	2-$NO_2C_6H_4CHO$	Ph	**3i**	30	92
10	3-$NO_2C_6H_4CHO$	Ph	**3j**	30	95
11	4-$NO_2C_6H_4CHO$	Ph	**3k**	25	95
12		Ph	**3l**	40	85
13		Ph	**3m**	40	80
14		Ph	**3n**	40	86
15		Ph	**3o**	25	86
16		Ph	**3p**	30	90

17[b]		Ph	**3q**	70	89
18		Ph	**3r**	50	86
19		Ph	**3s**	60	81
20		Ph	**3t**	40	89
21		Ph	**3u**	100	72
22		Ph	**3v**	40	82
23		Ph	**3w**	25	88
24		Ph	**3x**	40	84
25		Ph	**3y**	40	82
26		Ph	**3z**	35	82
27		Ph	**3aa**	25	90
28		Ph	**3ab**	35	82
29		Ph	**3ac**	90	75
30		Ph	**3ad**	100	73
31		Ph	**3ae**	40	86
32		Ph	**3af**	50	81
33		Ph	**3ag**	40	88
34	PhCHO	3-MeC_6H_4	**3ah**	40	89

35	4-$OMeC_6H_4CHO$	3-MeC_6H_4	**3ai**	55	85
36	4-ClC_6H_4CHO	3-MeC_6H_4	**3aj**	25	91
37	PhCHO	2,4,6-$Cl_3C_6H_2$	**3ak**	20	85
38	2-OHC_6H_4CHO	2,4,6-$Cl_3C_6H_2$	**3al**	40	82
39	4-ClC_6H_4CHO	2,4,6-$Cl_3C_6H_2$	**3am**	20	88
40		2-$OMeC_6H_4$	**3an**	20	86
41		2-$OMeC_6H_4$	**3ao**	30	85
42		2,4,6-$Cl_3C_6H_2$	**3ap**	40	80
43	4-ClC_6H_4CHO	^{t}Bu	**3aq**	50	76

[a] Isolated yield. [b]2 equivalents of phenylhydrazine were used and bis-hydrazone was obtained.

Scheme 1. Synthesis of hydrazones catalyzed by meglumine



1 **2** **3**

Scheme 2. Synthesis of (1*E*,2*E*)-1,2-dibenzylidenehydrazine (**4**) catalyzed by meglumine.

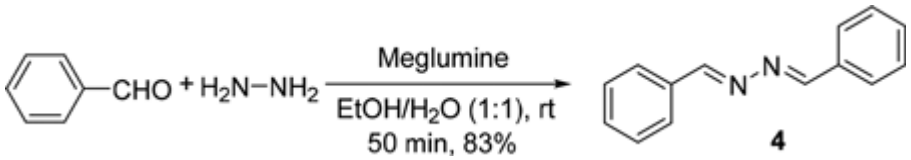


Figure 1. X-ray crystal structural of compound **3al**.