ISSN 1070-3632, Russian Journal of General Chemistry, 2016, Vol. 86, No. 12, pp. 2837–2844. © Pleiades Publishing, Ltd., 2016.

Lewis Acid-Promoted Direct Synthesis of N-Unsubstituted Hydrazones via the Reaction of Hydrazine with Acetophenone and Isatin Derivatives[1]

A. S. El-Azab[a,b]*, H. A. Ghabbour[a,c], W. M. El-Husseiny[d], A. R. Maarouf[c,e], M. A. Mohamed[b,f], and A. A.-M. Abdel-Aziz[a,c]**

[a] *Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh, 11451 Saudi Arabia*
**e-mail: adelazaba@yahoo.com; **alaa_moenes@yahoo.com*

[b] *Department of Organic Chemistry, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt*

[c] *Department of Medicinal Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura, 35516 Egypt*

[d] *Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura, 35516 Egypt*

[e] *Department of Pharmaceutical Chemistry, College of Pharmacy, Delta University for Science and Technology, Gamasa City, Egypt*

[f] *Department of Pharmaceutical Chemistry, College of Pharmacy, Prince Sattam Bin Abdulaziz University, AlKharj, Saudi Arabia*

Received June 30, 2016

Abstract—Hydrazones **2**–**22** were synthesized via the reaction of acetophenone with isatin derivatives and anhydrous hydrazine promoted by BF_3 as a Lewis acid at 0°C. Structures of the synthesized hydrazones were determined on the basis of NMR and X-ray crystallographic analyses.

Keywords: efficient method, N-unsubstituted hydrazone, Lewis acids, BF_3, X-ray crystal structure

DOI: 10.1134/S1070363216120471

Hydrazones due to the presence of azometine proton (–NHN=CH–R) in their structure are used in drug discovery and serve as building blocks in synthesis of heterocyclic compounds (Fig. 1) [1]. Therefore, development of new synthetic approaches to such compounds is important for organic and medicinal chemistry [1, 2]. Synthesis of pure N-unsubstituted hydrazones in high yield from aromatic ketones was retarded because of two reactive amino groups in the hydrazine structure that led to formation of corresponding azines as the main products [1, 2]. Several synthetic approaches to N-unsubstituted hydrazones have been reported [3–7]. The general method of synthesis of N-unsubstituted hydrazones was based on the reaction of ketones with hydrazine hydrate in ethanol, methanol or acetic acid in the presence or absence of catalysts [5–7]. Another synthetic approach to N-unsubstituted hydrazones involved the reaction of *N,N*-dimethylhydrazine with aromatic ketones or aldehydes, followed by the reaction of the generated hydrazone with hydrazine hydrate [5]. The above mentioned methods carried some disadvantages, such as expensive catalysts involved, low yields of hydrazones and contamination of products by the corresponding azines. Hence, a versatile synthesis of N-unsubstituted hydrazones under mild conditions was highly desirable.

RESULTS AND DISCUSSION

A convenient method for the synthesis of N-unsubstituted hydrazones via the reaction of an aromatic ketone or isatin with hydrazine in the presence of $BF_3 \cdot OEt_2$ as a Lewis acid at 0°C is presented. The reaction proceeded under mild conditions and led to the C–N bond formation. Such result initiated testing various Lewis acids and solvents in the process. Another objective was the study of influence of substituents attached to ketones and isatins skeleton on the reaction progress. Structures of the target compounds were elucidated by NMR spectrometry and X-ray crystallography.

[1] The text was submitted by the authors in English.

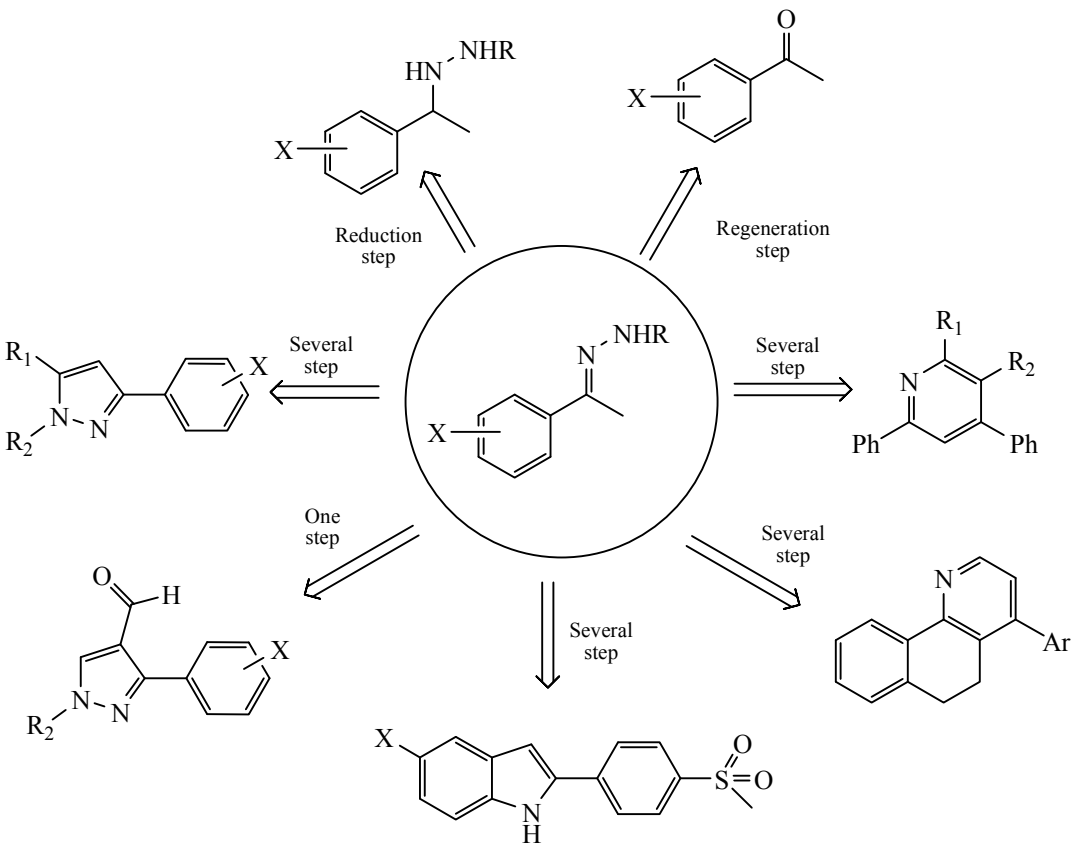


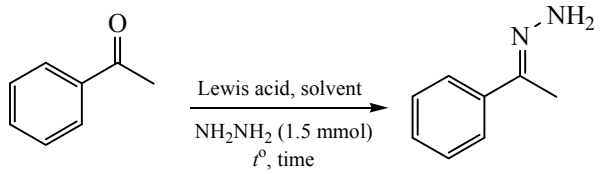
Fig. 1. Synthesis of hydrazine and other heterocyclic compounds based on hydrazones [1, 2].

According to the experimental data, $BF_3 \cdot OEt_2$ was determined to be more efficient than Et_2AlCl in the process of acetophenone formation (Table 1, entries 2 and 10). It promoted the rate of reaction and almost quantitative yield of hydrazones under mild conditions (Table 1, entry 2). In contrast, such Lewis acids as $LaCl_3$, $AlCl_3$, $ZnCl_2$, and $SnCl_4$ were inefficient in the process [2a, 2b, 3] (Table 1, entries 12 and 15). Study of effect of temperature and time upon the reaction (Table 1, entries 1, 3, 4, 10, and 11) indicated that it proceeded most efficiently at 0°C within 30 min. Solvents also affected the reaction rate and yields. For instance, in methylene chloride, toluene, acetonitrile, methanol, or ethanol yields were moderate. On the contrary, THF promoted hydrazone formation (Table 1, entries 2, 5–9).

The method was determined to be applicable to a wide range of acetophenone derivatives. The reaction was studied with acetophenone containing various electronic substituents including halogens, the methyl and methoxy groups (Table 2, compounds **2–10**) [1, 2]. The electron-attracting chlorine on acetophenone supported an increased yield of hydrazone, which may be attributable to higher electrophilic character of the ketone group of acetophenone (Table 2, compound **4**). The result was in contrast with acetophenone containing the electron-repelling methoxy or methyl groups, that suppressed yields of hydrazine (Table 2, compounds **2–4**). Due to steric reasons formation of hydrazone from 2-substituted acetophenone derivatives was lower than that of 4-substituted acetophenones (Table 2, compounds **2–7**).

4-Aminoacetophenone and its *N*-methyl substituted derivative and arylsulfonyl moieties [8] were tested in the reaction (Table 3). N-Substituted 4-aminoacetophenone gave higher yield of the products than the parent 4-aminoacetophenone (Table 3, compound **11** vs **12–17**). Methylsulfonyl derivative led to the product with the higher yield than phenysulfonyl derivatives (Table 3, compound **12** vs **13–17**). Chemical structures of the products were elucidated by NMR and X-ray crystallographic analysis (Fig. 2). Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre and may be

Table 1. Lewis acid promoted reaction of anhydrous hydrazine with acetophenone [2a, 2b, 3]



1

Entry	Lewis acid (equiv.)	Solvent	Temperature, °C	Time, min	Yield, %
1	$BF_3 \cdot Et_2O$ (1.0)	THF	0	30	76
2	$BF_3 \cdot Et_2O$ (1.5)	THF	0	30	96
3	$BF_3 \cdot Et_2O$ (1.5)	THF	0	60	89
4	$BF_3 \cdot Et_2O$ (1.5)	THF	25	60	86
5	$BF_3 \cdot Et_2O$ (1.5)	Acetonitrile	0	30	76
6	$BF_3 \cdot Et_2O$ (1.5)	MeOH	0	30	77
7	$BF_3 \cdot Et_2O$ (1.5)	Ethanol	0	30	79
8	$BF_3 \cdot Et_2O$ (1.5)	CH_2Cl_2	0	30	39
9	$BF_3 \cdot Et_2O$ (1.5)	Toluene	0	30	40
10	Et_2AlCl (1.5)	THF	0	30	67
11	Et_2AlCl (1.5)	THF	0	60	71
12	$LaCl_3$ (1.5)	THF	0	30	17
13	$AlCl_3$ (1.5)	THF	0	30	15
14	$SnCl_4$ (1.5)	THF	0	30	9
15	$ZnCl_2$ (1.5)	THF	0	30	11

obtained on request quoting the deposition number CCDC 1000219 from the CCDC, 12 Union Road, Cambridge CB21EZ, UK. Torsion angles, bond distances and bond angles are deposited as supplementary material.[2]

The carbonyl group containing isatin derivatives were selected due to their broad spectrum of biological activity [9]. Isatin derivatives were treated with anhydrous hydrazine in the presence of $BF_3 \cdot OEt_2$ as a Lewis acid at 0°C for 30 min (Table 4) [10]. Obviously, the reaction with isatin derivatives bearing an electron-repelling group, such as the methoxy group, led to isatin hydrazone in lower yield than isatin derivatives containing electron-attracting groups such as halogens or the NO_2 group (Table 4, compounds **19** vs **20–22**). It is apparent that phenyl substituents in isatin structure could influence the reaction yield. The electron-deficient moieties led to almost quantitative yield of isatin hydrazones.

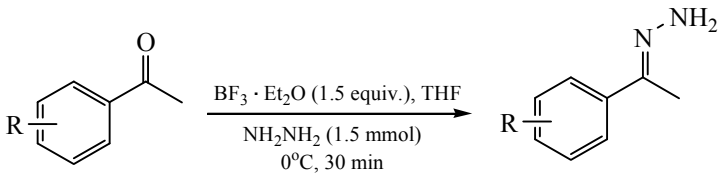
According to the plausible mechanism (Fig. 3) assumed, the first step of the reaction involved coordination of BF_3 with acetophenone or isatin via different complexation modes, including two open modes: *1, 2* (Fig. 3a), and one cyclic mode *3* (Fig. 3a). According to the relative energy calculations model *1* (Fig. 3b) is more favorable than model *2* (Fig. 3b) and model *3* (Fig. 3b). The above-stated coordination facilitated the reaction of hydrazine with ketone and isatin by accelerating the reaction rate by increasing the electrophilicity of the ketone group and a steric effect by hindering formation of azine. Based on these observations, a possible reaction mechanism might depend on electrophilic behavior of the ketone group and the coordination mode model *1*, which facilitated formation of hydrazone.

EXPERIMENATAL

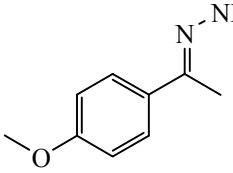
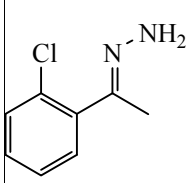
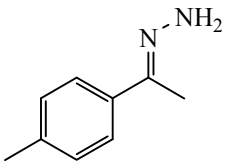
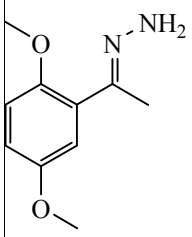
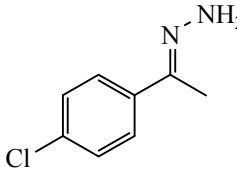
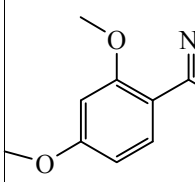
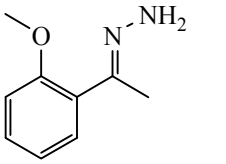
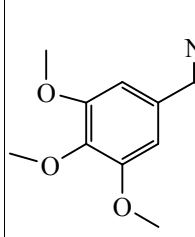
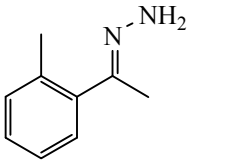
Melting points (uncorrected) were recorded on a Barnstead 9100 Electrothermal melting apparatus. IR

[2] Supplementary data is available from the authors.

Table 2. BF3 promoted reaction of anhydrous hydrazine with substituted acetophenones



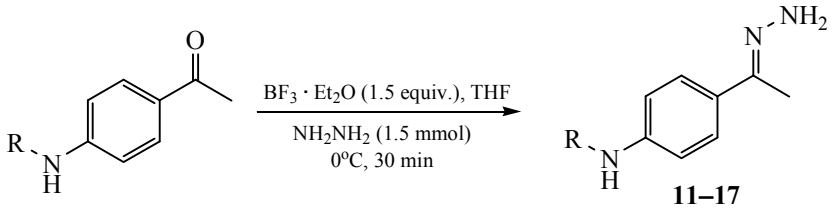
2–10

Comp. no.	R	Hydrazones	Yield, %	References	Comp. no.	R	Hydrazones	Yield, %	References
2	4-MeO		92	[3, 5]	**7**	2-Cl		91	[5]
3	4- Me		91	[3, 5]	**8**	2,5-DiMeO		86	[5]
4	4-Cl		99	[5]	**9**	2,4-DiMeO		87	[5]
5	2-MeO		84	[3, 5]	**10**	3,4,5-TriMeO		85	[6]
6	2-Me		81	[5]					

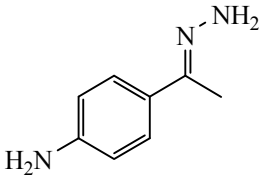
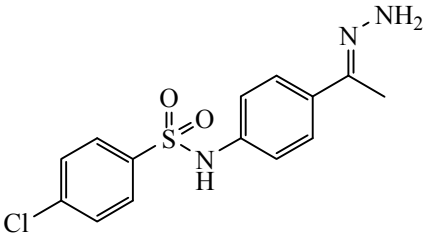
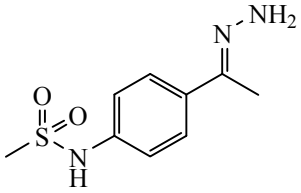
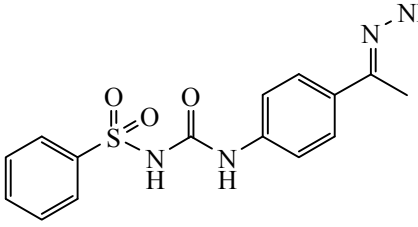
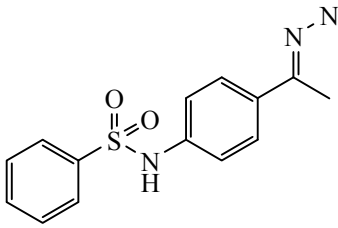
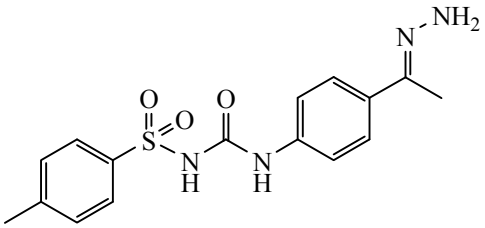
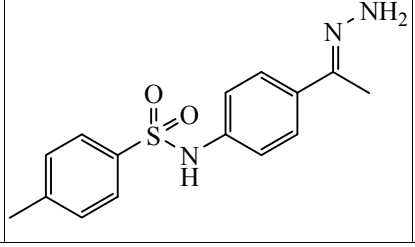
spectra were recorded on a FT-IR Perkin-Elmer spectrophotometer. ^{1}H and ^{13}C NMR were measured in DMSO-d_6 on a Bruker 500 using TMS as the internal standard. Mass spectra were measured on a Perkin-Elmer, Clarus 600T GC/MS and Varian TQ 320 GC/MS/MS mass spectrometers. TLC was performed on precoated (0.25 mm) silica gel GF254 plates (E. Merck, Germany) using 254 nm UV lamp. Silica gel column chromatography (60–230 mesh) was used for routine separations.

General method for hydrazones synthesis 2–22 (Tables 1–4). To a solution of acetophenone or isatin (5 mmol) in THF (10 mL), $BF_3{\cdot}OEt_2$ (7.5 mmol) was

Table 3. BF3 promoted reaction of anhydrous hydrazine with N-substituted 4-aminoacetophenones



11–17

Comp. no.	R	Hydrazones	Yield, %	Comp. no.	R	Hydrazones	Yield, %
11	H		84	**15**	4-Cl-PhSO$_2$–		92
12	MeSO$_2$–		99	**16**	PhSO$_2$–NH–CO–		91
13	PhSO$_2$–		95	**17**	4-Me–PhSO$_2$–NH–CO–		87
14	4-Me–PhSO$_2$–		93				

added at 0°C under the atmosphere of N_2 and the mixture was stirred for 10 minutes. To the cooled mixture, anhydrous hydrazine (7.5 mmol) was added in one portion and the reaction mixture was stirred at 0°C under the atmosphere of N_2 for 30 min. The reaction was quenched by the addition of a saturated solution of NH_4Cl (4 mL), extracted by ethyl acetate (3 × 15 mL) and purified by column chromatography (ethyl acetate–CH_2Cl_2; 3 : 7) to afford hydrazones **2–22**.

***N*-[4-(1-Hydrazonoethyl)phenyl]methanesulfonamide (12)**. mp 252–254°C. IR spectrum, ν, cm^{-1}: 3406, 3269, 1612, 1382, 1311, 1153. ^1H NMR spectrum, δ, ppm: 2.49 s (3H), 3.40 s (3H), 6.29 s (2H, br),

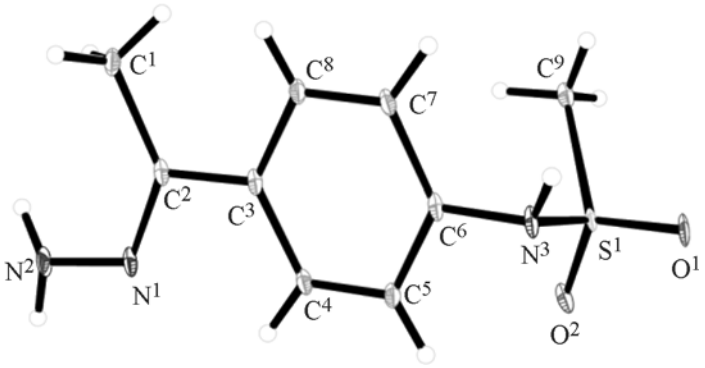


Fig. 2. ORTEP drawing of the basic crystallographic unit of compound **12** with atoms numbering. Displacement ellipsoids are drawn at the 40% probability level and all H atoms are shown as small spheres of arbitrary radii.

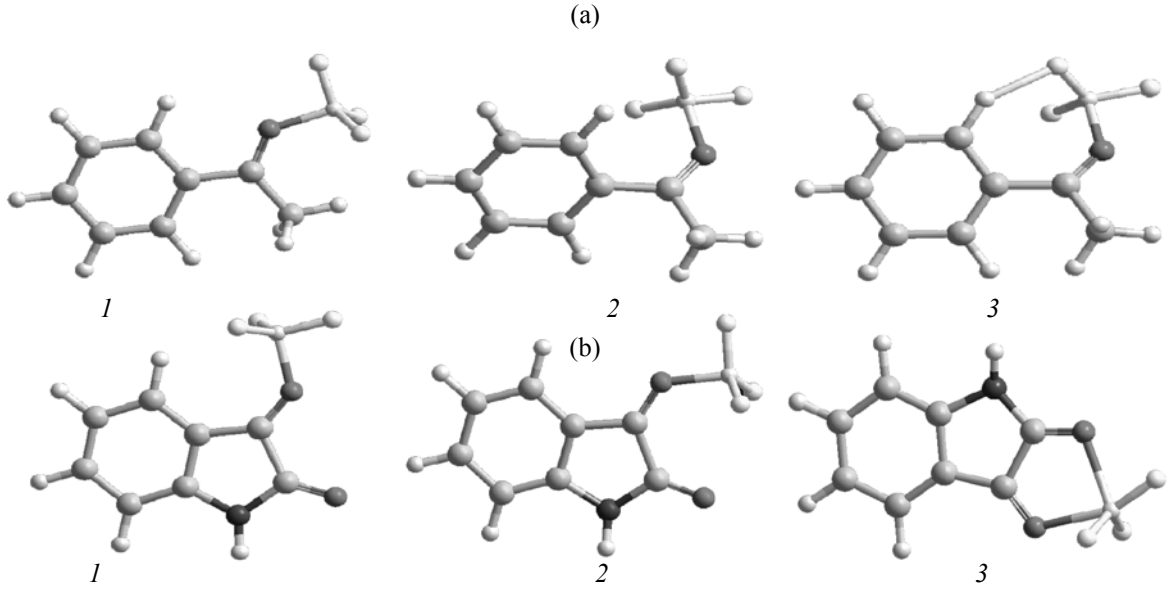


Fig. 3. Possible coordination models of BF_3 with (a) acetophenone and (b) isatin (lower panel) as calculated by PM3 semi-empirical molecular orbital calculations in THF: (*1*) *E*-isomer, (*2*) *Z*-isomer, (*3*) cyclic.

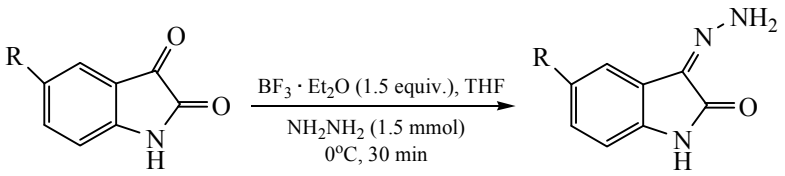
7.62–7.64 d (2H, *J* = 6.0 Hz), 7.99–8.00 d (2H, *J* = 6.0 Hz), 9.90 s (1H, br). ^{13}C NMR spectrum, δ, ppm: 10.96, 38.60, 119.19, 119.26, 119.34, 125.49, 125.60, 135.28, 137.16, 143.45. $C_9H_{13}N_3O_2S$. *m/z* 227.3.

***N*-[4-(1-Hydrazonoethyl)phenyl]benzenesulfonamide (13)**. mp 176–178°C. IR spectrum, ν, cm^{-1}: 3394, 3232, 1609, 1369, 1328, 1155. ^{1}H NMR spectrum, δ, ppm: 2.09 s (3H), 5.41 s (2H, br), 6.98–7.00 d (2H, *J* = 6.5 Hz), 7.41–7.43 t (2H, *J* = 5.5 Hz), 7.44–7.46 d (2H, *J* = 6.0 Hz), 7.51–7.53 t (1H, *J* = 5.5 Hz), 7.79–7.80 d (2H, *J* = 5.5 Hz). ^{13}C NMR spectrum, δ, ppm: 11.81, 120.42, 126.51, 127.17, 129.05, 132.99, 136.28, 136.50, 139.13, 146.87. $C_{14}H_{15}N_3O_2S$. *m/z* 227.3 (289.1).

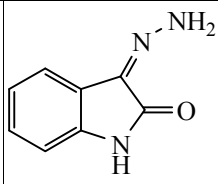
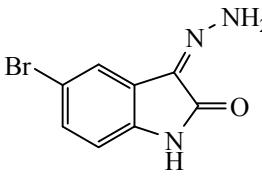
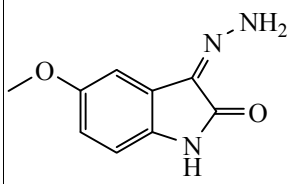
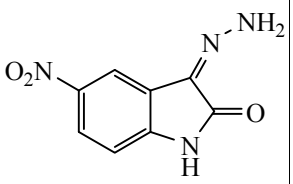
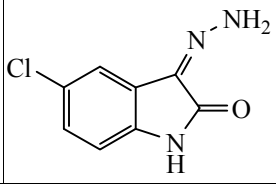
***N*-[4-(1-Hydrazonoethyl)phenyl]-4-methylbenzenesulfonamide (14).** mp 160–162°C. IR spectrum, ν, cm^{-1}: 3407, 3268, 1647, 1382, 1311, 1154. ^{1}H NMR spectrum, δ, ppm: 2.07 s (3H), 2.30 s (3H), 5.412 s (3H, br), 6.97–6.98 d (2H, *J* = 8.0 Hz), 7.14–7.15 d (2H, *J* = 7.0 Hz), 7.39–7.41 d (2H, *J* = 8.0 Hz), 7.65–7.66 d (2H, *J* = 7.5 Hz); ^{13}C NMR spectrum, δ, ppm: 11.81, 21.48, 121.50, 126.44, 127.16, 129.76, 135.92, 136.33, 136.83, 143.91, 147.07. $C_{15}H_{17}N_3O_2S$. *m/z* 227.3 (303.2).

4-Chloro-*N*-[4-(1-hydrazonoethyl)phenyl]benzenesulfonamide (15). mp 155–157°C. IR spectrum, ν, cm^{-1}: 3291, 1667, 1364, 1330, 1193. ^{1}H NMR spectrum, δ, ppm: 2.08 s (3H), 5.58 s (3NH, br), 6.94–6.95 d (2H, *J* = 7.5 Hz), 7.35–7.42 q (4H, *J* = 8.0 Hz), 7.69–7.75 t (2H, *J* = 7.0 Hz). ^{13}C NMR spectrum, δ, ppm: 11.96, 121.72, 126.60, 128.62, 129.33, 136.12, 136.62, 137.69, 139.42, 147.07. $C_{14}H_{14}ClN_3O_2S$. *m/z* 227.3 (323.8).

Table 4. Reaction of anhydrous hydrazine with isatin derivatives promoted by BF3 [9, 10]



18–22

Comp. no.	R	Hydrazones	Yield, %	Comp. no.	R	Hydrazones	Yield, %
18	H		85	**21**	Br		93
19	MeO		86	**22**	NO_2		97
20	Cl		94				

***N*-{[4-(1-Hydrazonoethyl)phenyl]carbamoyl}-benzenesulfonamide (16).** mp 121–123°C. IR spectrum, ν, cm^{-1}: 3393, 1717, 1636, 1327, 1154. ^1H NMR spectrum, δ, ppm: 2.96 s (3H), 5.35 s (2NH, br), 7.43 m (5H), 7.78–7.80 d (2H, *J* = 6.0 Hz), 7.82 m (2H), 7.90 s (1H), 8.01 s (1H). $C_{15}H_{16}N_4O_3S$. *m/z* 227.3 (332.3).

***N*-{[(4-(1-Hydrazonoethyl)phenyl]carbamoyl}-4-methylbenzenesulfonamide (17).** mp 105–107°C. IR spectrum, ν, cm^{-1}: 3394, 1718, 1634, 1328, 1155. ^1H NMR spectrum, δ, ppm: 1.96 s (3H), 2.30 s (3H), 5.02 s (2NH, br), 7.12–7.13 d (2H, *J* = 5.0 Hz), 7.35 s (4H), 7.76–7.77 d (2H, *J* = 5.0 Hz), 7.96 s (1H), 8.19 s (1H). ^{13}C NMR spectrum, δ, ppm: 11.60, 21.37, 117.63, 117.71, 125.42, 126.89, 128.62, 132.26, 140.07, 141.24, 143.40, 145.04, 159.01. $C_{16}H_{18}N_4O_3S$. *m/z* 227.3 (346.5).

X-ray crystallography. Data collection for compound **12** was carried out on a Bruker APEX-II CCD diffractometer equipped with a graphite monochromator MoK_α radiation, λ = 0.71073 Å at 100 K. The structure was elucidated by direct methods using SHELXS-97 [11]. Data collection, Bruker APEX2; [12 cell refinement Bruker SAINT; data reduction, Bruker SAINT [12] molecular graphics: Bruker SHELXTL; software was used to prepare material for publication: Bruker SHELXTL.

X-Ray crystal data for compound **12** $C_9H_{13}N_3O_2S$ [mp 124–125°C (hexane/CH_2Cl_2): m, $P2_1/c$, $F(000)$ = 480, *a* = 12.4458 (17) Å, *b* = 7.8073 (10) Å, *c* = 10.7101 (14) Å, *b* = 104.855 (4)°, *V* = 1005.9 (2) $Å^3$, *Z* = 4, μ = 0.31 mm^{-1}, R_{int} = 0.022. CCDC 1000219 contains the supplementary crystallographic data for compound **12**.

Computational method. Initial structures for complexes *1*, *2,* and *3* were constructed for acetophenone and isatin using the HyperChem software version 8.0 [13]. The MM+ (calculations in vacuo, bond dipole option for electrostatics, Polak-Ribiere algorithm, RMS gradient of 0.01 kcal $Å^{-1}$ mol^{-1}) [14] conformational analysis in torsional space was performed. Energy minima were determined by a semi-empirical method PM3 [15] in the presence of one molecule of THF.

CONCLUSIONS

We have developed an efficient method of synthesis of hydrazones from acetophenone and isatin

derivatives by their reaction with hydrazine under mild conditions in the presence of BF_3 as a Lewis acid. Chemical structures of hydrazones were determined by spectral methods and X-ray crystal structure analysis. Mechanism of the reaction was proposed on the basis of molecular orbital calculations.

ACKNOWLEDGMENTS

The authors express their appreciation to the Deanship of Scientific Research at King Saud University for funding the work through the research group project no. RGP-163.

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