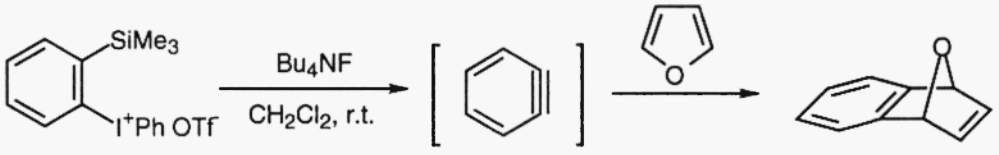
A CONVENIENT AND EFFICIENT SYNTHESIS OF BENZOTRIAZOLES AND BENZISOXAZOLINES USING A NEW HYPERVALENT IODINE-BENZYNE PRECURSOR

Tsugio Kitamura,* Mitsuru Todaka, Ichiro Shin-machi, and Yuzo Fujiwara

Department of Chemistry and Biochemistry, Graduate School of Engineering,
Kyushu University, Hakozaki, Fukuoka 812-8581, Japan

Abstract: Reaction of (phenyl)[*o*-(trimethylsilyl)phenyl]iodonium triflate with organic azides and nitrones using Bu_4NF gave benzotriazoles and benzisoxazolines in high yields, respectively. This reaction indicates that benzyne is generated under mild conditions and efficiently trapped with the 1,3-dipoles to give heterocyclic compounds.

Recently much attention has been paid to the use of hypervalent iodine compounds in organic synthesis (**1**-7). Previously we have found that (phenyl)[*o*-(trimethylsilyl)phenyl]iodonium triflate (**1**) acts as an excellent benzyne precursor and generates benzyne quantitatively by a simple treatment of *o*-(trimethylsilyl)phenyliodonium triflate **1** with Bu_4NF under very mild conditions as shown in Scheme 1 (8). The merits of the use of the hypervalent iodine-benzyne precursor **1** includes (a) the stability of the precursor **1**, (b) no requirement of a strong base or high temperature, and (c) the quantitative generation of benzyne under mild conditions.

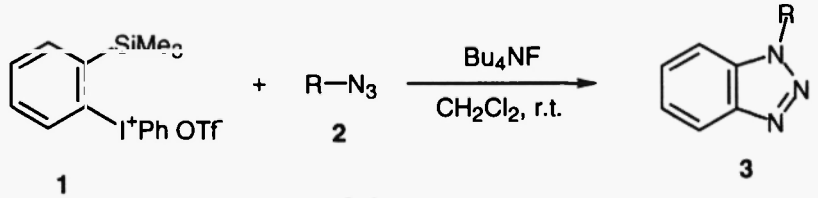


1 100%

Scheme 1.

If the hypervalent iodine-benzyne precursor **1** can be applied to the reactions with 1,3-dipoles such as azides and nitrones, the reaction of **1** will provides a useful methodology for synthesis of heterocyclic skeletons. In this paper, we report an efficient and convenient synthesis of benzotriazoles and benzisoxazolines by means of the hypervalent iodine-benzyne precursor **1**.

Reaction of *o*-(trimethylsilyl)phenyliodonium triflate **1** with aryl azides (**2 a-d**) could be conducted in CH_2Cl_2 simply by adding Bu_4NF. A solution of **1** and aryl azides in CH_2Cl_2 was treated with a THF solution of Bu_4NF at 0 ℃ and the reaction mixture was stirred at room temperature for 20 min. Separation by column chromatography on silica gel gave 1-arylbenzotriazoles (**3 a-d**) in high yields. The results are given in Table 1. This reaction was applied to ethyl 2-azidopropionate (**2 e**) and 2-azido-1-octadecene (**2 f**), which reacted with benzyne generated from **1** to yield the corresponding benzotriazoles (**3 e** and **f**). As shown in Table 1, *o*-(trimethylsilyl)phenyliodonium triflate **1** is a useful reagent for benzotriazole synthesis. Even in the reaction of a thermally unstable vinyl azide or an azide bearing functional ester group, **1** acts as the benzyne precursor and undergoes the 1,3-dipolar cycloaddition efficiently.



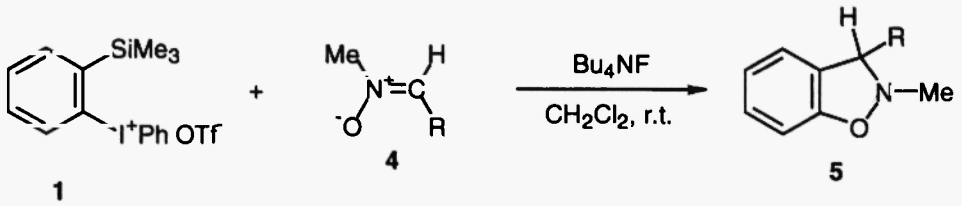
1 **2** **3**

Scheme 2.

Table **1**. Preparation of benzotriazoles **3** by reaction of **1** with azides **2**.

Azide **2**		Benzotriazole **3**	Yield (%)
PhN_3	**2a**	**3a** : R = Ph	96
4-$MeOC_6H_4N_3$	**2b**	**3b** : R = 4-$MeOC_6H_4$	99
4-$MeC_6H_4N_3$	**2c**	**3c** : R = 4-MeC_6H_4	97
4-$ClC_6H_4N_3$	**2d**	**3d** : R = 4-ClC_6H_4	79
$CH_3CH(N_3)COOEt$	**2e**	**3e** : R = —CH(CH3)COOEt	89
n-$C_{16}H_{33}$C(N_3)=CH_2	**2f**	**3f** : R = —C(C16H33-*n*)=CH_2	74

In analogy with the reaction of **1** with azides **2**, the reaction with nitrones **4** was examined. Similar treatment of *o*-(trimethylsilyl)phenyliodonium triflate **1** with Bu_4NF in the presence of nitrones 4 afforded the corresponding benzisoxazolines (**5**) in high yields, respectively. The results are given in Table 2. Again, in the case of nitrones, *o*-(trimethylsilyl)phenyliodonium triflate **1** behaves as an excellent benzyne precursor and provides a useful method of benzisoxazoline synthesis.



Scheme 2.

Table 2. Preparation of benzisoxazolines **5** by reaction of **1** with nitrones **4**.

Nitrone **4**	Benzisoxazoline **5**	Yield (%)
4a : R = Ph	**5a** : R = Ph	96
4b : R = 4-ClC_6H_4	**5b** : R = 4-ClC_6H_4	99
4c : R = *n*-C_6H_{13}	**4c** : R = *n*-C_6H_{13}	97
4d : R = 2-Furyl	**4d** : R = 2-Furyl	79

In summary, hypervalent iodine-benzyne precursor **1** generates benzyne efficiently by means of fluoride ion under very mild conditions. The in situ generated benzyne can be trapped with 1,3-dipoles to yield heterocyclic compounds. Although many types of benzyne precursors are known (11-13), this benzyne precursor **1** has outstanding advantages of the use in synthesis of heterocyclic compounds.

Acknowledgments

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(9) A general procedure: To a solution of **1** (1 mmol) and **2** (2 mmol) in CH_2Cl_2 was added a THF solution of Bu_4NF (1.2 mmol) at 0 °C and the mixture was stirred at room temperature for 20 min. After work-up of the reaction mixture, the product was separated by column chromatography on silica gel. Elution with CH_2Cl_2 gave benzotriazoles **3**.

3a: Mp. 88-89 °C (lit. (14) mp 89-90 °C).

3b: Mp 96.5 °C (lit. (15) mp 96.5 °C).

3c: Mp 92-94 °C (lit. (16) mp 95 °C).

3d: Mp 156 °C (lit. (17) mp 158 °C).

3e: Oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.19 (t, J = 7 Hz, Me, 3 H), 2.03 (d, J = 7 Hz, Me, 3 H), 4.20 (q, J = 7 Hz, CH_2, 2 H), 5.71 (q, J = 7 Hz, CH, 1 H), 7.30-7.56 (m, ArH, 3 H), 8.08 (d, J = 8 Hz, ArH, 1 H).

3f: Oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, J = 7 Hz, Me, 3 H), 1.23-1,52 (m, CH_2, 28 H), 2.91 (t, J = 7 Hz, CH_2, 2 H), 5.25 (s, =CH, 1 H), 5.40 (s, =CH, 1 H), 7.33 (t, J = 8 Hz, ArH, 1 H), 7.49 (t, J = 8 Hz, ArH, 1 H), 7.67 (d, J = 8 Hz, ArH, 1 H), 8.07 (d, J = 8 H, ArH, 1 H).

(10) A general procedure: To a solution of **1** (1 mmol) and **4** (2 mmol) in CH_2Cl_2 was added a THF solution of Bu_4NF (1.2 mmol) at 0 °C and the mixture was stirred at room temperature for 20 min. After work-up of the reaction mixture, benzisoxazolines **5** were obtained by column chromatography on silica gel (CH_2Cl_2).

5a: Mp. 57-58 °C (lit. (18) mp 59-59.5 °C).

5b: Oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.01 (s, Me, 3 H), 5.13 (s, CH, 1 H), 6.88-7.40 (m, ArH, 8 H).

5c: Oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.97 (t, J = 7 Hz, Me, 3 H), 1.27-1.72 (m, CH_2, 10 H), 2.78 (s, Me, 3 H), 3.99 (t, J = 7 Hz, CH, 1 H), 6.75-7.18 (m, ArH, 4 H).

5d: Oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.94 (s, Me, 3 H), 5.24 (s, CH, 1 H), 6.12 (s, furyl-H, 1 H), 6.29 (s, furyl-H, 1 H), 6.80-6.96 (m, ArH, 2 H), 7.12-7.22 (m, ArH, 2 H), 7.38 (s, furyl-H, 1 H).

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On the synthesis of mesoionic 1,3,4-thiadiazollum-2-aminide and precursors

Marcelo M. Britto[1], Carlos A. Montanari[1*], Claudio L. Donnici[1] and Quézia B. Cass[2]
[1]Núcleo de Estudos em Química Medicinal, Departamento de Química -Universidade Federal de Minas Gerais, Campus da Pampulha, 31270-901, Belo Horizonte, MG, Brazil
[2]Departamento de Química - Universidade Federal de São Carlos - São Carlos - SP - Brazil

Abstract: New synthetic routes for antimicrobial mesoionics 4-methyl-1.3.4-thiadiazolium-2-aminide and 4-aryl-1.3.4-thiadiazolium-2-aminide and their precursors are reported. Through the reported procedure, antimicrobial 1.4-diaroyl-thiosemicarbazides can be obtained in high purity degree.

Introduction

Mesoionic compounds are very useful in medicinal chemistry due to their well-known range of pharmacological activities and the synthesis of new analogues in order to gauge their potential as chemotherapic agents is very important (1). Recently, our group has synthesized mesoionics 1,3,4-oxadiazolium-2-aminide and 1,3,4-oxadiazolium-2-olate and evaluated their antimicrobial activity (2). We have also studied the antimicrobial activity of mesoionic 1,3,4-thiadiazolium-2-aminides using the biological microcalorimetric technique (3), and elucidated their structures (4-6). Mesoionic 1,3,4-thiadiazolium-2-aminides have also been assayed against some fungi and bacteria (7) and have shown some good activity against *Staphyloccocus aureus*, *Staphyloccocus epidermidis* and *Bacilus cereus*. Compound **2** (X = Y = Cl), Scheme 1, is the most potent: MIC = 0.14 μM/mL (7).

Such results have prompted us to synthesize mesoionic 1.3.4-thiadiazolium-2-aminides. Although there are well established synthetic routes for obtaining these compounds, a common problem is related to the substitution at position-4 of the mesoionic ring and also to get 1-aroyl-2-phenyl-1.4-thiosemicarbazides, **7**, by the reaction of acid chlorides, **4**, with 1.4-diphenyl-thiosemicarbazide. Compounds **7** can be obtained by the latter reaction under basic conditions in order to avoid direct cyclization to the corresponding mesoionic compound, since in neutral conditions the only isolated product is the mesoionic. The reaction undergoes an auto-acid catalysis and there is no other way of avoiding it unless basic conditions are employed. However, even under these conditions compounds **7** are not easily purified and the yields are very low. As we have interest in the biological activity of such compounds we have then followed a new route to synthesize **7** quantitatively and from it carry out the normal synthesis to mesoionic compounds, **2**.

Materials and methods

Gravity chromatography was performed on Merck Kieselgel 60 (70-230 Mesh). Mps are uncorrected and were determined on a Kofler hot-stage apparatus. IR spectra were obtained with a FT Mattson instrument. ^{1}H NMR and ^{13}C spectra were recorded on a Bruker AC-80 spectrometer with $SiMe_4$ as internal standard reference. Mass spectra were measured at 70eV with a Hewlett-Packard instrument.

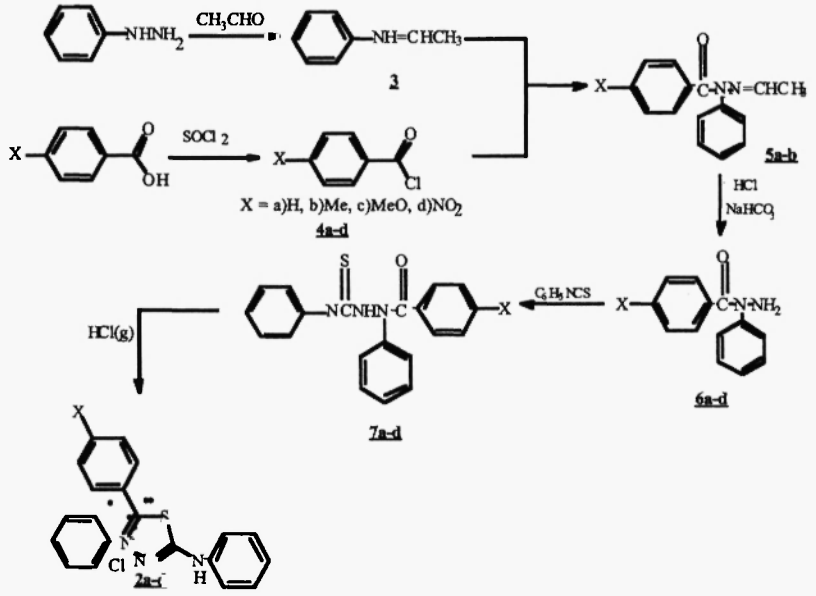
The aroyl chlorides **4a-d** were freshly prepared (8). Acylation of ethanal-hydrazone **3** yields the acyl-hydrazones **5a-d**. which on hydrolysis formed the hydrazides **6a-d**. that latter were converted into the acyl-thiosemicarbazides **7a-d**, and these undergo cyclization to 1,3,4-thiadiazolium-2-aminides **2a-d**.

Ethanal-phenylhydrazone, **3**, and ethanal-(α-benzoyl)-phenylhydrazones, **5a**, were prepared according to references (8) and (9).

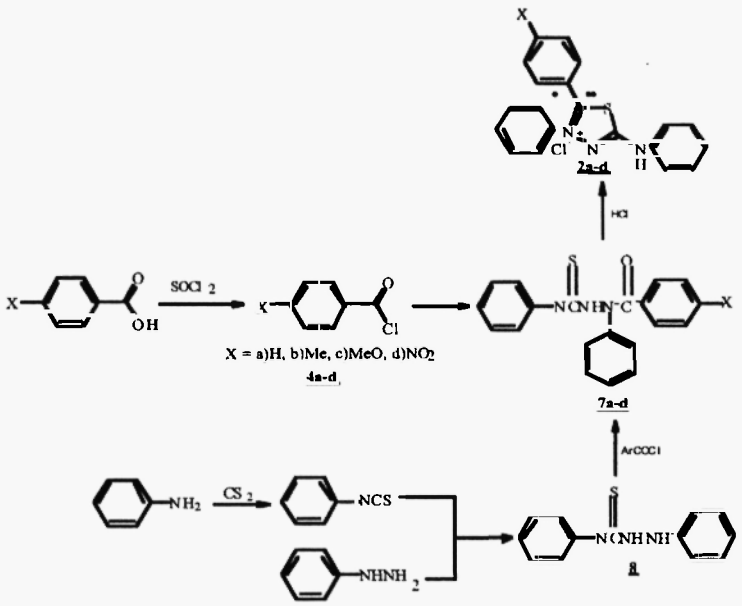
Results and discussion

The key-step of the synthesis is the intramolecular cyclization of immediate precursors with two active centers, with unsaturated bonds, to form an exocyclic group (10).

The synthesis of the mesoionic 1,3,4-thiadiazolium-4,5-diphenyl-2-aminide hydrochlorides **2a-d** go through the previous formation of the ethanal-hydrazone **3** intermediate (9), which is easily and selectively mono-acylated by any aroyl chloride **4a-d** to yield the corresponding acyl-hydrazones **5a-d**, which can form the monoacyl-hydrazines **6a-d**. the acylthiosemicarbazides **7a-d**. and finally the desired mesoionic 1,3,4-thiadiazolium-4,5-diphenyl-2-aminide **2a-d** (Scheme 1). The usual synthetic route through the intermediates **7a-d** (5, 6) formed by acylation of thiosemicarbazide **8** has not been proved successful in our hands, since the desired **7a-d** could not be isolated pure enough, (Scheme 2).

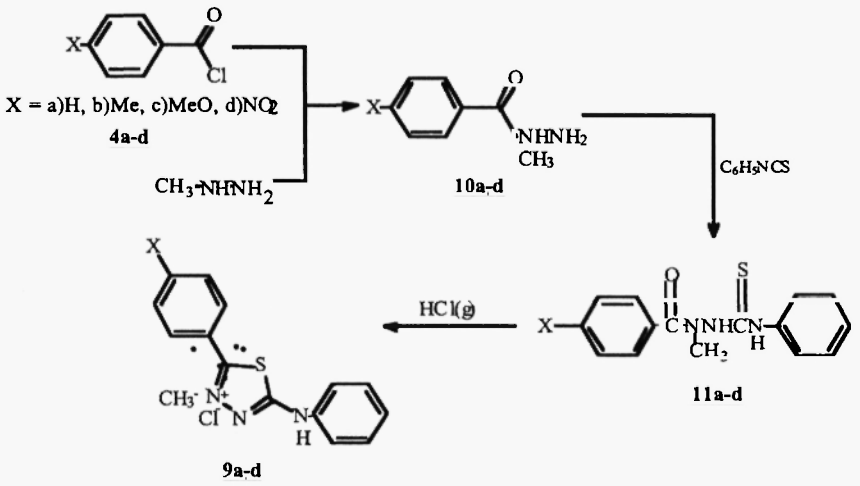


Scheme 1



Scheme 2

The synthesis of the mesoionic 1,3,4-thiadiazolium-4-methyl-2-aminide hydrochlorides **9a-d** goes through the acylation of methylhydrazine by **4a-d** to the corresponding hydrazides **10a-d**. The acylthiosemicarbazides **11a-d** can be obtained by reaction with phenylisothiocyanate and the 4-methyl mesoionic compounds **9a-d** are yielded by reaction of **11a-d** with HCl. **(Scheme 3)**.



Scheme 3

Experimental

Typical Procedure for **5b-d**:

A 100 mL, three-necked, round-bottomed flask equipped with a dropping funnel, magnetic stirring, a $CaCl_2$ drying tube and cooled in an ice-water bath was charged with 6.0 mL of benzoyl chloride (51.7 mmol). It was added dropwise (for 30 m) to a solution of 4.0 g (30 mmol) of **3** in 15.0 mL of anhydrous pyridine. The mixture was stirred at room temperature for 1 h and poured into crushed ice. The solid was filtered off under vacuum, dried, washed with petroleum ether (40-60 °C) and recrystallized from hexane/diethylether. **5 b** was obtained in 53% yield as pale yellow needles mp 102-103 °C (from n-hexane); IRν_{max} (KBr/cm^{-1}): 1632 (C=N); 1661 (C=O) ; δ ^{1}H (CDCl3): 1.78 (3H,d.J=5.3Hz,CH_3N=C), 2.35 (3 H,s, CH_3-Ar), 6.71(1H,q,J=5.2Hz, N=C-H), 7.23 and 7.58 (4H,dd,J=7.6 Hz)Ar) , 7.30-7.49 (5H,m, Ph) ; δ ^{13}C ($CDCl_3$): 169.16, 143.44, 139.92, 136.89, 132.83, 130.00, 129.44, 129.37, 128.85, 128.05, 21.03 and 18.28.MS m/z (relat. int.,%): 252 (M+.,6), 237 (3), 211(3), 133(1),119(100),77(3),65(13), 51(13). Ethanal-(α-para-methoxy-benzoyl)-phenylhydrazone, **5 c** was obtained in 64% yield as yellow crystals mp 84-86 °C (from ethanol);IRν_{max}(KBr/cm^{-1}):1620(C=N),1650(C=O);δ^{1}H($CDCl_3$):1.80(3h,J=5Hz,CH_3N=C) 3.81 (3 H,s, CH_3O-Ar), 6.70(1H,q,J=5Hz ,N=C-H), 7.10 and 7.71 (4H,dd,Ar,J=11.6 Hz) , 7.17-7.42 (5H,m, Ph) ; δ ^{13}C ($CDCl_3$): 168.55, 160.84, 143.22, 137.10, 131.65, 129.98, 129.41, 128.77, 127.46, 112.79, 55.27 and 18.30; MS m/z (relat. int.,%): 268 (M+.,7), 253(2),227(3), 135(100), 77(14),65(1), 51(3). Ethanal-(α-**para**-nitro-benzoyl)- phenylhydrazone, **5 d** was obtained in 42% yield as pale yellow needles mp 115.5-116.5 °C (from ethanol/diethylether)(Lit. (9), mp 115-116 °C); MS m/z (relat. int.,%): 283 (M+.,20),268(3),242(37), 150(100), 133(40),77(45),65(15), 51(18).

Preparation of α-benzoyl-phenyl-hydrazines **6a-6d**,Typical Procedure for **6a**:

A 250 mL, three-necked, round-bottomed flask equipped with a bubblier (for anhydrous HCl), and magnetic stirring and cooled in an ice-water bath was charged with 4.0 g (17 mmol) of **5** a in 100 mL of ethanol. Gaseous hydrogen chloride was bubbled for 2 hours. The product was filtered, washed with cold ethanol and slowly poured into a $NaHCO_3$ solution. After washing with water and drying, a pale yellowish solid was obtained (2.3g, 74.3% yield) mp 67-68 °C (Lit. (9), mp 69-70 °C). MS m/z (relat. int.,%): 212 (M+.8), 105(100), 107(4), 77(48), 51(8).

The others acylhydrazines **6b-d** were prepared similarly: α -*para*-methyl-benzoyl- phenylhydrazine **6 b** was obtained in 83% yield as pale yellowish crystals mp 72-73 °C. IRν_{max} (KBr/cm^{-1}): 3330 (N-H), 1641 (C=O) ; δ ^{1}H ($CDCl_3$), 2.26 (3 H,s, CH_3-Ar). 5.45 (s,2H, NH_2), 7.07 and 7.30 (4H,dd,J=8.1 Hz,Ar), 7.24 (5H,m, Ph) ; δ ^{13}C ($CDCl_3$): 168.65, 144.24, 139.15, 133.07, 129.85, 129.41, 129.34, 128.11, 125.48 and 20.74 MS m/z (relat. int.,%): 226 (M+.,7), 211(2), 119(100),107(1), 91(30), 77(7), 65(11), 51(4); Requires: $C_{14}H_{14}N_2O$ C, 74.34; H, 6.19; N,12.38 Found C, 74.33; H, 6.17; N,12.30. α -*para*-methoxy-benzoyl- phenylhydrazine **6 c** was obtained in 74% yield as pale yellowish crystals mp 75-76 °C. IRν_{max} (KBr/cm^{-1}): 3340 (N-H), 1610 (C=O) ; δ ^{1}H ($CDCl_3$): 3.73 (3 H,s, CH_3O-Ar), 5.42 (s,2H, NH_2), 6.72 and 7.36 (4H,dd,J=8.7 Hz,Ar) , 7.10-7.24 (5H,m, Ph) ; δ ^{13}C ($CDCl_3$) 168.33, 160.16, 144.52, 131.20, 130.43 128.32, 127.81,125.48, 112.86 and 55.04; MS m/z (relat. int.,%): 242 (M+.,6), 227(3), 135 (100), 107(9), 92(6), 77(18), 64(6), 51(3). Requires: $C_{14}H_{14}N_2O_2$ C, 69.42; H, 5.79; N,11.57 Found C, 69.60; H, 5.78; N,11.48. α -*para*-nitro-benzoyl-phenylhydrazine **6 d** was obtained in 71% yield as yellow crystals mp 141-142°C(Lit. (9), mp 140-141 ° C). MS m/z (relat. int.,%): 257 (M+.,17), 150(100), 107(97), 104(38), 77(86), 51(21).

Preparation of α-benzoyl-N-phenyl-1,4-diphenylthiosemicarbazide **7a-d**,Typical Procedure for **7a**:

A 50 mL , three-necked, round-bottomed flask equipped with a dropping funnel, magnetic stirring and $CaCl_2$ drying tube is charged with 2.13 g (10 mmol) of **6a** in 30 mL of ethanol. It was added 1.35g (10 mmol) of phenylisotiocianate and the mixture allowed to react , at room temperature, for 12 hours. The product was filtered, washed many times with cold ethanol giving after drying 2.9g (83% yield) of a white solid (74.3% yield) mp 319-320 °C. (Lit. (9), mp 310-312 °C), MS m/z (relat. int.,%): 347 (M+.,52), 314(60) ,212(84), 180(80), 150 (15),135(100), 105(98), , 77(90), 65(10),51(16); Requires: $C_{20}H_{17}N_3OS$ C, 69.16; H, 4.90; N,12.10 Found C, 69.33; H, 4.85; N,12.17.

The others acyltiosemicarbazides **7b-d** were prepared similarly: α -*para*-methyl-benzoyl-N-phenyl-1,4-diphenylthiosemicarbazide **7b** was obtained in 82% yield as white crystals mp 177-179 °C; IRν_{max} (KBr/cm^{-1}):3000-3400 (N-H); 1651 (C=O) , 1231 (C=S); δ ^{1}H (CDCl3), 2.33 (3 H,s, CH_3-Ar), 7.20-7.54 (4H,dd, J=8.1Hz), 7.29-7.34 (10H,m), 10.03(s,1H,NH) and 10,54 (s, 1H, NH); δ ^{13}C ($CDCl_3$): 180.36, 169.20; 144.83, 140.07, 138.40, 132.10, 128.88, 128.16, 127.70, 126.80, 126.40, 125.90, 125.33, 124.44 and 20.20; MS m/z (relat. int.,%): 361 (M+.,20), 328(5) ,226(100), 211(30), 194(20), 150 (15),135(10), 119(98), , 77(50), 65(12),51(10); Requires: $C_{21}H_{19}N_3OS$ C, 69.80; H, 5.26; N,11.63 Found C, 69.99; H, 5.17; N,11.62. α -*para*-methoxy-benzoyl-N-phenyl-1,4-diphenylthiosemicarbazide **7c** was obtained in 80% yield as white crystals mp 170-171 °C. IRν_{max} (KBr/cm^{-1}): 3000-3400(N-H); 1640(C=O) , 1240(C=S); δ ^{1}H (CDCl3), 3.77 (3 H,s, CH_3O-Ar), 7.20-7.37 (5H,m), 7.40-7.45 (5H,m), 7.82 and 7.63 (4H,dd,J=11.1 Hz), 10.10 (s, 1H, NH) and 10,64 (s, 1H, NH); δ ^{13}C ($CDCl_3$) 181.40, 169.72; 160.87, 142.19, 138.62, 132.03, 130.20, 128.70, 128.34, 127.30, 126.40, 125.38, 124.49, , 123.01 and 55.19; MS m/z (relat. int.,%)): 377 (M+.,5), 344(15), 242(50), 211(30), 210(30), 150 (10), 135(98), 77(20), 65(5),51(10); Requires: $C_{21}H_{19}N_3O_2S$ C, 66.84; H, 5.04; N,11.14 Found C, 66.94; H, 4.94; N, 11.18. α-*para*-nitro-benzoyl-N-phenyl-1,4-diphenylthiosemicarbazide **7d** was obtained in 72% yield as yellow crystals mp 175-177 °C. IRν_{max} (KBr/cm^{-1}): 3000-3400 (N-H); 1670 (C=O) , 1220 (C=S); δ ^{1}H (CDCl3), 7.00-7.14 (5H,m), 7.43-7.49 (5H,m), 7.73 and 8.16 (4H,dd,J=8.8 Hz), 10.09 (s, 1H, NH) and 10,40 (s, 1H, NH); δ ^{13}C ($CDCl_3$) 180.00, 168.65; 147.51, 144.37, 141.73, 138.52, 129.27, 128.11, 126.45, 126.40, 125.58, 125.10, 124.90, , 122.34; MS m/z (relat. int.,%): 392 (M+.,15), 359(10) ,257(70), 225(50), 150 (10), 135(100), 105(80) 77(40), 65(15), 51(10); Requires: $C_{20}H_{16}N_4O_3S$ C, 61.22; H, 4.08; N,14.29 Found C, 61.35; H, 3.99; N,14.18.

Preparation of mesoionic 1,3,4-thiadiazolium-4,5-diphenyl-2-aminide hydrochloride **2a-d**.

A 100 mL, three-necked, round-bottomed flask equipped with a bubblier (for anhydrous HCl), magnetic stirring and cooled in an ice-water bath is charged with 2.0 g (5.7 mmol) of **6a** in 50 mL of acetone. It was passed (for 20 m) gaseous hydrogen chloride. The mixture was poured into crushed ice and a white solid precipitated. This product was filtered, washed with much cold water until neutral and dried giving 1.6 g (85%) of a white solid mp 255-258 °C. (Lit. (5), mp 258-260 °C); MS m/z (relat. int.,%): 329 (M+.,100), 180(20) ,121(60), 91(10),77(30), 65(5),51(8); Requires: $C_{20}H_{16}N_3SCl$ C, 65.57; H, 4.65; N,11.50 Found C, 65.64; H, 4.52; N,11.43.

The others mesoionic compounds **2b-d** were prepared similarly: Mesoionic 1,3,4-thiadiazolium-4-phenyl-5-(*para*-methyl)phenyl-2-aminidehydrochloride **2b** was obtained in 70% yield as white crystals mp 274-276 °C IR ν_{max} (KBr/cm^{-1}): 2750-(N-H), 1575 (C=N); δ ^{1}H ($CDCl_3$): 2.37 (3H,s,CH_3-Ar), 6.94-7.58 (14H,m) and 12,51 (s, 1H, NH); δ ^{13}C

($CDCl_3$):161.20, 152.00; 141.34, 140.12, 134.00, 133.08, 130.40, 129.20, 128.70, 128.50, 127.80, 124.95, 120.90, 120.40 and 20.47; MS m/z (relat. int.,%): 343 (M+.,100), 226(8), 194(12) ,135(40), 91(8), 77(40), 65(7),51(15); Requires: $C_{21}H_{18}N_3SCl$ C, 66.49; H, 4.48; N,11.08 Found C, 66.54; H, 4.42; N,10.95. Mesoionic 1,3,4-thiadiazolium-4-phenyl-5-(*para*-methoxy)phenyl-2-aminidehydrochloride **2c** was obtained in 80% yield as white crystals mp 247-249 °C(Lit. (5), mp 243-244 ^{0} C) IR ν_{max} (neat/cm^{-1}) 2820-(N-H), 1560 (C=N); δ_H ($CDCl_3$): 3.79 (3H,s,CH_3O-Ar). 6.97-7.87 (14H,m) and 12,47 (s,1H, NH) δ_C ($CDCl_3$) 161.40, 161.10; 150.80, 139.00, 134.39, 130.20, 129.17, 128.70, 125.41, 120.40, 120.00, 118.80, 113.97, 112.80 and 55.19; MS m/z (relat. int.,%): 359 (M+.,88), 242(10), 210(15), 151(100),136(5), 91(10), 77(18), 65(5),51(8); Requires: $C_{21}H_{18}N_3OSCl$ C, 63.79; H, 4.30; N,10.60 Found C, 63.70; H, 4.27; N,10.90. Mesoionic 1,3,4-thiadiazolium-4-phenyl-5-(*para*-nitro)phenyl- 2-aminidehydrochloride **2d** was obtained in 72% yield as white crystals mp 242-245 °C (Lit. (5) mp 238-239^0 C); IR ν_{max} (neat/cm^{-1}): 2780-(N-H), 1550 (C=N); δ ^{1}H ($CDCl_3$): 7.19-8.41 (14H,m) and 12,83 (s, 1H, NH_2) δ ^{13}C ($CDCl_3$): 159.90, 151.43, 148.51, 138.20; 133.41, 130.12,129.42, 129.27, 129.00, 125.12, 123.50, 122.70, 120.25 and 116.10;MS m/z (relat. int.,%): 374 (M+.,100), 258(12), 225(20), 166(10), 150(8), 136(60), 91(20), 77(87), 65(10),51(21); Requires: $C_{20}H_{15}N_4O_2SCl$ C, 58.53; H, 3.41; N,13.65 Found C, 58.75; H, 3.49; N,13.42.

Synthesis of mesoionic 1,3,4-thiadiazolium-4-phenyl-5-methyl-2-aminide hydrochloride 2a-d. The aroyl chlorides **4a-d**. methylhydrazine (11) and phenylisothiocyanate (12) were prepared elsewhere (8). The acylated methylhydrazine, **10**, were transformed in the acylthiosemicarbazide **11a-d** and finally in the corresponding mesoionic 1,3,4- thiadiazolium-2-aminides **9a-d**. Typical procedures for the synthesis of compounds **9-11** are described below .

Preparation of α-benzoyl-methyl-hydrazines **10a-d. Typical Procedure for 10a:**

A 250 mL , three-necked, round-bottomed flask equipped with a dropping funnel, magnetic stirring and $CaCl_2$ drying tube is charged with 1.84 g (40 mmol) of methylhydrazine in 50 mL of anhydrous dichloromethane. The mixture was kept at -50 ^{0}C and 2.8g (20 mmol) of benzoyl chloride **4a** , in 50 mL anhydrous dichloromethane, was slowly (2 h) added. On warming to the room temperature and upon addition of 10 mL of diethylether, a white solid was obtained. The product was filtered, dried and 2.9g (81%) of the solid was obtained mp 91-92 ^{0}C (Lit. (9) mp 90-91^{0}C). MS m/z (relat. int.,%): 150 (M+.,20), 105(100), 77(71), 51(22).

The others acylhydrazines **10b-d** were prepared similarly: α-*para*-methyl-benzoyl-methylhydrazine **10b** was obtained in 84% yield as pale yellowish crystals mp 59-61 °C. IRν_{max} (KBr/cm ^{1}): 3240 (N-H), 1651 (C=O) ; δ ^{1}H ($CDCl_3$), 2.31 (3 H,s, CH_3-Ar), 3.13 (s,3H,CH_3), 4.85(s,2H, NH_2), 7.16 (2H,d,J=7.5Hz,Ar) and 7.43 (2H,d,J=7.5Hz,Ar) ; δ ^{13}C ($CDCl_3$): 168.89, 138.73, 133.29, 131.99, 128.08, 38.99 and 20.87; MS m/z (relat. int.,%): 164 (M+.,14), 119(100), 91(56), 77(1), 51(2). α -*para*-methoxy-benzoyl- phenylhydrazine **10c** was obtained in 83% yield as pale yellowish crystals mp 61-62 °C. IRν_{max} (KBr/cm^{-1} 3300 (N-H), 1620 (C=O) ; δ ^{1}H ($CDCl_3$): 3.80 (3 H,s, CH_3O-Ar), 3.13 (s,3H,CH_3), 4,87(s,2H, NH_2), 6.92 (2H,d,J=8.8Hz,Ar) and 7.54 (2H,d,J=8.8Hz,Ar) ; δ ^{13}C ($CDCl_3$) 168.82, 159.93, 130.21, 128.40, 112.70, 55.11 and 39.30; MS m/z (relat. int.,%): 180 (M+.,10), 135(100), 107(14), 77(21), 51(1.7). α -*para*-nitro-benzoyl- phenylhydrazine **10d** was obtained in 78% yield as yellow crystals mp 137-139°C(Lit. (5), mp 140-141 ^{0} C). IRν_{max} (KBr/cm ^{1}): 3340 (N-H), 1620 (C=O) ; δ ^{1}H ($CDCl_3$): 3.26(s,3H), 4.56 (s,2H, NH_2), 7.66 (2H,d,J=8.7 Hz,Ar) , 7.54

(2H,d, J=8.7Hz) ; δ ^{13}C ($CDCl_3$): 168.79, 147.18, 143.54, 129.27, 122.40 and 37.20; MS m/z (relat. int.,%): 195 (M+.,40), 151(100), 149(77),134(60), 104(76), 77(16), 51(7).

Preparation of α-benzoyl-N-methyl-1,4-diphenylthiosemicarbazide 11**a-d**

The acylthiosemicarbazides 11**a-d** were prepared similar to the procedure described for the semicarbazide 7**a**. α -benzoyl-N-methyl-1.4-diphenylthiosemicarbazide 11**a** was obtained in 79% yield as white crystals mp 165-167 °C; IRν_{max} (KBr/cm^{-1}): 3300-3500 (N-H); 1650 (C=O) , 1191 (C=S); δ ^{1}H ($CDCl_3$), 3.20 (3 H,s, CH_3-Ar), 7.21-7.44 (5H,m), 7.52-7.64 (5H,m), 9,96 (s,1H) and 10.19(s,1H); δ ^{13}C ($CDCl_3$): 182.43, 171.84; 139.49, 136.70, 134.93, 129.82, 129.31, 127.32, 126.70, 125.63 and 36.94; MS m/z (relat. int.,%): 285 (M+.,24), 150(12), 105(100), 77(43), 51(10); Requires:$C_{15}H_{15}N_3OS$ C, 63.16; H, 5.26; N,14.74 Found C, 62.99; H, 5.25; N,14.85. α -*para*-methyl-benzoyl-N-methyl-1,4-diphenylthiosemicarbazide 11**b** was obtained in 77% yield as white crystals mp 150-152 °C; IRν_{max} (KBr/cm^{-1} 3300-3500 (N-H); 1621 (C=O), 1190 (C=S); δ ^{1}H ($CDCl_3$), 2.32 (3 H,s, CH_3-Ar), 3.18(S,3H), 7.48 and 7.20 (4H,dd, J=8.1Hz), 7.26-7.33 (5H,m), 9,95 (s,1H) and 10.05(s,1H); δ ^{13}C ($CDCl_3$): 181.20, 171.70; 141.76, 139.70, 133.10, 128.64, 128.19, 127.30, 126.40, 125.31, 36.81 and 20.87; MS m/z (relat. int.,%): 299 (M+.,16), 266(25), 164(5), 91(24), 77(10), 65(4), 51(4); Requires: $C_{16}H_{17}N_3OS$ C, 64.21; H, 5.69; N,14.05 Found C, 64.29; H, 5.65; N,13.97. α -*para*-methoxy-benzoyl- 1,4-diphenylthiosemicarbazide 11**c** was obtained in 74% yield as white crystals mp 169-170 °C. IRν_{max} (KBr/cm^{-1}): 3400-3500(N-H); 1620(C=O) , 1180(C=S); δ ^{1}H ($CDCl_3$): 3.79 (3 H,s, CH_3O-Ar), 3.16 (s,3H), 7.24-7.33 (5H,m), 7.80 and 8.30 (4H,dd,J=8.6 Hz), 9,98 (s,1H) and 10.10(s,1H); δ ^{13}C ($CDCl_3$) 178.13, 171.17; 160.65, 138.90, 129.40, 128.12, 127.30, 126.09, 125.60, 113.01, 55.23 and 36.34; MS m/z (relat. int.,%): 315 (M+.,58) , 282(10), 180 (5), 135(100), 107(5), 77(18),51(3); Requires: $C_{16}H_{17}N_3O_3S$ C, 60.95; H, 5.40; N,13.33 Found C, 60.76; H, 5.31; N,13.47. α -*para*-nitro-benzoyl- 1,4-diphenylthiosemicarbazide 11**d** was obtained in 68% yield as yellow crystals mp 172-174 °C. IRν_{max} (KBr/cm^{-1}): 3390-3500 (N-H); 1660 (C=O) , 1190 (C=S); δ ^{1}H ($CDCl_3$): 3.23 (s,3H); 7.24-7.33 (5H,m), 7.80 and 8.30 (4H,dd,J=8.6 Hz), 9,98 (s,1H) and 10.10(s,1H) ; δ ^{13}C ($CDCl_3$) 180.94, 170.12; 147.94, 141.96, 138.61, 128.26, 127.20, 126.40, 125.50, 122.97 and 36.10; MS m/z (relat. int.,%): 330 (M+.,83), 297(43), 195(63), 150(100), 104 (34), 77(44), 51(10); Requires: $C_{15}H_{14}N_4O_3S$ C, 54.54; H, 4.24; N,16.97 Found C, 54.26; H, 4.25; N,16.81.

Preparation of mesoionic 1,3,4-thiadiazolium-5-methyl-4-phenyl-2-aminidehydrochloride 9**a-d**

The mesoionic compounds 9**a-d** were prepared following the method described for obtaining 2**a**. Mesoionic 1,3,4-thiadiazolium-4-methyl-5-phenyl-2-aminidehydrochloride 9**a** was obtained in 79% yield of mp 165-167 °C IR ν_{max} (neat/cm^{-1}) 2800-(N-H), 1570 (C=N); δ ^{1}H ($CDCl_3$): 7.14-7.72 (15H,m) and 12,65 (s, 1H, NH) δ ^{13}C($CDCl_3$): 160.73, 157.59; 138.69, 135.57, 129.97, 129.48, 129.40, 124.59, 123.80, 118.43 and 42.69; MS m/z (relat. int.,%): 267 (M+.,80), 209(3) ,180(60), 121(5),91(98),77(100),51(50); Requires: $C_{15}H_{14}N_3SCl$ C, 59.41; H, 4.29; N,13.86 Found C, 60.10; H, 4.09; N,13.54. Mesoionic 1,3,4-thiadiazolium-5-methyl-4-(*para*-methyl-phenyl)-2-aminidehydrochloride 9**b** was obtained in 77% yield, mp 150-152 °C IR ν_{max} (neat/cm^{-1}) 2750-(N-H), 1575 (C=N); δ ^{1}H ($CDCl_3$): 2.37 (3H,s,CH_3-Ar), 6.94-7.58 (14H,m) and 12,51 (s, 1H, NH); δ ^{13}C ($CDCl_3$):160.80, 157.71; 141.70, 137.80, 129.81, 129.33, 128.91, 124.20, 123.20, 118.70, 43.21 and 20.88; MS m/z (relat. int.,%): 281 (M+.,20), 223(15), 194(100) ,135(2), 91(40), 77 (60),51(40); Requires: $C_{16}H_{16}N_3SCl$ C, 60.56; H, 4.73; N,13.24 Found C, 60.82; H, 4.58; N,13.01. Mesoionic 1,3,4-thiadiazolium-5-methyl-4-(*para*-methoxy-phenyl-2-aminidehydrochloride 9**c** was obtained in 74% yield, mp 169-170 °C;

IR ν_{max} (neat/cm^{-1}) 2820-(N-H), 1560 (C=N); δ_H ($CDCl_3$): 3.79 (3H,s,CH_3O-Ar), 6.97-7.87 (14H,m) and 12,47 (s,1H, NH) δ_C ($CDCl_3$): 162.92, 161.30, 159.92, 137.90, 132.04, 129.33, 123.69, 118.26, 115.04, 114.74, 55.77 and 42.63; MS m/z (relat. int.,%)): 297 (M+.,90), 239(1), 210(8), 151(100), 91(40), 77(50),51(30); Requires: $C_{16}H_{16}N_3OSCl$ C, 57.08; H, 4.50; N,12.61 Found C, 57.18; H, 4.38; N,12.21. Mesoionic 1,3,4-thiadiazolium-5-methyl-4-(*para*-nitro-phenyl-2-aminidehydrochloride **9 d** was obtained in 68% yield, mp 172-174 °C; IR ν_{max} (neat/cm^{-1}): 2780-(N-H), 1550 (C=N); δ ^1H ($CDCl_3$): 7.19-8.41 (14H,m) and 12,83 (s, 1H, NH_2) δ ^{13}C ($CDCl_3$): 162.80, 161.20, 150.20, 137.30, 129.19, 128.67, 131.33, 124.86, 124.73 ,119.16 and 42.99; MS-m/z (relat.int.,%)):312(M+.,60), 254(1), 225(5), 166(10), 91(60), 77(100), 51(60); Requires: $C_{15}H_{13}N_4O_2SCl$ C, 51.72; H, 3.45; N,16.09 Found C, 51.93; H, 3.37; N,15.91.

Conclusions

A novel synthetic route for mesoionic 1,3,4-thiadiazolium-4-phenyl-5-methyl-2-aminides **2a-d**. with better overall yields, has been established. Ten newly synthesized compounds, **2 b**, **5b-c**, **9a-d**, and **11b-d** were fully characterized.

The proposed routes seem to be more general and can be readily achieved from common chemicals.

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