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An efficient synthesis of *N*-(1-arylethylidene)-*N*'-(4-arylthiazol-2-yl)hydrazones from α,α-dibromoacetophenones and N-(1-arylethylidene) thiosemicarbazones

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ABSTRACT

An efficient synthesis of N-(1-arylethylidene)-N'-(4-arylthiazol-2-yl)hydrazones has been achieved by the reaction of α,α-dibromoacetophenones and N-(1-arylethylidene)thiosemicarbazones under mild reaction conditions.

Keywords: *N*-(1-arylethylidene)thiosemicarbazones; N-(1-arylethylidene)-N'-(4-arylthiazol-2-yl)hydrazones; α,α-dibromoacetophenones; lachrymatory.

INTRODUCTION

A major challenge of modern drug discovery is the design of highly efficient chemical reaction sequences that provide maximum structural complexity and diversity with a minimum number of synthetic steps to assemble compounds with interesting properties. Great efforts have been focused on synthesizing libraries of small heterocyclic molecules because of their high degree of structural diversity and extensive utility as therapeutic agents. Thiazoles and their derivatives have attracted continuing interest over the years because of their varied biological activities, recently found application in drug development for the treatment of allergies, hypertension, inflammation, HIV infections, and hypnotics[1-4]. In view of above mentioned findings, we tried to synthesize thiazolyl compounds by easier methods that may be value in designing new, potent, selective and less toxic antimicrobial agents. Though the synthetic utility of α-halocarbonyl compounds in heterocyclic chemistry is well known for more than a century and they have been widely used as versatile intermediates[5-11] for the synthesis of variety of heterocyclic systems, these compounds suffer with serious handling problems due to highly lachrymatory properties associated with them. Therefore, there has been considerable interest in developing alternate approaches in synthetic chemistry.

Recently, α,α-dihalocarbonyl compounds are found to be important intermediates in the synthesis of pharmaceutically important heteroaromatics, unsaturated acids and ynol esters[12-14]. They have been used as synthetic equivalents[15-17] to the corresponding α-halocarbonyl compounds as they possess high reactivity in most of the reactions. Being non-lachrymatory, generally solid at room temperature and soluble in commonly used reaction solvents, these compounds are easy to work with and can be handled easily[18,19]. In the present work, α,α-dibromocarbonyl compounds are being used with *N*-(1-arylethylidene)thiosemicarbazones with an aim (i) to compare their reactivity pattern with α-bromocarbonyl compounds and (ii) to develop an alternative and efficient synthetic route for the synthesis of *N*-(1-phenylethylidene)-*N*-(4-arylthiazol-2-yl)hydrazones (**3**).

MATERIALS AND METHODS

Experimental Section

Melting points were taken in open capillaries and are uncorrected. Elemental analyses (C, H, N) were carried out University Science Instrumentation Centre, University of Delhi, Delhi, India. ^{1}H nmr and ^{13}C nmr spectra were recorded on a Bruker 300 MHz instrument using tetramethylsilane (TMS) as an internal standard with δ =0 ppm. Infrared (ir) spectra were recorded on a Buck Scientific IR M-500 spectrophotometer. The purity of the synthesized compounds was tested by thin-layer chromatography (tlc). The α,α-dibromoacetophenones needed for the present study were prepared by stirring different acetophenones with bromine (2.5 eq.) in $CHCl_3$ for 24 h[21] and *N*-(1-arylethlidene)thiosemicarbazones were synthesized by refluxing different acetophenones with thiosemicarbazide in EtOH according to the literature procedure[22] and were confirmed by comparison with literature mp. Acetophenones, thiosemicarbazide and bromine were taken from the commercial suppliers and are used as such without further purification.

Synthesis of *N*-(1-arylethylidene)-*N*'-(4-arylthiazol-2-yl)hydrazones (3aa- 3bd)

General Procedure

A solution of α,α-dibromoacetophenone (**1**, 5 mmol) in ethanol (20 mL) was mixed with appropriate *N*-(1-arylethylidene)thiosemicarbazone (**2**, 5 mmol) and stirred at room temperature for about 2 h. After completion of the reaction as monitored by tlc, a solid was separated out. The solid product was filtered *in vacuo* and washed with cold ethanol. The crude product, so obtained, was recrystallized from methanol and petroleum ether (1:1) to obtain the pure thiazolyl hydrazones **3** in good % yield.

Characterization Data

***N*-(1-Phenylethylidene)-*N*'-(4-phenylthiazol-2-yl)hydrazone (3aa)**

ir (υmax., KBr): 1597 (C=N), 3333 (NH) cm^{-1}. ^{1}H nmr ($CDCl_3$): δ 2.26 (s, 3H, CH_3), 7.12 (s, 1H, C_5-H, thiazolyl), 7.33-7.81 (m, 10H, Ar-H).

***N*-(1-Phenylethylidene)-*N*'-{4-(4-methylphenyl)thiazol-2-yl}hydrazone (3ba)**

ir (υmax., KBr): 1605 (C=N), 3325 (NH) cm^{-1}. ^{1}H nmr ($CDCl_3$): δ 2.29 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 7.19 (s, 1H, C_5-H, thiazolyl), 7.22-7.73 (m, 9H, Ar-H).

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***N*-(1-Phenylethylidene)-*N'*-{4-(4-chlorophenyl)thiazol-2-yl}hydrazone (3ca)**
Ir (υmax., KBr): 1612 (C=N), 3325 (NH) cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.22 (s, 3H, CH_3), 7.32-7.98 (m, 9H, Ar-H, 1H, C_5-H, thiazolyl).

***N*-(1-Phenylethylidene)-*N'*-{4-(4-bromophenyl)thiazol-2-yl}hydrazone (3da)**
Ir (υmax., KBr): 1597 (C=N), 3317 (NH) cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.22 (s, 3H, CH_3), 7.22 (s, 1H, C_5-H, thiazolyl), 7.41-7.75 (m, 9H, Ar-H).

***N*-(1-Phenylethylidene)-*N'*-{4-(4-fluorophenyl)thiazol-2-yl}hydrazone (3ea)**
ir (υmax., KBr): 1605 (C=N), 3322 (NH) cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.44 (s, 3H, CH_3), 7.15 (s, 1H, C_5-H, thiazolyl), 7.18-7.77 (m, 9H, Ar-H). *Anal*. Calcd. for $C_{17}H_{14}FN_3S$: C, 65.59; H, 4.50; N, 13.50. Found: C, 65.67; H, 4.49; N, 13.34.

***N*-(1-Phenylethylidene)-*N'*-{4-(4-nitrophenyl)thiazol-2-yl}hydrazone (3fa)**
ir (υmax., KBr): 1597 (C=N), 3324 (NH) cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.33 (s, 3H, CH_3), 7.16 (s, 1H, C_5-H, thiazolyl), 7.42-7.83 (m, 9H, Ar-H). *Anal*. Calcd. for $C_{17}H_{14}N_4O_2S$: C, 60.35; H, 4.14; N, 16.57. Found: C, 60.26; H, 4.11; N, 16.64.

***N*-{1-(4-Fluorophenyl)ethylidene}-*N'*-(4-phenylthiazol-2-yl)hydrazone (3ab)**
IR (υmax., KBr): 1605 (C=N), 3364 (NH) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz, δ = ppm): 2.15 (s, 3H, CH_3), 6.95-7.77 (m, 9H, Ar-H, 1H, C_5-H, thiazolyl). *Anal*. Calcd. for $C_{17}H_{14}FN_3S$: C, 65.59; H, 4.50; N, 13.50. Found: C, 65.48; H, 4.51; N, 13.62.

***N*-{1-(4-Fluorophenyl)ethylidene}-*N'*-{4-(4-methylphenyl)thiazol-2-yl}hydrazone (3bb)**
ir (υmax., KBr): 1612 (C=N), 3418 (NH) cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 7.07-7.73 (m, 9H, Ar-H, 1H, C_5-H, thiazolyl). ^{13}C nmr ($CDCl_3$): δ 14.35 (-CH_3), 21.39 (-C_6H_4-**C**H_3), 112.98-149.54 (C=N-, aromatic and thiazolyl carbons), 169.30 (-C_5H_4**C**F). *Anal*. Calcd. for $C_{18}H_{16}FN_3S$: C, 66.40; H, 4.92; N, 12.92. Found: C, 66.34; H, 4.94; N, 12.52.

***N*-{1-(4-Fluorophenyl)ethylidene}-*N'*-{4-(4-chlorophenyl)thiazol-2-yl}hydrazone (3cb)**
ir (υmax., KBr): 1605 (C=N), 3410 (NH) cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.16 (s, 3H, CH_3), 7.10-7.71 (m, 9H, Ar-H, 1H, C_5-H, thiazolyl). *Anal*. Calcd. for $C_{17}H_{13}ClFN_3S$: C, 59.02; H, 3.76; N, 12.15. Found: C, 58.87; H, 3.71; N, 12.34.

***N*-{1-(4-Fluorophenyl)ethylidene}-*N'*-{4-(4-bromophenyl)thiazol-2-yl}hydrazone (3db)**
ir (υmax., KBr): 1597 (C=N), 3365 (NH) cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.18 (s, 3H, CH_3), 6.93-7.73 (m, 9H, Ar-H, 1H, C_5-H, thiazolyl). ^{13}C nmr ($CDCl_3$): δ 14.70 (-CH_3), 115.64-147.85 (C=N-, aromatic and thiazolyl carbons), 170.10 (-C_5H_4**C**F). *Anal*. Calcd. for $C_{17}H_{13}BrFN_3S$: C, 52.30; H, 3.33; N, 10.76. Found: C, 52.37; H, 3.39; N, 10.64.

***N*-{1-(4-Fluorophenyl)ethylidene}-*N'*-{4-(4-fluorophenyl)thiazol-2-yl}hydrazone (3eb)**
ir (υmax., KBr): 1597 (C=N), 3356 (NH) cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.14 (s, 3H, CH_3), 7.03-7.72 (m, 9H, Ar-H, 1H, C_5-H, thiazolyl). *Anal*. Calcd. for $C_{17}H_{13}F_2N_3S$: C, 62.00; H, 3.95; N, 12.76. Found: C, 62.12; H, 3.98; N, 12.68.

***N*-{1-(4-Fluorophenyl)ethylidene}-*N'*-{4-(4-nitrophenyl)thiazol-2-yl}hydrazone (3fb)**
ir (υmax., KBr): 1597 (C=N), 3356 (NH) cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.33 (s, 3H, CH_3), 7.21-8.30 (m, 9H, Ar-H, 1H, C_5-H, thiazolyl). ^{13}C nmr ($CDCl_3$): δ 14.47 (-CH3), 109.01-146.60 (C=N-, aromatic and thiazolyl carbons), 170.68 (-C_5H_4**C**F). *Anal*. Calcd. for $C_{17}H_{13}FN_4O_2S$: C, 57.30; H, 3.65; N, 15.73. Found: C, 57.38; H, 3.58; N, 15.62.

***N*-{1-(4-Chlorophenyl)ethylidene}-*N'*-{4-(4-fluorophenyl)thiazol-2-yl}hydrazone (3ac)**
ir (υmax., KBr): 1605 (C=N), 3333 (NH) cm^{-1}. ^1H nmr ($CDCl_3$, 300 MHz, δ = ppm): 2.44 (s, 3H, CH_3), 7.18 (s, 1H, C_5-H, thiazolyl), 7.42-7.76 (m, 9H, Ar-H). *Anal*. Calcd. for $C_{17}H_{13}ClFN_3S$ C, 59.04; H, 3.76; N, 12.15. Found: C, 59.12; H, 3.80; N, 12.09.
***N*-{1-(4-Chlorophenyl)ethylidene}-*N'*-{4-(4-nitrophenyl)thiazol-2-yl}hydrazone (3bc)**
ir (υmax. KBr): 1612 (C=N), 3348 (NH) cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.28 (s, 3H, CH_3), 7.15 (s, 1H, C_5-H, thiazolyl), 7.22-7.81 (m, 9H, Ar-H). *Anal*. Calcd. for $C_{17}H_{13}ClN_4O_2S$: C, 55.21; H, 3.52; N, 15.15. Found: C, 55.28; H, 3.56; N, 15.06.

***N*-{1-(4-Bromophenyl)ethylidene}-*N'*-{4-(4-fluorophenyl) thiazol-2-yl}hydrazone (3ad)**
ir (υmax., KBr): 1605 (C=N), 3402 (NH) cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.24 (s, 3H, CH_3), 6.95-7.76 (m, 9H, Ar-H, 1H, C_5-H, thiazolyl). ^{13}C nmr ($CDCl_3$): δ 13.84 (-CH_3), 112.92-149.71 (C=N-, aromatic and thiazolyl carbons), 169.19 (-C_5H_4**C**F). *Anal*. Calcd. for $C_{17}H_{13}BrFN_3S$: C, 52.30; H, 3.33; N, 10.77. Found: C, 52.48; H, 3.31; N, 10.62.

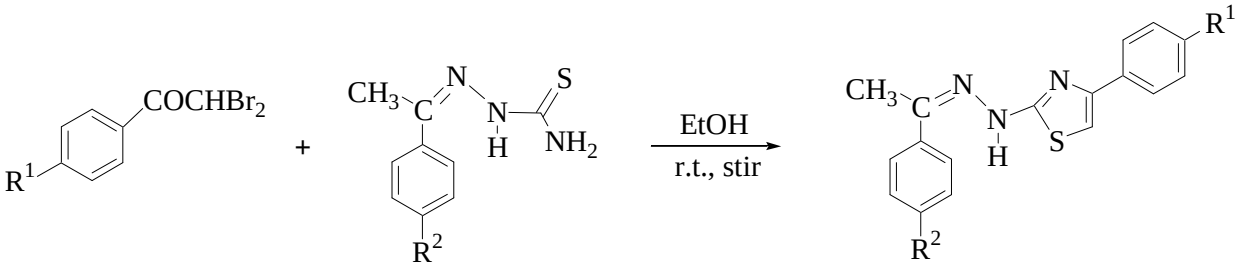
***N*-{1-(4-Bromophenyl)ethylidene}-*N'*-{4-(4-nitrophenyl)thiazol-2-yl}hydrazone (3bd)**
ir (υmax., KBr): 1597(C=N), 3333(NH) cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.32 (s, 3H, CH_3), 7.60-8.29 (m, 9H, Ar-H, 1H, C_5-H, thiazolyl). *Anal*. Calcd. for $C_{17}H_{13}BrN_4O_2S$: C, 48.92; H, 3.11; N, 13.42. Found: C, 48.90; H, 3.07; N, 13.52.

RESULTS AND DISCUSSION

Initially, the synthesis of title compounds was attempted with *N*-(1-phenylethylidene)thiosemicarbazone (**2a**) and simple α,α-dibromoacetophenone (**1a**). *N*-(1-phenylethylidene)thiosemicarbazone (**2a**) was stirred with 1 equivalent of α,α-dibromoacetophenone (**1a**) at room temperature in ethanol (**Scheme 1**). A light brown solid was separated out within 2 h. The solid was separated by filtration, washed with cold ethanol and recrystallized from a mixture of methanol and petroleum ether in 1:1 ratio to give the pure product. The product obtained **3aa** was found to be the same as obtained in the reaction of α-bromoacetophenone. An authentic sample was prepared using α-bromoacetophenone and compared with **3aa** for IR and mp. Both the products were found to be the same showing same mp and mixed mp (135°C)[20]. The ^1H-NMR spectrum of **3aa** showed a three proton singlet at δ 2.26 due to CH_3 and a proton singlet at δ 7.12 due to thiazolyl proton (C_5H). In the IR spectrum of **3aa,** there is no carbonyl absorption but absorption bands were observed at 3333 cm^{-1} due to N-H stretching and at 1597 cm^{-1} due to C=N stretching.

Encouraged by the result of this reaction, the work was extended with variously substituted α,α-dibromoacetophenones (**1b-f**) and different *N*-(1-arylethylidene)thiosemicarbazones (**2a-d)** to generalize the method. The adopted procedure in all the cases, afforded the expected thiazolyl hydrazones (**3ba-bd**) (**Scheme 1, Table 1**) in good yields (66-77%). Out of the sixteen title

compounds synthesized, twelve are not known in literature. The known samples (3aa-3da) were confirmed by comparison of their mp and ^{1}H-NMR with the literature. The new compounds (3ea-3bd) were characterized by the combined application of elemental analysis, IR, ^{1}H and ^{13}C-NMR spectroscopy.



1 **2** **3**

Scheme-1

Table 1: Physical data of 3 as prepared according to Scheme 1

Compounds	R^1	R^2	mp°C	Lit.mp°C[16]	% Yield
3aa	C_6H_5	C_6H_5	135	137	69
3ba	4-$CH_3C_6H_4$	C_6H_5	139	140	72
3ca	4-ClC_6H_4	C_6H_5	170	170	74
3da	4-BrC_6H_4	C_6H_5	174	175	71
3ea	4-FC_6H_4	C_6H_5	168	-	67
3fa	4-$NO_2C_6H_4$	C_6H_5	210	-	70
3ab	C_6H_5	4-FC_6H_4	195	-	66
3bb	4-$CH_3C_6H_4$	4-FC_6H_4	182	-	70
3cb	4-ClC_6H_4	4-FC_6H_4	144	-	73
3db	4-BrC_6H_4	4-FC_6H_4	186	-	76
3eb	4-FC_6H_4	4-FC_6H_4	198	-	69
3fb	4-$NO_2C_6H_4$	4-FC_6H_4	192	-	77
3ac	4-FC_6H_4	4-ClC_6H_4	184	-	72
3bc	4- $NO_2C_6H_4$	4-ClC_6H_4	207	-	68
3ad	4-FC_6H_4	4-BrC_6H_4	188	-	72
3bd	4- $NO_2C_6H_4$	4-BrC_6H_4	224	-	75

CONCLUSION

The present study offers:

1. Superior approach for the synthesis of thiazolyl hydrazones **3** as it is easier to prepare and handle α,α-dibromoacetophenones as compared to α-bromoacetophenones. Thus, it can be added that the method adopted during this effort is significant since the reaction involves very simple experimentation under mild conditions.
2. The study revealed the behavioral analogy of α,α-dibromoacetophenones with α-bromoacetophenones in the present work.

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