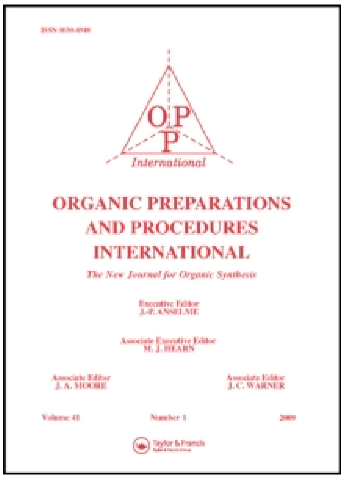

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A NEW AND CONVENIENT SOLVENT-FREE METHOD FOR THE PREPARATION OF 1,4-DIARYL THIOSEMICARBAZIDES

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A NEW AND CONVENIENT SOLVENT-FREE METHOD FOR THE PREPARATION OF 1,4-DIARYLTHIOSEMICARBAZIDES

Submitted by (11/20/00)

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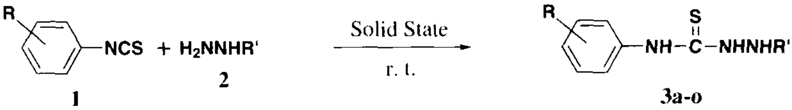
1,4-Disubstituted thiosemicarbazides exhibit a wide spectrum of biological activities, some having been used as anticollibacillus, antituberculosis, insecticides, herbicides and plant-growth regulator.[1-5] Generally, their synthesis have been carried out in solvent or using phase-transfer catalyst.[6-7] Although these methods have some merits, they also have drawbacks such as the use of large amounts of volatile and dangerous solvents, addition of expensive phase-transfer catalysts, need for heating and stirring apparatus. There is increasing interest in the use of environmentally benign reagents and conditions,[8-10] and particularly solvent-free procedures.[11-13] The many advantages include high efficiency and selectivity,[14] ease of isolation and purification, mild reaction conditions,[15] and environmental acceptability,[16,17] which are in keeping with the green requirements of energy-savings and high efficiency. Solvent-free procedures have been widely used in a variety of organic syntheses of substitution,[18] condensation,[19] oxidation-reduction,[20,21] rearrangement[22] and elimination.[23] However the solvent-free addition of aryl isothiocyanate and hydrazines has not been reported so far. We now report a new solvent-free route for the synthesis 1,4-disubstituted thiosemicarbazides.



a) R = *p*-Cl, R' = *p*-$CH_3C_6H_4$ b) R = *p*-Cl, R' = *p*-ClC_6H_4 c) R = *p*-Cl, R' = *p*-BrC_6H_4
d) R = *p*-Cl, R' = *p*-IC_6H_4 e) R= *p*-Br, R' = *p*-$CH_3C_6H_4$ f) R = *p*-Br, R' = *p*-ClC_6H_4
g) R = *p*-Br, R' = *p*-BrC_6H_4 h) R= *p*-Br, R' = *p*-IC_6H_4 i) R = *p*-EtO, R' = *p*-$CH_3C_6H_4$
j) R= *p*-EtO, R' = *p*-ClC_6H_4 k) R= *p*-EtO, R' = *p*-BrC_6H_4 l) R= *p*-EtO, R' = *p*-IC_6H_4
m) R = *p*-Br, R' = *o*-ClC_6H_4 n) R = *p*-Cl, R' = *m*-ClC_6H_4CO o) R = *p*-Br, R' = *m*-ClC_6H_4CO

By this new method, we have synthesized fifteen 1,4-disubstituted thiosemicarbazides in excellent yields (88~96%) at room temperature in short reaction time (8~18min). As might be expected, electron-withdrawing substituents as Cl, Br at the *para*-position facilitated the reaction when on the isothiocyanates and retarded it when on the hydrazines; the reverse was true for electron-donating groups. Although acylhydrazines (*2n* and *2o*) reacted readily, so far *p*-nitro- and *p*-cyanophenylhydrazines failed to react.

Table 1. Physical Data and Elemental Analyses of *3a-o*

Cmpd[a]	Yield (%)	mp (°C)	Time (min)	Elemental Analyses (Found) C	H	N
3a	91	135-137	8	57.63 (57.54)	4.80 (4.87)	14.41 (14.33)
3b	95	151-152	15	50.00 (49.89)	3.53 (3.52)	13.46 (13.51)
3c	94	163-165	14	43.76 (43.59)	3.09 (3.01)	11.78 (11.57)
3d	92	168-169	17	38.66 (38.47)	2.73 (2.51)	10.41 (10.32)
3e	89	167-169	9	50.00 (50.15)	4.17 (3.98)	12.50 (12.44)
3f	92	173-175	13	43.76 (43.61)	3.09 (2.96)	11.78 (11.63)
3g	94	168-169	14	38.90 (38.77)	2.74 (2.51)	10.47 (10.52)
3h	96	171-172	13	34.82 (35.07)	2.46 (2.38)	9.38 (9.39)
3i	91	171-173	11	63.79 (63.59)	6.31 (6.22)	13.95 (13.74)
3j	95	179-181	18	55.99 (55.86)	4.98 (4.79)	13.06 (12.94)
3k	93	189-191	15	49.18 (49.02)	4.37 (4.25)	11.48 (11.38)
3l	95	196-198	16	43.58 (43.44)	3.87 (3.75)	10.17 (9.92)
3m	90	177-179	14	43.76 (44.02)	3.09 (2.91)	11.78 (11.65)
3n	88	186-188	9	49.41 (49.67)	3.24 (3.52)	12.35 (12.61)
3o	89	190-191	8	43.63 (43.78)	2.86 (2.61)	10.92 (10.77)

a) White needle or powder.

EXPERIMENTAL SECTION

Melting points were determined with a Kofler micro melting point apparatus and were uncorrected. IR spectra were recorded on a SP3-300 spectrophotometer in KBr. ^{1}HNMR spectra were measured on a FT-80A spectrometer using TMS as internal standard and $(CD_3)_2CO$ as solvent. Elemental analyses were performed on Carlo-Erba 1102 elemental analyzer. Mass spectra were obtained on a VG-2AS-HS at 70ev.

Table 2. IR and ^{1}H NMR data of *3a-o*

Compd	IR (cm^{-1})	^{1}H NMR (δ)
3a	3265, 3163, 3030, 2950, 2850, 1595, 1506, 1336, 1250, 826	2.33 (s,3H,CH$_3$), 6.72~7.87 (m, 9H, ArH, NH), 8.85 (s, 1H, NH), 9.68 (s, 1H, NH)
3b	3260, 3210, 3160, 3040, 1595, 1550, 1245, 820	6.63~7.83 (m, 9H, ArH, NH), 8.86 (s, 1H, NH), 9.70 (s, 1H, NH)
3c	3293; 3206, 3170, 3030, 1594, 1506, 1490, 1235, 825	6.78~7.62 (m, 9H, ArH, NH), 8.88 (s, 1H, NH), 9.79 (s, 1H, NH).
3d	3290, 3200, 3170, 3030, 1598, 1550, 1480, 1240, 826	6.64~7.83 (m, 9H, ArH, NH), 8.89 (s, 1H, NH), 9.61(s, 1H, NH).
3e	3310, 3225, 3030, 2985, 2850, 1600, 1495, 1350,1245, 830	2.24 (s, 3H, CH3), 6.72~7.63 (m, 9H, ArH, NH), 8.78 (s, 1H, NH), 9.78 (s, 1H, NH).
3f	3343, 3248, 3151, 3030, 1598, 1553, 1488, 1269, 1237, 824	6.05 (s, 1H, NH) 6.79~7.66 (m, 9H, ArH, NH), 8.91 (s, 1H, NH).
3g	3315, 3220, 3180, 3030, 1600, 1500, 1485, 1245, 826	6.78~7.79 (m, 9H, ArH, NH), 8.91 (s, 1H, NH), 9.79 (s, 1H, NH).
3h	3300, 3259, 3160, 1590, 1542, 1485, 1238, 830	6.68~7.79 (m, 9H, ArH, NH), 8.90 (s, 1H, NH), 9.76 (s, 1H, NH).
3i	3307, 3200, 3170, 3078, 2995, 2850, 1600, 1551, 1494, 1243, 825	1.35 (t, 3H, CH3), 4.02 (q, 2H, CH2), 6.73~7.59 (m, 9H, ArH, NH), 8.56 (s, 1H, NH), 9.50 (s, 1H, NH).
3j	3300, 3200, 2990, 2850, 1595, 1488, 1385, 1245, 830	1.34 (t, 3H, CH3), 4.02 (q, 2H, CH2), 6.79~7.56 (m, 9H, ArH, NH), 8.68 (s, 1H, NH), 9.52 (s, 1H, NH).
3k	3292, 3164, 2995, 2860, 1558, 1514, 1481, 1392, 1247, 825	1.35 (t, 3H, CH3), 4.02 (q, 2H, CH2), 6.79~7.56 (m, 9H, ArH, NH), 8.71 (s, 1H, NH), 9.52 (s, 1H, NH).
3l	3290, 3170, 3030, 2995, 2890, 1595, 1500, 1400, 1355, 825	1.34 (t, 3H, CH3), 4.02 (q, 2H, CH2), 6.66~7.64 (m, 9H, ArH, NH), 8.68 (s, 1H, NH); 9.50 (s, 1H, NH).
3m	3341, 3230, 3154, 3035, 1598, 1557, 1490, 1269, 1239, 823, 750	6.21 (s, 1H, NH) 6.63~7.54 (m, 9H, ArH, NH), 8.95 (s, 1H, NH).
3n	3318, 3215, 3153, 3033, 1671, 1638, 1620,1546, 1209, 822, 735, 673	7.32~7.99 (m, 8H, ArH), 8.98 (s, 1H, NH), 9.61 (s, 1H, NH), 9.96 (s, 1H, NH)
3o	3317, 3213, 3151, 3075, 1671, 1638, 1622, 1546, 1211, 819, 770, 673	7.46~7.98 (m, 8H, ArH), 8.99 (s, 1H, NH), 9.61 (s, 1H, NH), 9.97 (s, 1H, NH)

General Procedure for the Preparation of 1, 4-Disubstituted Thiosemicarbazides (3a-o).- A mixture of aryl isothiocyanate (1 mmol) and hydrazine (1 mmol) was ground manually thoroughly in an agate mortar. The reaction was monitored by Thin Layer Chromatography. After the reaction was complete (8~18 min), the crude products were recrystallized from chloroform and petroleum ether (1:3), and dried in vacuum to yield the pure products. The structures of the products were confirmed by IR, ^{1}HNMR and elemental analysis. All the compounds gave satisfactory analytical and spectral data.

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SYNTHESIS OF 2-CYANO-3-DIMETHYLAMINO-*N*-PHENYLACRYLAMIDES USING THE VILSMEIER REACTION

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The Vilsmeier reaction involves the electrophilic substitution of halomethyleniminium salts, on suitable carbon nucleophiles such as electron-rich aromatic compounds,[1] alkene derivatives,[2] activated methyl or methylene compounds.[3] Our group has been exploiting the Vilsmeier reaction as the main route or one of the steps in the synthesis of heterocyclic and carbocyclic compounds.[4] During the course of our work, we required 2-chloro-3-cyanoquinolines (**4**) for some fungicidal activity studies related to leather. A search of the literature revealed that 2-cyano-3-(dimethylamino)-*N*-phenylacrylamides (**2**) are excellent precursors to cyanoquinolines.[5,6] Such compounds have been prepared by the action of Vilsmeier reagent or triethyl orthoformate on cyanoacetanilides (**1**). The first method involving the reaction of cyanoacetanilide with DMF/$POCl_3$ at 90° for 5 h. gave a very low overall yield (< 26%) of (**2a**) together with 12% yield of pyrimidine derivative (**3**) thus making this route unattractive.[7] The second method reported by Adams and Adams[6] involves the reaction of a mixture of triethyl orthoformate and DMF with cyanoacetanilides in the presence of catalytic amount of *p*-toluenesulfonic acid at 120° for 20 h. In an effort to find milder conditions for this purpose, we carried out the Vilsmeier reaction on cyanoacetanilides using DMF/$POCl_3$ at various temperatures as the temperature plays a very important role in determining the nature of the products and yields. We envisaged that better yields of cyanoacrylamides could be obtained by conducting the Vilsmeier reaction on cyanoacetanilides at lower temperature rather than heating at 100°.