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A Challenging Synthesis of New 1,3,4-Thiadiazole Derivatives Starting from 2-Acylamino-3,3-dichloroacrylonitriles

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ABSTRACT: *Available 2-acylamino-3,3-dichloroacrylonitriles, when treated with hydrazine hydrate, provide 2-alkyl- or 2-aryl-5-hydrazino-1,3-oxazole-4-carbonitriles that readily add alkyl or aryl isothiocyanates and the adducts formed recyclize on heating. Finally, the synthesis results in 5-alkyl(aryl)amino-1,3,4-thiadiazol-2-yl(acylamino)acetonitriles or the products of their further cyclization, 2-(5-amino-1,3-oxazol-2-yl)-1,3,4-thiadiazole derivatives. The structures of the novel substituted 1,3,4-thiadiazoles are corroborated spectroscopically as well as by X-ray diffraction method.* © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:454–458, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20041

INTRODUCTION

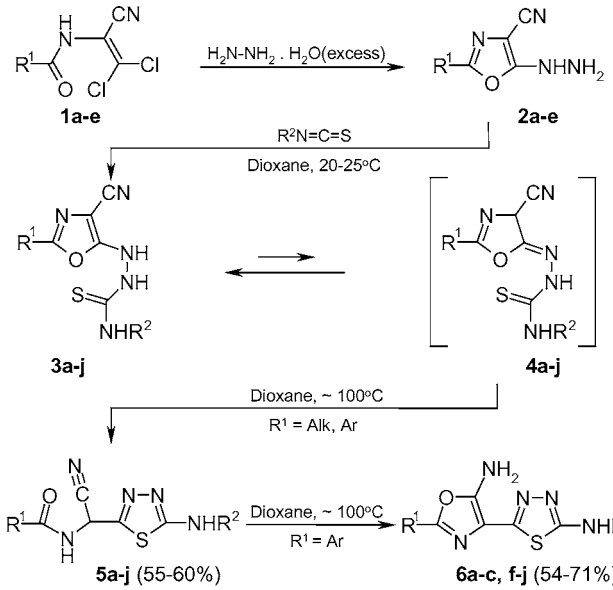
It is more than 30 years since two research teams, in Japan and Ukraine, started systematic studies on the conversions of 2-acylamino-3,3-dichloroacrylonitriles demonstrating unique properties as reagents for heterocyclizations [1–11]. Starting from these reagents, the preparative syntheses were elaborated for a number of functional derivatives of 1,3-oxazole [1–7,10,11], 4*H*-imidazole [8], and 1,3,4-oxadiazole [9]. The present work addresses a new line in harnessing of 2-acylamino-3,3-dichloroacrylonitriles for the preparation of interesting 1,3,4-thiadiazole derivatives.

RESULTS AND DISCUSSION

To obtain novel 1,3,4-thiadiazole derivatives, **1a–e** were first treated with an excess of hydrazine hydrate and then heated with alkyl or aryl isothiocyanates in dioxane. In doing so, the conversions **1**→**2**→**3**→**4**→**5**→**6** successively proceeded as shown in Scheme 1.

The cyclocondensation **1**→**2** was studied before [4,9]. It represents a particular case of a quite general synthetic route to 5-hydrazino-1,3-oxazole derivatives containing various electron acceptor groups, such as CN, C(O)OAlk, $P(O)(OAlk)_2$, PPh_3^+, etc., at the position 4 [4,9,12].

In the reaction with alkyl and aryl isothiocyanates, compounds **2a–e** first produce substituted thiosemicarbazidooxazoles **3a–j** that can occasionally be isolated in the individual state (Table 1) and studied by IR and ^{1}H NMR spectroscopy to verify the presence of the nitrile group and the C(S)-NH-NH-Het moiety (Table 2). If heated in dioxane, compounds **3d,e** containing alkyl substituents at the position 2 of the oxazole ring recyclize to give products



1-6	a	b	c	d	e	f	g	h	i	j
R^1	Ph	4-MeC_6H_4	4-$MeOC_6H_4$	Me	Et	Ph	Ph	4-MeC_6H_4	4-MeC_6H_4	4-$MeOC_6H_4$
R^2	Ph	Ph	Ph	Ph	4-MeC_6H_4	4-MeC_6H_4	Et	n-Bu	4-MeC_6H_4	4-MeC_6H_4

SCHEME 1

5d,e. The IR spectra of these compounds exhibit the signals from the C=O and C≡N bonds, whereas the ^{1}H NMR spectra point to the presence of the CHNH fragment giving rise to doublets in the regions 6.4–6.5 and 9.4–9.5 ppm (Table 2).

For a reliable identification of compounds **5a–e**, we have made use of the spectral data for their analogs synthesized recently by a similar recyclization and containing, instead of a nitrile group, other electron acceptor residues, C(O)OAlk and P(O)(OAlk)$_2$ [12]. Prototropic tautomers **4** are likely to play a significant part in the conversion **3**→→**5**, since their nonaromatic structure favors the recyclization **4**→**5**. By structural features, this reaction

TABLE 1 Physical and Analytical Data of Compounds **2,3,5,6**

				Analysis (%) Found (Calcd.)			
	mp (°C)	*Yield (%)*	*Mol. Formula (Mol. Wt.)*	*C*	*H*	*N*	*S*
2e	85–87[a]	75	$C_6H_8N_4O$ (152.2)	47.53 (47.36)	5.42 (5.30)	36.50 (36.82)	–
3b	182–184	89	$C_{18}H_{15}N_5OS$ (349.4)	62.09 (61.87)	4.27 (4.33)	20.23 (20.04)	8.93 (9.18)
3g	176–177	85	$C_{13}H_{13}N_5OS$ (287.4)	54.51 (54.34)	4.83 (4.56)	24.49 (24.37)	11.08 (11.16)
5d	209–211[b]	55	$C_{12}H_{11}N_5OS$ (273.3)	52.98 (52.73)	4.21 (4.06)	25.75 (25.62)	11.59 (11.73)
5e	222–223[b]	60	$C_{14}H_{15}N_5OS$ (301.4)	56.28 (56.00)	5.16 (5.02)	23.07 (23.23)	10.43 (10.64)
6a	210–212[c]	61	$C_{17}H_{13}N_5OS$ (335.4)	61.09 (60.88)	4.15 (3.91)	20.73 (20.88)	9.69 (9.56)
6b	236–238[c]	66	$C_{18}H_{15}N_5OS$ (349.4)	62.11 (61.87)	4.12 (4.33)	20.28 (20.04)	9.33 (9.18)
6c	207–208[c]	58	$C_{18}H_{15}N_5O_2S$ (365.4)	59.41 (59.17)	4.38 (4.14)	19.01 (19.17)	8.92 (8.77)
6f	205–207[c]	63	$C_{18}H_{15}N_5OS$ (349.4)	61.99 (61.87)	4.69 (4.33)	20.17 (20.04)	9.28 (9.18)
6g	183–185[d]	69	$C_{13}H_{13}N_5OS$ (287.4)	54.51 (54.34)	4.79 (4.56)	24.35 (24.37)	11.38 (11.17)
6h	198–200[d]	64	$C_{16}H_{19}N_5OS$ (329.5)	58.61 (58.34)	6.16 (5.81)	21.11 (21.26)	9.95 (9.73)
6i	205–207[c]	54	$C_{19}H_{17}N_5OS$ (363.4)	63.09 (62.79)	4.96 (4.71)	23.39 (19.27)	9.56 (8.82)
6j	201–202[c]	57	$C_{19}H_{17}N_5O_2S$ (349.4)	60.02 (60.14)	4.78 (4.52)	18.59 (18.46)	8.61 (8.45)

[a]Recrystallization from hexane.
[b]Recrystallization from MeOH.
[c]Recrystallization from the mixture MeCN-DMF.
[d]Recrystallization from MeCN.

TABLE 2 Spectroscopic Data of Compounds **3,5,6**

	IR (KBr) (cm^{-1})	*^{1}H NMR (DMSO-d_6/TMS) δ, J (Hz)*	*MS: m/z $(M+H)^+$*
3b	2220 (C≡N) 3120–3200 (NH)	2.38 (s, 3H, CH_3), 7.16–7.73 (m, 9H, C_6H_5, C_6H_4), 10.02 (br s, 2H, NH, NH), 10.37 (s, 1H, NH)	350
3g	2230 (C≡N) 3150–3300 (NH)	1.09 (t, 3H, CH_3), 3.50 (q, 2H, CH_2), 7.50–7.80 (m, 5H, C_6H_5), 8.50 (br s, 1H, NH), 9.70 (s, 1H, NH),10.37 (s, 1H, NH)	–
5d	2320 (C≡N) 1670 (NC═O) 3200–3300 (NH)	1.95 (s, 3H, CH_3), 6.45 (d, 1H, $J = 7.5$, CH), 7.00–7.59 (m, 5H, C_6H_5), 9.49 (d, 1H, $J = 7.5$, NH), 10.45 (br s, 1H, NH)	274
5e	1650 (NC═O) 3200–3420 (NH)	1.06 (t, 3H, CH_3), 2.19 (q, 2H, CH_2), 2.28 (s, 3H, CH_3), 6.42 (d, 1H, $J = 7.5$, CH), 7.13–7.43 (m, 4H, C_6H_4), 9.41 (d, 1H, $J = 7.5$, NH), 10.30 (s, 1H, NH)	302
5h[a]	–	0.94 (t, 3H, CH_3), 1.41 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 2.36 (s, 3H, CH_3), 3.27 (m, 2H, NCH_2), 6.48 (d, 1H, $J = 7.5$, CH), 7.27–7.80 (m, 4H, C_6H_4), 7.78 (t, 1H, NH), 9.81 (d, 1H, $J = 7.5$, NH)	–
6a	1645[b] (δ, NH_2), 3200–3440 (NH, NH_2)	6.95–7.82 (m, 10H, 2 × C_6H_5), 7.07 (br s, 2H, NH_2), 10.19 (s, 1H, NH)	336
6b	1630[b] (δ, NH_2) 3200–3370 (NH, NH_2)	2.36 (s, 3H, CH_3), 6.99–7.73 (m, 9H, C_6H_4, C_6H_5), 7.11 (br s, 2H, NH_2), 10.26 (s, 1H, NH)	350
6c	1630[b] (δ, NH_2) 3200–3450 (NH, NH_2)	3.82 (s, 3H, CH_3), 6.92 (br s, 2H, NH_2), 6.94–7.78 (m, 9H, C_6H_4, C_6H_5), 10.14 (s, 1H, NH)	366
6f	1640[b] (δ, NH_2) 3200–3440 (NH, NH_2)	2.28 (s, 3H, CH_3), 7.03 (br s, 2H, NH_2), 7.09–7.84 (m, 9H, C_6H_5, C_6H_4), 10.06 (s, 1H, NH)	350
6g	1635[b] (δ, NH_2) 3180–3400 (NH, NH_2)	1.23 (t, 3H, CH_3), 3.31 (q, 2H, CH_2), 6.86 (br s, 2H, NH_2), 7.38–7.80 (m, 6H, C_6H_5, NH)	288
6h	1640[b] (δ, NH_2) 3200–3400 (NH, NH_2)	0.94 (t, 3H, CH_3), 1.41 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 2.36 (s, 3H, CH_3), 3.29 (m, 2H, CH_2), 6.77 (br s, 2H, NH_2), 7.24–7.69 (m, 4H, C_6H_4), 7.49 (t, 1H, NH)	330
6i	1640[b] (δ, NH_2) 3180–3400 (NH, NH_2)	2.28 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 6.97 (br s, 2H, NH_2), 7.08–7.73 (m, 8H, 2 × C_6H_4), 10.05 (s, 1H, NH)	364
6j	1640[b] (δ, NH_2) 3140–3450 (NH, NH_2)	2.28 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 6.83 (br s, 2H, NH_2), 6.98–7.77 (m, 8H, 2 × C_6H_4), 9.97 (s, 1H, NH)	380

[a]The data refer to the ca. 1:1 mixture of compounds **5h** and **6h**.
[b]An unidentified absorption band is also present in this region.

belongs to a particular rearrangement type studied by Boulton et al. [13] that involves azole side chains.

As regards compounds **3a–c,f–j** bearing aryl substituents at the position 2 of the oxazole ring, it is notable that on long heating them in dioxane, reaction products **5a–c,f–j** are as a rule inseparable as they undergo further cyclization **5**→**6**. Cyclizations of this kind affording substituted 5-amino-1,3-oxazoles are well known for α-acylaminonitriles of a simpler structure [14]. At the same time, heating compound **3h** in dioxane for a short time results in a mixture of products **5h** and **6h**, which is confirmed by the ^{1}H NMR spectra. On further long heating in dioxane, this mixture turns into the only compound, **6h**.

The structures of the final products yielded by the complex conversions **3**→**4**→**5**→**6** are corroborated by a combined spectroscopic study. Thus it is found that the last cyclization involves the C≡N bond and causes formation of the primary amino group (Table 2). In addition, an unequivocal structural determination using X-ray diffraction method has been performed for one compound of this family, 2-(5-amino-2-phenyl-1,3-oxazol-4-yl)-5-ethylamino-1,3,4-thiadiazole **6g** (Fig. 1 and Table 3).

A molecule of **6g** contains a practically planar system consisting of two five-membered heterocycles

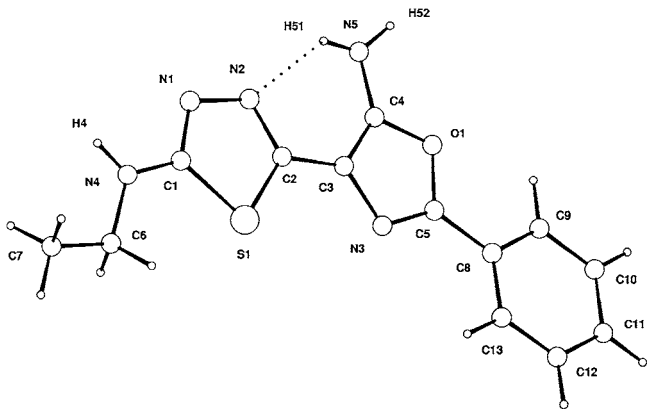


FIGURE 1 Perspective view and labeling scheme for the molecule **6g**.

TABLE 3 Selected Bond Lengths and Bond Angles of **6g**

S(1)–C(1)	1.747(2)	C(1)–S(1)–C(2)	86.42(12)
S(1)–C(2)	1.739(2)	C(4)–O(1)–C(5)	105.28(16)
O(1)–C(4)	1.363(2)	N(2)–N(1)–C(1)	112.08(18)
O(1)–C(5)	1.380(3)	N(1)–N(2)–C(2)	113.17(19)
N(1)–N(2)	1.385(3)	C(3)–N(3)–C(5)	104.56(17)
N(1)–C(1)	1.304(3)	C(1)–N(4)–C(6)	122.6(2)
N(2)–C(2)	1.299(3)	S(1)–C(1)–N(1)	114.24(17)
N(3)–C(3)	1.402(3)	S(1)–C(2)–N(2)	114.09(17)
N(3)–C(5)	1.293(3)	N(3)–C(3)–C(4)	109.47(19)
N(4)–C(1)	1.348(3)	O(1)–C(4)–C(3)	107.42(18)
N(4)–C(6)	1.434(3)	O(1)–C(5)–N(3)	113.26(18)
N(5)–C(4)	1.349(3)		
C(2)–C(3)	1.440(3)		
C(3)–C(4)	1.357(3)		

and the benzene ring. The dihedral angle between the five-membered rings S(1)C(1)N(1)N(2)C(2) and O(1)C(4)C(3)N(3)C(5) amounts to only 0.9°, whereas the benzene ring C(8–13) makes with the plane O(1)C(4)C(3)N(3)C(5) a dihedral angle of 7.1°. An efficient π-conjugation in the moieties *n*N(4)—πC(1)=N(1) and *n*N(5)—πC(4)=C(3) leads to a notable shortening of the bonds N(4)—C(1) and N(5)—C(4) down to 1.348(3) and 1.349(3) Å, respectively (a standard length of a single bond N(sp^2)—C(sp^2) amounts to 1.43–1.45 Å [15,16]). Among the structural peculiarities of compound **6g** is the intramolecular hydrogen bond [17] N(5)—H(51)...N(2) with the relevant bond lengths and angles as follows: N(5)...N(2) 2.973(3) Å, H(51)...N(2) 2.36(3) Å, N(5)—H(51) 0.81(3) Å, N(5)H(51)N(2) 132(3)°, which closes the six-membered ring N(2)C(2)C(3)C(4)N(5)H(51).

Thus, the conversion of reagents **2a–e** into hitherto unknown 1,3,4-thiadiazole derivatives **5d,e** and **6a–c,f–j** is supported by solid evidence. The approach developed is of undeniable preparative significance, since the starting reagents are easy to obtain from the available adducts formed by carboxamides with chloral [2,18]. Moreover, the conversions **2**→→**5** and **2**→→**6** are quite straightforward and furnish the 1,3,4-thiadiazole derivatives unobtainable by the previously described methods [19]. Finally, compounds **5d,e** and **6a–c,f–j** can in turn be converted with ease into other novel 1,3,4-thiadiazole derivatives that will be considered elsewhere.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Gemini 300 spectrometer at 300 MHz using TMS as an internal standard. IR spectra were measured on a Specord M-80 spectrometer for KBr disks. Mass spectra were measured on a Surveyor MSQ instrument (Thermo Finnigan) using the APCI ionization method, and 0.1% aqueous solution of formic acid and acetonitrile as solvents.

2-Alkyl(aryl)-5-hydrazino-1,3-oxazole-4-carbonitriles **2a–e**

To a solution of **1a–e** (10 mmol) obtained by the known procedure [2,3] in EtOH (30 mL) was added hydrazine hydrate (35 mmol). The mixture was allowed to stand at r.t. for 24 h. After filtering off hydrazine hydrochloride, the solvent was evaporated in vacuo, and the residue was treated with H_2O, filtered off, dried, and purified by recrystallization from EtOH or hexane to give **2a–e** (Table 1). Compounds **2a–d** were described before [4,9].

2-Alkyl(aryl)-5-[4-alkyl(aryl)thiosemicarbazido]-1,3-oxazole-4-carbonitriles **3a–j**

To a solution of **2a–e** (10 mmol) in anhydrous dioxane (60 mL) was added the corresponding alkyl or aryl isothiocyanate (11 mmol). The mixture was allowed to stand at r.t. for 72 h. The resulting precipitate was filtered off, washed with dioxane, and dried in vacuo. Analytical and spectral data were obtained for **3b,g** (Table 1) whereas their analogs **3a,c–f,h–j** were immediately used in the preparation of **5d,e** and **6a,c–f,h–j** without isolation.

Acylamino[5-alkyl(aryl)amino-1,3,4-thiadiazol-2-yl]acetonitriles **5a–j**

To a solution of **2a–e** (10 mmol) in anhydrous dioxane (60 mL) was added the corresponding alkyl or aryl isothiocyanate (11 mmol). The mixture was refluxed for 8 h, and dioxane was removed in vacuo. For crystallization, the residue was treated with H_2O; then it was filtered off and recrystallized from an appropriate solvent (Table 1). Analytical and spectral data were obtained for **5d,e** whereas their analogs **5a–c,f–j** were not isolated, since they cyclize rapidly to give **6a–c,f–j**.

2-[5-Amino-2-aryl-1,3-oxazol-4-yl]-5-alkyl(aryl)amino-1,3,4-thiadiazoles **6a–c,f–j**

To a solution of **2a–c** (10 mmol) in anhydrous dioxane (60 mL) was added the corresponding alkyl or aryl isothiocyanate (11 mmol). The mixture was refluxed for 8 h, and dioxane was removed in vacuo. The product was purified by recrystallization from an appropriate solvent (Table 1).

Compound **6b** was also obtained from **3b** (10 mmol) by boiling in dioxane (60 mL) for 8 h.

The product was isolated as described in the general procedure, yield 71%, mp 236–238°C. The IR spectra for the samples of compound **6b** obtained from **2b** and **3b** were identical.

X-ray Structure Determination for **6g**

Crystal Data. $C_{13}H_{13}N_5OS$, M = 287.35, monoclinic, $a = 15.394(9)$, $b = 7.839(3)$, $c = 11.431(6)$ Å, $\beta = 90.31(5)^\circ$, V = 1379(1) Å^3, $Z = 4$, $d = 1.38$ g cm^{-3}, space group $P2_{1/c}$, $\mu = 20.74$ cm^{-1}, F(000) = 602.8, crystal size ca. 0.31 × 0.46 × 0.48 mm.

Data Collection. All crystallographic measurements were performed at 20°C on a CAD-4 Enraf-Nonius diffractometer operation in the ω–2θ scan mode (the ratio of the scanning rates $\omega/2\theta = 1.2$). Intensity data were collected within the range $2 < \theta < 70^\circ$ ($0 \le h \le 18$, $0 \le k \le 9$, $-13 \le l \le 13$) using graphite-monochromated Cu K_α radiation ($\lambda = 1.54178$ Å). Intensities of 2794 reflections (2491 unique reflections, $R_{int} = 0.013$) were measured. Data were corrected for Lorentz and polarization effects, and an empirical absorption correction based on azimuthal scan data was applied [20].

Structure Solution and Refinement. The structure was solved by direct methods and refined by full-matrix least-squares technique in the anisotropic approximation using the CRYSTALS program package [21]. In the refinement, 1939 reflections with $I > 3\sigma(I)$ were used. All hydrogen atoms were located in the difference Fourier maps and included in the final refinements with fixed positional and thermal parameters (only H(4), H(51), and H(52) atoms participating in hydrogen bonding were refined isotropically). Convergence was obtained at $R = 0.041$ and $R_w = 0.044$, GOF = 1.108 (193 refined parameters; obs/variabl. = 10.0; the largest and minimal peaks in the final difference map, 0.27 and −0.31 e/Å^{-3}). The Chebyshev weighting scheme [22] with the parameters 1.23, −0.38, 0.55, and 0.44 was used [23].

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