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FORMATION OF 2,5-DIHYDRO-2-IMINOPYRROLES, 2,5-DIHYDRO-2-IMINOFURANS AND (*Z*)-3-ALKYLAMINO-2,3-DICYANOACRYLATES *VIA* 4-CHLORO-5*H*-1,2,3-DITHIAZOL-5-YLIDENE DERIVATIVES

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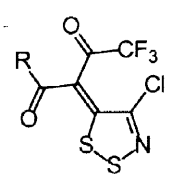
Abstract: *Treatment of 4-chloro-5H-1,2,3-dithiazol-5-ylidene derivatives* ***1-3*** *with primary and secondary alkylamines in CH_2Cl_2 at room temperature gave 2,5-dihydro-2-iminopyrroles (22-55%) and 2,5-dihydro-2-iminofurans (18-62%). However, similar treatment of alkyl (4-chloro-5H-1,2,3-dithiazol-5-ylidene)cyanoacetates under the same conditions gave (Z)-3-alkylamino-2,3-dicyanoacrylate esters (39-72%).*

In the preceding paper[1] we described the synthesis of (*E*)-(**1a**) and (*Z*)-3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-1,1,1-trifluoropentane-2,4-diones (**2a**) and their analogs, **1b**, **2b-d**, and **3** and how to determine the ratios of the stereoisomers by ^{19}F NMR spectroscopy. We have been interested in exploring the potential synthetic utility of dithiazol-5-ylidene derivatives in view of the formation of a variety of products from the



a, R = Me
b, R = EtO

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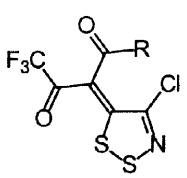

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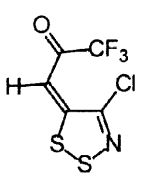
a, R = Me
b, R = EtO
c, R = Ph
d, R = 2-naphthyl



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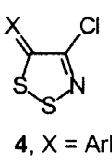
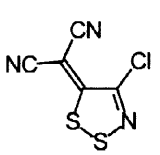


4, X = ArN
5, X = S



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reactions of 5-arylimino-1,2,3-dithiazoles **4**[2] and 1,2,3-dithiazole-5-thione **5**[3] with primary and secondary alkylamines. Much effort has been devoted to extending the reactions of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) (**6**) with other active methylene compounds to obtain new dithiazol-5-ylidenes since Appel et al. had prepared alkyl (4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)cyanoacetates (**7**). Recently Rees et al.[5] reported the synthesis of (4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)propanedinitrile (**8**) by treatment of **6** with tetracyanoethylene oxide and obtained 3-morpholino- and 3-chloroisothiazol-4,5-dicarbonitriles from compound **8** and morpholine, and benzyl(triethyl)ammonium chloride, respectively. The results prompted us to disclose our results obtained from the reactions of a mixture of **1b** and **2b**, **2c**, and **3** with primary and secondary alkylamines.

Treatment of fluorine containing 1,2,3-dithiazol-5-ylidenes foregoing (1 - 3 mmol) with primary alkylamines (5 - 10 mmol) for an appropriate time in either CH_2Cl_2 or THF (4 - 100 mL) at room temperature gave 2,5-dihydro-2-iminopyrroles **9** (Scheme 1). Reaction conditions and yields of **9** are summarized in Table 1.

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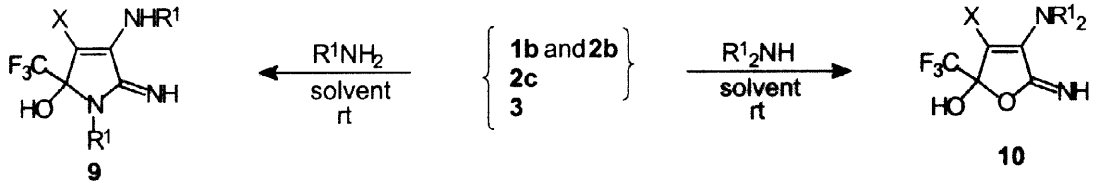
PII: S0040-4039(98)01445-2



Scheme 1

Table 1. Reaction conditions and yields of **9**

Compound	X	R^1	Solvent[b]	Time (h)	Yields[a] (%)
9a	H	*i*-Pr	CH_2Cl_2	8	22
9b	H	*n*-Pent	CH_2Cl_2	5	46
9c	CO_2Et	Me	THF	2	55
9d	CO_2Et	Et	THF	2	49
9e	CO_2Et	*i*-Pr	CH_2Cl_2	4	31
9f	COPh	Me	THF	2	40
9g	COPh	Et	THF	3	24

[a] Isolated yields. Compound **9a-b**, **9c-e**, and **9f-g** are prepared from compounds **3**, a mixture of **1b** and **2b**, and **2c**, respectively. [b] THF was used as a solvent when R = Me (40% aq. $MeNH_2$) and R = Et (70% aq. $EtNH_2$).

The structures of **9** were determined on the basis of the spectroscopic (^1H, ^{13}C NMR, IR, MS) data and elemental analyses.[6] The most diagnostic features in the ^{13}C NMR spectra are the carbon absorptions of CF_3, at 123.6-125.7 ppm, exhibiting a quartet due to splitting by three fluorine atoms with J_{CF} = 285 Hz and the absorptions of the quaternary carbon C-5 at 77.1-81.1 ppm, exhibiting a quartet with J_{CCF} = 30 Hz.[7] In addition, the absorptions assignable to C-2, C-3, and C-4 appeared at 165,8-170.1, 141.4-151.7, and 95.3-105 ppm, respectively, which were confirmed by HMBC spectrum of **9c**.

The synthesis of **9** *via* 1,2,3-dithiazol-5-ylidenes is a complement to relevant methods[8,9] which are of limited use for the synthesis of 2,5-dihydropyrroles.

Treatment of a mixture of **1b** and **2b**, and **2c** with secondary alkylamines under the same conditions, however, gave 2,5-dihydro-2-iminofurans **10**. Reaction conditions and yields of **10** are summarized in Table 2.

Table 2. Reaction conditions and yields of **10**

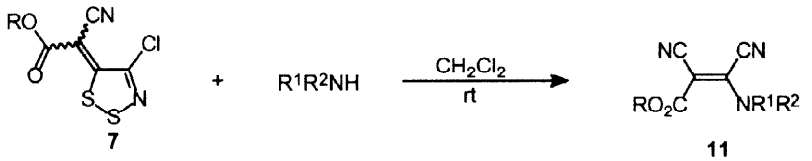
Compound	X	R^1_2	Solvent	Time (h)	Yields[a] (%)
10a	CO_2Et	Et_2	THF	9	42
10b	CO_2Et	$CH_2CH_2OCH_2CH_2$[b]	THF	14	62
10c	CO_2Et	$(n\text{-Pr})_2$	THF	15	18
10d	COPh	Et_2	THF	14	26
10e	COPh	$CH_2CH_2OCH_2CH_2$[b]	THF	16	56

[a] Isolated yields. Compounds **10a-c** and **10d-e** are from a mixture of **1b** and **2b**, and **2c**, respectively. [b] Morphorine.

^{13}C NMR spectra of **10** exhibited two quartets at 81.3-85.1 ppm with J_{CCF} = 33 Hz and at 122.5-124.0 ppm with J_{CF} = 288 Hz. The former quartet was assigned as a quaternary carbon C-5 and the latter as CF_3 carbon. In addition, the absorptions assignable to C-2, C-3, and C-4 appeared at 166.4-167.2, 146.1-148.7, and 99.5-110.4 ppm, respectively.[10] Up until now the synthesis of 2,5-dihydro-2-iminofurans has been achieved by only one method[11] which involves the reactions of (*Z*)-2-alkoxy-3-methyl-1-alkenecarbonitriles with KOH. So the formation of **10** from 1,2,3-dithiazol-5-ylidenes **1-2** may provide a complementary route for preparing the 2,5-dihydro-2-iminofuran skeleton having different substituents at C-3 and C-4 depending

upon secondary alkylamines and a substituent R.

Similar treatment of **7** (0.5 - 1.8 mmol) with primary and secondary alkylamines (1.6 - 4.7 mmol) in CH_2Cl_2 (30 - 60 ml) under the same conditions gave (*Z*)-3-alkylamino-2,3-dicyanacrylate esters **11** in 39-72% yields (Scheme 2). Reaction conditions and melting points, C=O absorptions, and yields of **11** are summarized in Table 3.



Scheme 2

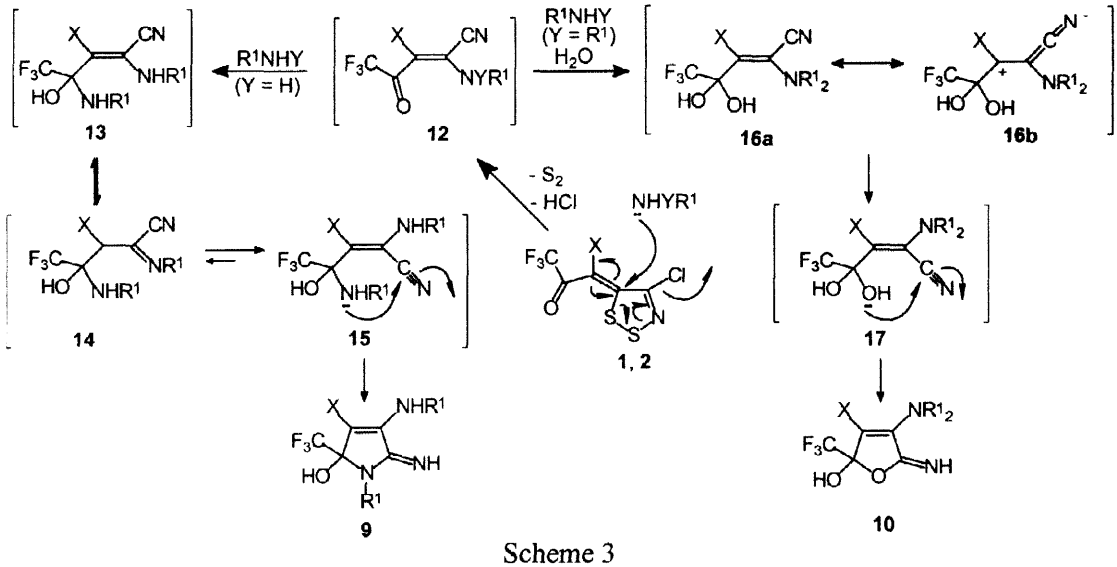
Table 3. Reaction conditions, melting points, C=O absorptions and yields of **11**

Compound	R	R^1	R^2	Time (h)	Yields[a] (%)	mp (°C)	C=O[c] (cm^{-1})
11a	Me	Me	H	1	68	172-173[b]	1680
11b	Me	Et	H	1.5	64	157-159[b]	1688
11c	Me	*i*-Pr	H	3	39	143-145	1690
11d	Me	*t*-Bu	H	3	54	170-171	1686
11e	Me	*n*-Pent	H	3	69	57-58	1688
11f	Me	*i*-Pr	Me	6	47	115-117	1712
11g	Me	*n*-Pr	*n*-Pr	10	55	liquid	1715
11h	Me	*n*-Bu	*n*-Bu	15	56	liquid	1716
11I	Me	Allyl	Allyl	8	41	liquid	1720
11j	Me	$CH_2CH_2OCH_2CH_2$		16	51	138-140[b]	1709
11k	Et	*i*-Pr	H	3	72	60-61	1675
11l	Et	*t*-Bu	H	5	41	110-113[b]	1680
11m	Et	Et	Et	7	61	52-53	1706
11n	Et	*i*-Pr	Me	6	55	106-108	1706
11o	Et	*n*-Bu	*n*-Bu	11	60	liquid	1709
11p	Et	Allyl	Allyl	8	44	liquid	1709

[a] Isolated yields. [b] Recrystallized from *n*-hexane-$CHCl_3$, otherwise from CH_2Cl_2. [c] Recorded in a KBr pellet.

The stereochemistry of **11** was assigned based on the ester carbonyl stretching frequencies. That is, compounds **11a-e** and **11k-l** having a secondary amino group exhibited C=O stretching absorptions at 1675-1690 cm^{-1}, while compounds **11f-j** and **11m-p** having a tertiary amino group exhibited the corresponding absorptions at 1706-1720 cm^{-1}. The lower frequencies of the former may be attributable to the hydrogen bonding formed between a N-H hydrogen and a carbonyl oxygen, whereas the latter does not have a hydrogen atom on nitrogen for hydrogen bonding. As a result, the C=O absorptions of the latter appear at higher frequencies.

The mechanism for the formation of **9** may be explained by nucleophilic attack of a primary alkylamine to C-5 of compound **1** and /or **2** concomitant with extrusion of S_2 and HCl to give an enamino ketone **12**, which reacts with a second molecule of the primary alkylamine to give an enamino hemiaminal **13**[12] rather than its stereoisomer **15** in view of the stereochemistry of **11**. The intermediate **13** isomerizes to **15** *via* an iminohemiaminal **14**, followed by cyclization to yield **9** (Scheme 3). However, in the case of the reactions with secondary alkylamines, water originated from either moist alkylamine or the moisture in the air instead of a bulky secondary alkylamine attacking the carbonyl carbon of the intermediate **12** to form a hydrate form **16a**, which may be isomerized to **17** *via* its polar resonance form **16b**. The intramolecular cyclization of **17** gives **10**.



Scheme 3

Treatment of **2c** with dried morpholine under the same conditions as for **10e** gave a mixture showing a major spot of which R_f value (0.10, *n*-hexane-EtOAc = 2:1) was different from that of **10e** (R_f = 0.25, the same solvent mixture). However, **10e** (29%) in addition to several unidentifiable materials were isolated after chromatography.

In summary, treatment of fluorine containing 1,2,3-dithiazol-5-ylidenes **1-3** with primary and secondary alkylamines in CH_2Cl_2 at room temperature afforded 2,5-dihydro-2-iminopyrroles **9** and 2,5-dihydro-2-iminofurans **10**, respectively. However, the reactions of alkyl (4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)cyanoacetate **7** with the same alkylamines gave (*Z*)-3-alkylamino-2,3-dicyanoacrylate esters **11**. A mechanism is proposed for the formation of compounds **9-11**.

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Reference and Notes

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6. **9a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.01 (d, 3H, J = 6.5 Hz, CH_3), 1.07 (d, 3H, J = 6.5 Hz, CH_3), 1.20 (d, 6H, J = 6.5 Hz, $2CH_3$), 1.60 (s, 1H, OH), 2.92 (septet, 1H, J = 6.5 Hz, CH), 3.39 (octet, 1H, J = 6.5 Hz, CH), 4.31 (d, 1H, J = 6.5 Hz, NH), 4.83 (s, 1H, =CH), 7.41 (s, 1H, =NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.2, 25.7, 26.0, 43.3, 45.8, 78.3 (q, J_{CCF} = 30.0 Hz, C-5), 95.5 (C-4), 124.6 (q, J_{CF} = 284.5 Hz), 141.4 (C-3), 170.1 (C-2); IR (KBr) 3304, 2960, 1709, 1678, 1643, 1509, 1458, 1403 cm^{-1}. *Anal* Calcd for $C_{11}H_{18}F_3N_3O$: C, 49.80; H, 6.84; N, 15.84. Found: C, 49.92; H, 6.85; N, 15.37.
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10. **10a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (t, 6H, J = 7.0 Hz, $2CH_3$), 1.34 (t, 3H, J = 7.0 Hz, CH_3), 3.69 (q, 2H, J = 7.0 Hz, CH_2), 3.77 (q, 2H, J = 7.0 Hz, CH_2), 4.30 (q, 2H, J = 7.0 Hz, CH_2), 5.57 (br s, 1H, OH), 7.35 (s, 1H, =NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 14.6, 47.0, 61.4, 84.5 (q, J_{CCF} = 33.4 Hz), 99.5, 123.8 (q, J_{CF} = 288.1 Hz), 146.9, 163.9, 166.9; IR (KBr) 3200, 2976, 1712, 1643, 1578, 1462, 1356, 1299 cm^{-1}. *Anal* Calcd for $C_{12}H_{17}F_3N_2O_4$: C, 46.45; H, 5.52; N, 9.03. Found: C, 46.55; H, 5.53; N, 8.98.
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