Cycloaddition of Sodium Azide to Polarized Ketene *S,S*- and *S,N*-Acetals: Synthesis of Novel Substituted Triazole and Tetrazole Derivatives[1]

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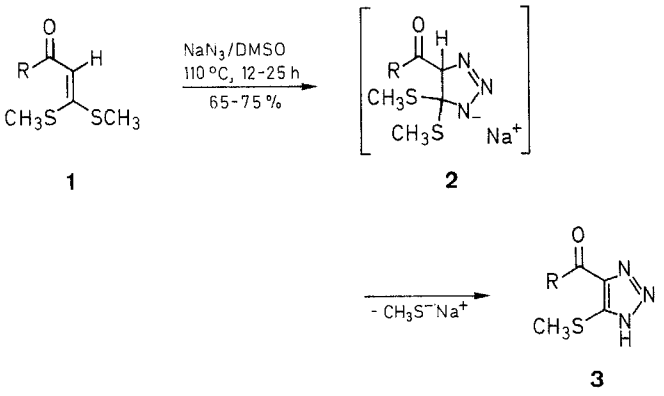
Thermal [3+2] cycloadditon of aroylketene dithioacetals **1a–e** with sodium azide affords novel 4-aroyl-5-methylthio-1*H*-1,2,3-triazoles **3a–e**. The corresponding *S,N*-acetals **5a–m** derived from primary amines react with sodium azide through different pathway involving cyclization of initially formed imidoyl azide intermediates to give novel 1,5-disubstituted tetrazole **7a–m** in good yields. The *S,N*-acetal **5n** obtained from malononitrile, however, undergoes cycloaddition on one of the nitrile groups to give a tetrazole **8**.

The enamines, enaminones, enediamines, enol ethers (or enols), ketene *O,O*-acetals and *β*-chlorovinylketones are known to undergo facile thermal [3+2] cycloadditions with sodium azide and organic azides to give 4,5-dihydro-1*H*-1,2,3-triazoles. These dihydrotriazoles on spontaneous or thermal elimination of the leaving groups afford the corresponding substituted triazoles.[2,3] However, to our knowledge, there are no reports on azide cycloaddition to either vinyl thioethers or ketene *S,S*-acetals to give substituted triazoles. In continuation of our studies on the synthetic applications of polarized ketene *S,S*- and *S,N*-acetals,[1] we now report the reaction of these compounds with sodium azide to afford novel substituted triazoles and tetrazoles, respectively.



1 2 3

1–3	R	1–3	R	1–3	R
a	C_6H_5	**c**	$4\text{-}ClC_6H_4$	**e**	$3,4\text{-}Cl_2C_6H_3$
b	$4\text{-}CH_3C_6H_4$	**d**	$4\text{-}CH_3OC_6H_4$	**1f**	CH_3

Scheme A

When **1a** was reacted with sodium azide at 110 °C in dimethyl sulfoxide, the product isolated was identified as 4-benzoyl-5-methylthio-1*H*-1,2,3-triazole **(3a)** (73%). The triazole **3a** is evidently formed by elimination of the methylthio group from the initially formed sodium 5,5-bis(methylthio)-4,5-dihydro-1*H*-1,2,3-triazol-1-ide **(2a)**. The reaction was found to be general with other dithioacetals **1b–e**, which afforded the corresponding 5-methylthiotriazoles **3b–e** in 65–75% overall yields. The corresponding 1-acetyl-2,2-bis(methylthio)ethylene **(1f)**, however, yielded the unstable azidoolefin **4** under similar conditions. This is probably due to the greater electron-acceptor ability of the acetyl group in comparison to an aroyl group, thus resulting

Table 1. Triazoles **3a–e** and **4** Prepared

Product	Reaction Time (h)	Yield (%)	mp[a] (°C)	Molecular Formula[b]	IR (KBr)[c] ν_{max} (cm^{-1})	^{1}H-NMR ($CDCl_3$/DMSO-d_6)[d] δ, J(Hz)	MS (70 eV)[e] *m/z* (%)
3a[f]	15	73	123–124	$C_{10}H_9N_3OS$ (219.2)	3170, 1615, 1570, 910	2.63 (s, 3H, SCH_3); 7.31–7.75 (m, $3H_{arom}$); 8.23–8.44 (m, $2H_{arom}$); 12.28 (br, 1H, NH, exchangeable with D_2O)	219 (M^+, 100)
3b	12	72	160–161	$C_{11}H_{11}N_3OS$ (233.2)	3120, 1605, 1590, 900	2.41 (s, 3H, CH_3); 2.59 (s, 3H, SCH_3); 7.30 (d, $2H_{arom}$, J = 9); 8.22 (d, A_2B_2, $2H_{arom}$, J = 9); 12.50 (br, 1H, NH, exchangeable with D_2O)	233 (M^+, 34)
3c	12	75	157–158	$C_{10}H_8ClN_3OS$ (253.7)	3160, 1600, 1580, 900	2.55 (s, 3H, SCH_3); 7.50 (d, A_2B_2, $2H_{arom}$, J = 9); 8.31 (d, $2H_{arom}$, J = 9); 12.47 (br, 1H, NH, exchangeable with D_2O)	255 (38); 253 (M^+, 100)
3d	12	65	184–185	$C_{11}H_{11}N_3O_2S$ (249.2)	3120, 1609, 1584, 909	2.61 (s, 3H, SCH_3); 3.88 (s, 3H, OCH_3); 6.98 (d, $2H_{arom}$, J = 9); 8.37 (d, A_2B_2, $2H_{arom}$, J = 9 Hz); 12.35 (br, 1H, NH, exchangeable with D_2O)	249 (M^+, 40)
3e	25	75	208–209	$C_{10}H_7Cl_2N_3OS$ (288.3)	3200, 1608, 1581, 903	2.5 (s, 3H, SCH_3); 7.45 (d, 1H, J = 8, 5′-H); 7.70 (dd, 1H, J = 8, 2, 6′-H); 7.90 (d, 1H, J = 2, 2′-H); 12.59 (br, 1H, NH, exchangeable with D_2O)	287 (M^+ – 1, 14); 289 (12); 291 (2)
4	18	52	[g]	$C_5H_7N_3OS$ (157.2)	2200, 1596	2.25 (s, 3H, CH_3); 2.54 (s, 3H, SCH_3); 7.40 (s, $1H_{olef}$)	–

[a] Uncorrected, recorded on Thomas Hoover apparatus.
[b] Satisfactory microanalyses obtained: C ±0.31, H ±0.29, N ±0.27, except for **4**, see footnote g.
[c] Recorded on a Perkin Elmer 297 spectrophotometer.
[d] Recorded on a 90 MHz Varian EM 390 spectrometer.
[e] Recorded on a Jeol JMS D-300 mass spectrometer.
[f] ^{13}C-NMR ($CDCl_3$): δ = 14.67 (SCH_3); 128.38, 130.24, 133.24 (CH, arom); 133.56 (C-1′ aryl); 136.52 (C-4); 141.13 (C-5); 185.95 (CO).
[g] Unstable viscous oil that decomposes on further purification for microanalysis.

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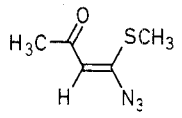
in nucleophilic addition of the azide ion at C-2 of **1f**, rather than cycloaddition to give **4** after elimination of methylthiolate. The corresponding 1-nitro-2,2-bis(methylthio)ethylene gave only a mixture of products under identical conditions.



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When the *S,N*-acetal **5a** was reacted with sodium azide, the reaction took a different direction, and the product isolated was identified as 1-phenyl-5-(*p*-toluoyl)methyltetrazole (**7a**) (72%), instead of the corresponding 5-anilinotriazole. The formation of tetrazole **7a** apparently involves cyclization of the imidoyl azide intermediate **6'** obtained by replacement of the methylthiolate group in **5a** by the azide ion (Scheme **B**).[4,5] The other substituted tetrazoles **7b–j** were similarly obtained from the respective **5b–j** in 60–79% overall yields. The α-cyanobenzylketene *S,N*-acetal **5k** derived from phenylacetonitrile similarly afforded the tetrazole **7k** in good yield. However the products (**7l** and **7m**) obtained from the corresponding cyano(ethoxycarbonyl)ketene

Table 2. Tetrazoles **7a–m** and **8** Prepared

Product	Reaction Time (h)	Yield (%)	mp[a] (°C)	Molecular Formula[b] or Lit. mp (°C)	IR (KBr)[c] ν_{max} (cm^{-1})	^{1}H-NMR ($CDCl_3$)[d] δ, J(Hz)	MS (70 eV)[e] *m/z* (%, rel.int.)
7a	15	72	85–86	$C_{16}H_{14}N_4O$ (278.3)	1678, 1599	2.36 (s, 3H, CH_3); 4.65 (s, 2H, CH_2); 7.24 (d, A_2B_2, $2H_{arom}$, $J = 9$); 7.50 (s, $5H_{arom}$); 7.84 (d, A_2B_2, $2H_{arom}$, $J = 9$)	278 (M^+, 5); 250 ($M^+ - 28$, 23)
7b	15	67	86–87	$C_{15}H_{11}ClN_4O$ (298.7)	1682, 1592	4.58 (s, 2H, CH_2); 7.18–7.63 (m, $7H_{arom}$); 7.80 (d, $2H_{arom}$, $J = 8$)	300 (3); 298 (M^+, 12); 272 (12); 270 ($M^+ - 28$, 35)
7c[g]	25	63	120	$C_{16}H_{14}N_4O$ (278.3)	1680, 1595	4.43 (s, 2H, CH_2); 5.48 (s, 2H, $C_6H_5CH_2$); 7.00–7.61 (m, $8H_{arom}$); 7.72–7.92 (m, $2H_{arom}$)	278 (M^+, 2); 250 ($M^+ - 28$, 11)
7d	33	64	104	$C_{17}H_{16}N_4O_2$ (308.3)	1665, 1590	3.90 (s, 3H, OCH_3); 4.34 (s, 2H, CH_2); 5.63 (s, 2H, $C_6H_5CH_2$); 6.97 (d, $2H_{arom}$, $J = 8$); 7.25–6.30 (m, $5H_{arom}$); 7.98 (d, $2H_{arom}$, $J = 8$)	308 (M^+, 2); 280 ($M^+ - 28$, 5)
7e	50	79	156–157	157–158[7]	1678, 1580	4.02 (s, 3H, NCH_3); 4.77 (s, 2H, CH_2); 7.40–7.70 (m, $3H_{arom}$); 7.97–8.11 (m, $2H_{arom}$)[f]	202 (M^+, 21); 174 ($M^+ - 28$, 100)
7f	48	65	80–81	$C_{11}H_{12}N_4O$ (216.2)	1675, 1590	1.49 (t, 3H, $J = 7$, CH_3); 4.28 (q, 2H, $J = 7$, CH_3CH_2); 4.88 (s, 2H, CH_2); 7.34–7.76 (m, $3H_{arom}$); 7.90–8.18 (m, $2H_{arom}$)[f]	216 (M^+, 6); 188 ($M^+ - 28$, 35)
7g	28	74	oil	$C_{12}H_{14}N_4O$ (230.3)	1682, 1595	0.90 (t, 3H, $J = 7$, CH_3); 1.94 (sext, 2H, $J = 7$, CH_3CH_2); 4.20 (t, 2H, $J = 7$, $CH_3CH_2CH_2$); 4.74 (s, 2H, CH_2); 7.30–7.65 (m, $3H_{arom}$); 7.73–8.12 (m, $2H_{arom}$)	230 (M^+, 11); 202 ($M^+ - 28$, 42)
7h	35	60	104–105	$C_{12}H_{14}N_4O$ (230.3)	1680, 1590	1.61 (d, 6H, $J = 7$, CH_3); 4.56 (sept, 1H, $J = 7$, $(CH_3)_2CH$); 4.66 (s, 2H, CH_2); 7.35–7.68 (m, $3H_{arom}$); 7.95–8.15 (m, $2H_{arom}$)	230 (M^+, 11); 202 ($M^+ - 28$, 63)
7i	71	67	89–90	$C_{15}H_{18}N_4O$ (270.2)	1673, 1590	1.05–2.23 (m, 10H, ring-CH_2); 4.15 (quint, 1H, $J = 6$, CH); 4.70 (s, 2H, CH_2); 7.38–7.73 (m, $3H_{arom}$); 7.99–8.20 (m, $2H_{arom}$)	270 (M^+, 1); 242 ($M^+ - 28$, 6)
7j	30	64	oil	$C_6H_{10}N_4O$ (154.2)	1718, 1605	1.54 (t, 3H, $J = 7$, CH_3); 2.32 (s, 3H, CH_3); 4.14 (s, 2H, CH_2); 4.21 (q, 2H, $J = 7$, CH_3CH_2)	154 (M^+, 7); 112 (100)
7k	12	76	99–100	$C_{15}H_{11}N_5$ (261.2)	2220, 1590, 1487	5.62 (s, 1H, –CHCN); 7.05–7.62 (m, $10H_{arom}$)	261 (M^+, 6); 233 ($M^+ - 28$, 6)
7l	15	77	190–191	$C_{12}H_{11}N_5O_2$ (257.2)	3165, 2197, 1647, 1570	1.22 (t, 3H, $J = 7$, CH_3); 4.20 (q, 2H, $J = 7$, CH_3CH_2); 7.64 (s, $5H_{arom}$); 12.50 (br, 1H, NH, exchangeable with D_2O)[f]	257 (M^+, 9); 156 (79); 157 (58)
7m[h]	32	73	151–152	$C_{13}H_{13}N_5O_2$ (271.3)	3160, 2195, 1645, 1580	1.31 (t, 3H, $J = 7$, CH_3); 4.32 (q, 2H, $J = 7$, CH_3CH_2); 5.76 (s, 2H, $C_6H_5CH_2$); 7.21–7.57 (m, $5H_{arom}$); 3.32 (br, 1H, NH, exchangeable with D_2O)	271 (M^+, 21); 242 (29); 170 (30)
8	35	65	220	$C_{11}H_9ClN_6S$ (292.8)	3130, 3039, 2200, 1622, 1560	2.26 (s, 3H, SCH_3); 7.38 (s, $4H_{arom}$); 10.78 (br, 1H, NH, exchangeable with D_2O); 12.88 (br, 1H, ring-NH, exchangeable with D_2O)[f]	292 (M^+, 29); 245 (49)

[a] As in Table 1.
[b] Satisfactory microanalyses obtained: C ±0.32, H ±0.28, N ±0.31.
[c–e] As in Table 1.
[f] In $CDCl_3$/DMSO-d_6.
[g] ^{13}C-NMR ($CDCl_3$): $\delta = 34.17$ (CH_2); 51.46 ($ArCH_2N$); 127.80, 128.31, 128.44, 128.83, 129.05, 134.25 (CH_{arom}); 132.62, 134.82 (C-1' arom); 149.75 (C-5); 191.97 (CO).
[h] ^{13}C-NMR ($CDCl_3$): $\delta = 14.37$ (CH_3); 51.44 ($ArCH_2N$); 61.40 (OCH_2); 117.04 (CN); 128.30, 128.43, 129.05, 129.08 (=C(CO)CN, CH_{arom}); 132.54 (C-1' arom); 148.41 (C-5); 168.70 (CO_2Et).

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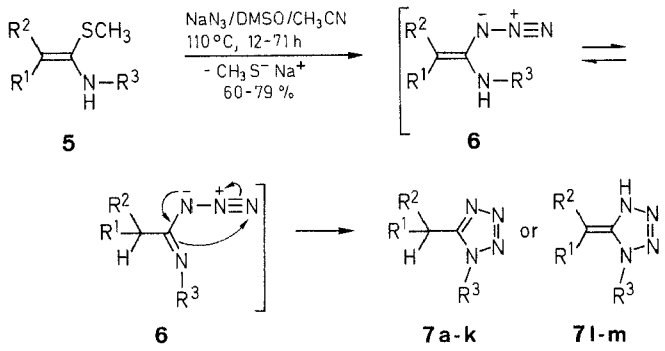
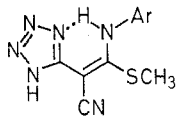


5–7	R^1	R^2	R^3
a	4-$CH_3C_6H_4CO$	H	C_6H_5
b	4-ClC_6H_4CO	H	C_6H_5
c	C_6H_5CO	H	$C_6H_5CH_2$
d	4-$CH_3OC_6H_4CO$	H	$C_6H_5CH_2$
e	C_6H_5CO	H	CH_3
f	C_6H_5CO	H	CH_3CH_2
g	C_6H_5CO	H	$CH_3CH_2CH_2$
h	C_6H_5CO	H	$(CH_3)_2CH$
i	C_6H_5CO	H	C_6H_{11}
j	CH_3CO	H	CH_3CH_2
k	C_6H_5	CN	C_6H_5
l	CO_2Et	CN	C_6H_5
m	CO_2Et	CN	$C_6H_5CH_2$
5n	CN	CN	4-ClC_6H_4

Scheme **B**

S,N-acetals **5l** and **5m** were shown to exist in the 5-[cyano(ethoxycarbonyl)-methylene]-Δ^2-tetrazoline tautomeric form, apparently due to the presence of two electron-withdrawing groups on the 5-methyl group. On the other hand, the *S,N*-acetal **5n** obtained from malononitrile gave the tetrazole **8** formed by



8 Ar = 4-ClC_6H_4

cycloaddition of the azide ion with one of the nitrile groups. The difference in behavior of **5l–5m** and **5n** can be rationalized in terms of greater delocalization of non-bonding electrons of amino nitrogen over the more polar nitrile group in **5l–5m** than over the ester group. The presence of two nitrile groups in **5n** facilitates the addition to one of the cyano groups.

Whereas, the *S,S*-acetals provide facile entry to novel substituted 5-methylthiotriazoles, the *S,N*-acetals derived from primary amines afford novel substituted tetrazoles. The alkylthiotriazoles are usually obtained in two steps by Dimorth rearrangement of 5-amino-1,2,3-thiadiazole followed by alkylation of the resulting 5-methylthiotriazoles.[6] In the literature[7] the tetrazole **7e** is synthesized by cycloaddition of sodium azide to unstable *N*-methylbenzoylketimine formed by ring opening of 2-*N*-methyl-5-phenylisoxazolium salt. The present procedure, on the other hand, utilizes easily accessible *S,N*-acetals derived from active methylene compound with wide structural variations.

The required *S,S*-acetals **1a–f**,[8] *S,N*-acetals **5a–k**,[9] **5l–m**[10] and **5n**[10] are prepared according to reported procedures.

4-Aroyl-5-methylthio-1*H*-1,2,3-triazoles (3a–e); 1-Azido-1-methylthio-1-buten-3-one (4); General Procedure:

To a stirred solution of *S,S*-acetal **1** (10 mmol) in DMSO (15 mL), a solution of NaN_3 (0.65 g, 10 mmol) in DMSO (15 mL) is added (10 min), and the mixture is heated with stirring at 110°C for 12–25 h (monitored by TLC, silica gel, solvent systems: EtOAc/hexane, 1:20) (Table 1). The mixture is then cooled to room temperature, poured into crushed ice (150 g), acidified with 20% AcOH (10 mL), and extracted with $CHCl_3$ (3 × 50 mL). The organic layer is washed with water (3 × 100 mL), dried (Na_2SO_4), and evaporated to give dark colored residues, which are column chromatographed on silica gel (Acme 60–120 mesh) using EtOAc/hexane (3:1) as eluent to give **3a–e**, crystallized from $CHCl_3$/hexane. The product **4** is obtained as a yellow viscous liquid, which decomposes on keeping for two days.

5-Substituted 1-Alkyl/aryltetrazoles 7a–m and 5-[1-Cyano-2-(4-chlorophenylamino)-2-methylthioethenyl]tetrazole (8); General Procedure:

To a stirred solution of *S,N*-acetals **5** (10 mmol) in CH_3CN (30 mL), a solution of NaN_3 (0.65 g, 10 mmol) in DMSO (15 mL) is added (10 min), and the mixture is heated at 110°C with stirring for 12–71 h (monitored by TLC; silica gel, solvent systems: EtOAc/hexane, 1:20) (Table 2). Work-up of the reaction mixture as for **3** gives crude tetrazoles, which are purified either by crystallization (**7b–e, 7k–m, 8**) from EtOH or by column chromatography (**7a, 7f–j**) on a silica gel (Acme 60–120 mesh) column using $CHCl_3$/hexane (1:3) as eluent.

R.T.C. thanks D.S.T. New Delhi for Junior Research Fellowship. Financial assistance from D.S.T. and U.G.C. New Delhi under the COSSIST program is also acknowledged.

Received: 5 October 1987; revised: 28 January 1988

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