SYNTHESIS OF 5-MERCAPTOALKYLAMINO- AND 5-ANILINOALKYLTHIOPYRAZOLYL-1,2,4-TRIAZOLES BY RING CHAIN TRANSFORMATION

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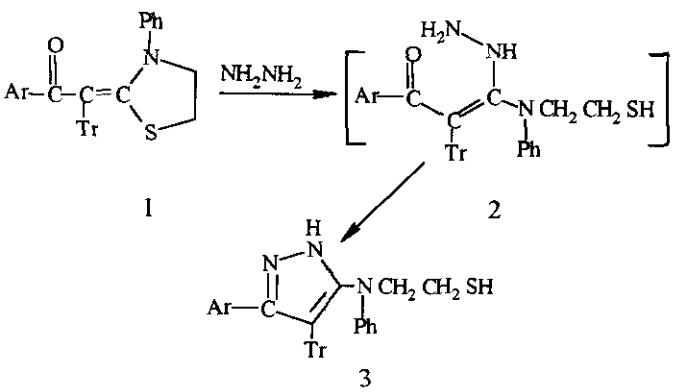
Abstract - Cyclic α-oxo-α-(1,2,4-triazol-1-yl)ketene *N*,*S*-acetals (**1a—d**) and (**4a—d**) react with hydrazine by a ring chain transformation affording title compounds (**3a—d**, **6a—d and 6′a—d**)

α-Oxoketene *N*, *S*; *S*, *S*-acetals are of great interests as synthetic intermediates in heterocyclic syntheses.[1,2] The reaction of these acetals with hydrazine and hydroxylamine can be applied to the preparation of substituted pyrazoles and isoxazoles.[3-8] In contrast to the open chain α-oxoketene *N*,*S*;*S*, *S*-acetals, the cyclic α-oxoketene *N*,*S*;*S*,*S*-acetals have not been paid attention yet. In this paper, therefore, the reaction of cyclic α-oxoketene *N*,*S*-acetals with hydrazine is first investigated. The cyclic α-oxo-α-(1,2,4-triazol-1-yl)ketene *N*,*S*-acetals (**1a—d**) and (**4a—d**) are chosen as the starting materials in connection with our systematic work of probing bioactive triazole compounds.[9] The acetals

Scheme I



1 2 3

Ar: **a**, C_6H_5; **b**, 4-ClC_6H_4; **c**, 4-$CH_3OC_6H_4$; **d**, 4-$CH_3C_6H_4$

Tr: 1,2,4-triazol-1-yl

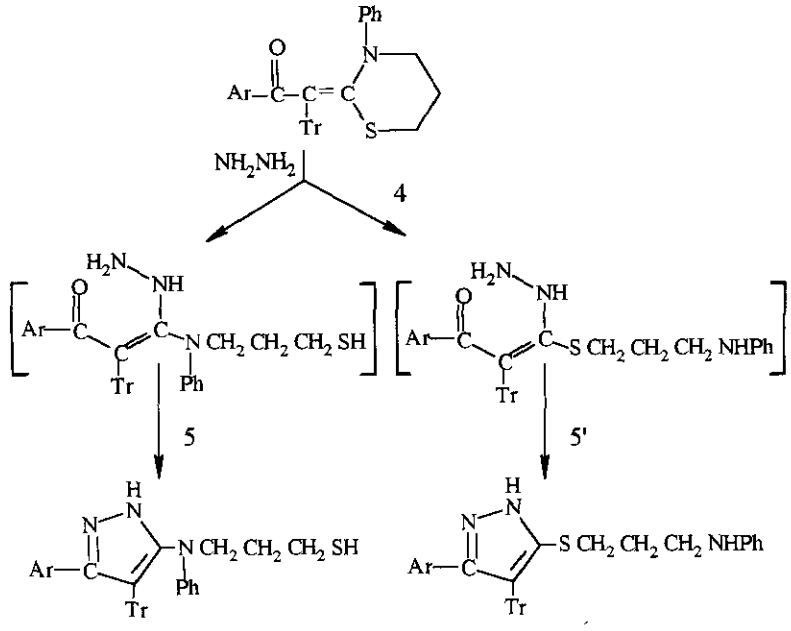
(**1a—d**) and (**4a—d**) are easily available by condensation of α-(1,2,4-triazol-1-yl) substituted acetophenone with phenyl isothiocyanate in the presence of powder potassium hydroxide and subsequent alkylation by 1,2-dibromoethane and 1,3-dibromopropane.[10,11]

When the mixture of **1** and 3—5 fold excess of 85% hydrazine hydrate in ethanol was refluxed under a nitrogen atmosphere for an hour, the final products (**3**) were obtained in moderate yields.

The formation of **3** can be explained by a initial attack of hydrazine at the ring-C atom in **1** leading to the assumed intermediate (**2**) and the final cyclization. Thus the whole reaction sequence indeed shows a process of ring chain transformation in which a pyrazole ring is formed by condensation while a thiazolidine ring of the substrate is opened to give an ω-substituted alkylheteroatomic side chain possessing two heteroatoms at its ends (Scheme I). A few of such ring transformations have been studied.[12-17]

Further, the similar reaction of acetals (**4a—d**) with hydrazine was also investigated. To our surprise, the reaction of **4** with hydrazine in refluxing ethanol gave aminopyrazolyltriazoles (**6a—d**) and thio-isomers (**6'a—d**), respectively (Scheme II).

Scheme II



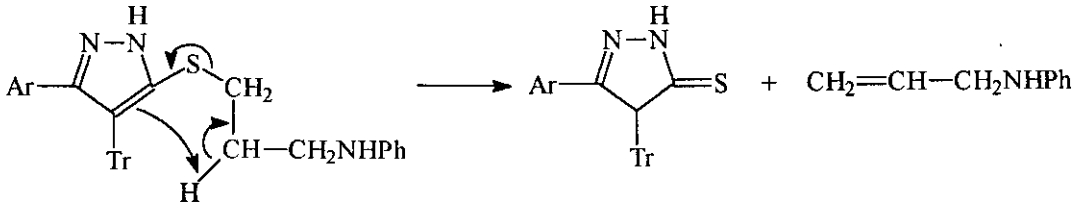
No	Ar	Yield(%) 6	6'	6 : 6'
a	C_6H_5	23	44	34 : 66
b	4-ClC_6H_4	33	47	41 : 59
c	4-$CH_3OC_6H_4$	26	38	41 : 59
d	4-$CH_3C_6H_4$	18	55	25 : 75

Tr: 1,2,4-triazol-1-yl

Obviously the C-N cleavage of **4a—d** under the attack of hydrazine affords **6'a—d**. It is worthy of note that the C-N cleavage predominated in the course of ring chain transformation as compared to only the C-S cleavage depicted in Scheme I. Such preferential C-N cleavage in the process of ring chain transfor-

mation has been reported by Patzel and Iwata.[16,17]

These products have been confirmed by elemental analyses and spectral methods, particularly by the mass spectra. In the mass spectra, the mercaptoalkylamino substituent of **3** and **6** gives the dominant fragments due to an α- and β-cleavage, whereas **6′** presents its characteristic base peak (m/z=106, $PhNHCH_2^+$) according to an α-cleavage of anilinopropylthio side chain; meanwhile, the McLafferty rearrangement typical for the anilinopropylthio substituent of **6′** is observed in the way as follows.



6′	Ar	m/z(%)	m/z=133 (%)
6′a	C_6H_5	243(32)	(13)
6′b	4-ClC_6H_4	277(14)	(9)
6′c	4-$CH_3OC_6H_4$	273(23)	(18)
6′d	4-$CH_3C_6H_4$	257(28)	(12)

In addition, the identical fragment derived from the characteristic cleavage of 3-arylpyrazole of **3**, **6** and **6′** to arylcarbonitrile ($Ar\text{-}C{\equiv}N^+$) appears in the mass spectra. Melting points, yields and spectral data of these novel compounds thus obtained are described in the experimental section.

In conclusion, the forgoing results preliminarily demonstrate cyclic α-oxo-α-(1,2,4-triazol-1-yl)ketene *N*,*S*-acetals can be successfully employed in the synthesis of heterocycles like the open chain α-oxo-α-(1,2,4-triazol-1-yl)ketene *N*,*S*-acetals[9,18] based on the concept of ring chain transformation. In this way, it is probably assumed that other types of cyclic α-oxoketene *N*,*S*-acetals would possibly be applied to the preparation of heterocycles. Besides, this approach provides a convenient method for the preparation of ω-functionalized alkylheteroatomic substituted pyrazolyl-1,2,4-triazoles which are otherwise difficult to prepare.

EXPERIMENTAL

Melting points were determined with a Yanaco MT-500 apparatus without correction. ^{1}H-Nmr spectra were taken with a Bruker Ac-P200 spectrometer using TMS as an internal reference and mass spectra on a VG-7070E spectrometer. Ir spectra were recorded on a Shimadzu-IR 435 spectrophotometer. Elemental analyses were performed by a Yanaco CHN RDER MT-3 analyzer.

Starting materials (1a—d and 3a—d) were prepared according to the literatures.[10,11]

General procedure for the preparation of 3a—d

A mixture of **1** (2 mmol) and 85% hydrazine hydrate (300 mg, 8 mmol) in ethanol (25 ml) was refluxed under nitrogen for an hour. After evaporation of some solvent and cooling, the resultant precipitates were collected by suction and purified by recrystallization.

1-[5-(*N*-Phenyl-*N*-mercaptoethyl)amino-3-phenyl-1*H*-pyrazol-4-yl]-1,2,4-triazole. (**3a**)
mp 207-209℃ (DMF/H_2O), yield 55%; ^{1}H-nmr (DMSO-d_6): δ 3.02 (m, 2H, SCH_2), 3.94 (m, 2H, NCH_2), 6.60-7.35 (m, 10H, ArH), 7.88, 8.20 (2s, 2H, Tr), 13.40 (br, 1H, NH); ms: (m/z) 362 (M^+, 8%), 360 (28), 315(92), 104(49), 103(16), 77(100). Ir: 3119 cm^{-1}(NH). Anal. Calcd for $C_{19}H_{18}N_6S$: C, 62.96; H, 5.01; N, 23.19. Found: C, 63.35; H, 5.05; N, 23.20.

1-[5-(*N*-Phenyl-*N*-mercaptoethyl)amino-3-*p*-chlorophenyl-1*H*-pyrazol-4-yl] -1,2,4-triazole (**3b**)
mp 240-242℃ (DMF/H_2O), yield 70%; ^{1}H-nmr (DMSO-d_6): δ 2.94 (m, 2H, SCH_2), 3.90 (m, 2H, NCH_2), 6.64-7.34 (m, 9H, ArH), 8.00, 8.40 (2s, 2H, Tr), 13.60 (br, 1H, NH); ms: (m/z) 396(M^+, 21%), 394(30), 363(37), 362(31), 349(82), 138(19), 137(13), 91(36), 77 (100). Ir: 3115 cm^{-1}(NH). Anal. Calcd for $C_{19}H_{17}N_6ClS$: C, 57.50; H, 4.32; N, 21.17. Found: C, 57.79; H, 3.93; N, 21.50.

1-[5-(*N*-Phenyl-*N*-mercaptoethyl)amino-3-*p*-methoxyphenyl-1*H*-pyrazol-4-yl]-1,2,4-triazole (**3c**)
mp 141-142℃ (ethanol), yield 61%; ^{1}H-nmr (DMSO-d_6): δ 2.90(m, 2H, SCH_2), 3.75 (s, 3H, OCH_3), 3.94(m, 2H, NCH_2), 6.76-6.28(m, 9H, ArH), 7.84 (s, 2H, Tr), 13.34 (br, 1H, NH); ms: (m/z) 392 (M^+, 13%), 290 (36), 359(41), 358(35), 345(100), 134 (26), 133(10), 77(78), 28(37). Ir: 3145 cm^{-1}(NH). Anal. Calcd for $C_{20}H_{20}N_6OS$: C, 61.21; H, 5.14; N, 21.41. Found: C, 60.95; H, 4.80; N, 20.97.

1-[5-(*N*-Phenyl-*N*-mercaptoethyl)amino-3-*p*-methylphenyl-1*H*-pyrazol-4-yl]-1,2,4-triazole (**3d**)
mp 215-216℃ (ethanol), yield 73%; ^{1}H-nmr (DMSO-d_6): δ 2.24(s, 3H, CH_3), 2.88(m, 2H, SCH_2), 3.90(m, 2H, NCH_2), 6.70-7.20 (m, 9H, ArH), 7.80, 7.90 (2s, 2H, Tr), 13.20 (br, 1H, NH); ms: (m/z) 376 (M^+,8%), 374(28), 343(23), 342(17), 329(63), 118(25), 117(16), 91(31), 77(74), 28(100). Ir: 3105 cm^{-1}(NH). Anal. Calcd For $C_{20}H_{20}N_6S$: C, 63.81; H, 5.35; N, 22.32. Found: C, 64.00; H, 4.94; N, 22.45.

General procedure for the preparation of 6a—d/6'a—d

A mixture of **4** (3 mmol) and 85% hydrazine hydrate (450 mg, 12 mmol) in ethanol (30 ml) was refluxed under nitrogen for 2 hrs. After evaporation of solvent and cooling, the residue was diluted with water (20 ml) and extracted with ethyl acetate (3×12 ml). The organic layer was dried with sodium sulfate and evaportued to give a mixture of **6a—d** and **6'a—d**, which were seperated by column chromatography on silica gel with petroleum/ethyl actate (1:1) as eluents.

1-[5-(*N*-Phenyl-*N*-mercaptopropyl)amino-3-phenyl-1*H*-pyrazol-4-yl]-1,2,4-triazole (**6a**)
mp 152-154℃, yield 23%; ^{1}H-nmr ($CDCl_3$): δ 2.09 (m, 2H, $NCH_2\underline{CH_2}CH_2SH$), 2.79(t, 2H, J=

7.0 Hz, SCH_2), 3.81 (t, 2H, J=7.3 Hz, NCH_2), 6.86-7.26(m, 10H, ArH), 8.50(br, 1H, NH); ms: (m/z) 376 (M^+, 37%), 374(59), 342(18), 315(90), 301(10), 104(41), 103(19), 77 (100), 47(10). Ir: 3084 cm^{-1}(NH). Anal. Calcd for $C_{20}H_{20}N_6S$: C, 63.81; H, 5.35; N, 22.32. Found: C, 63.70; H, 5.23; H, 22.58.

1-[5-(3-Anilinopropylthio)-3-phenyl-1*H*-pyrazol-4-yl]-1,2,4-triazole (**6'a**)
mp 137-138℃, yield 44%; ^{1}H-nmr($CDCl_3$): δ 1.94 (m, 2H, $SCH_2\underline{CH_2}CH_2N$), 2.93(t, 2H, J=6.8 Hz, SCH_2), 3.27 (t, 2H, J=6.3 Hz, NCH_2), 6.79-7.35 (m, 10H, ArH), 8.15, 8.18 (2s, 2H, Tr); ms: (m/z) 376(M^+, 18%), 243(32), 242(11), 133(13), 132(22), 106(100), 104(15), 103 (6). Ir: 3127, 3115 cm^{-1}(PhNH, NH). Anal. Calcd for $C_{20}H_{20}N_6S$: C, 63.81; H, 5.35; N, 22.32. Found: C, 63.86; H, 5.16; N, 22.07.

1-[5-(*N*-Phenyl-*N*-mercaptopropyl)amino-3-*p*-chlorophenyl-1*H*-pyrazol-4-yl]-1,2,4-triazole (**6b**)
mp 145.5-147.5℃, yield 33%; ^{1}H-nmr($CDCl_3$): δ 2.08 (m,2H, $NCH_2\underline{CH_2}CH_2SH$), 2.79(t, 2H, J=7.0 Hz, SCH_2), 3.82(t, 2H, J=6.8 Hz, NCH_2), 6.88-7.26(m, 9H, ArH), 7.70, 7.79(2s, 2H, Tr); ms: (m/z) 410(M^+, 40%), 408(34) 377(12), 376(37), 349(53), 138(18), 137(21), 106(31), 104(35), 77(100), 47(18). Ir: 3105 cm^{-1}(NH). Anal. Calcd for $C_{20}H_{19}N_6ClS$: C, 58.45; H, 4.66; N, 20.45. Found: C, 58.21; H, 4.62; N, 20.19.

1-[5-(3-Anilinopropylthio)-3-*p*-chlorophenyl-1*H*-pyrazol-4-yl]-1,2,4-triazole (**6'b**)
mp 165-166℃, yield 47%; ^{1}H-nmr ($CDCl_3$); δ 1.85 (m, 2H, $SCH_2\underline{CH_2}CH_2N$), 2.86(t, 2H, J=7.0 Hz, SCH_2), 3.17(t, 2H, J=6.3 Hz, NCH_2), 8.60-7.29(m, 9H, ArH), 8.18, 8.19 (2s, 2H, Tr); ms: (m/z) 410(M^+,10%), 277(14), 138(4), 137(4), 133(9), 132(18), 106(100), 77 (21). Ir: 3163, 3110 cm^{-1}(PhNH, NH). Anal. Calcd for $C_{20}H_{19}N_6ClS$: C, 58.45; H, 4.66; N, 20.45. Found: C, 58.62; H, 4.75; N, 20.63.

1-[5-(*N*-Phenyl-*N*-mercaptopropyl)amino-3-*p*-methoxyphenyl-1*H*-pyrazol-4-yl]-1,2,4-triazle (**6c**).
mp 117-118℃, yield 26%; ^{1}H-nmr($CDCl_3$): δ 2.05(m, 2H, $NCH_2\underline{CH_2}CH_2SH$), 2.25(t, 2H, J=7.1 Hz, SCH_2), 2.78(t, 2H, J=6.8 Hz, NCH_2), 3.74(s, 3H, CH_3O), 6.72-7.17(m, 9H, ArH), 7.75, 7,83(2s, 2H, Tr); ms: (m/z) 406(M^+, 12%), 345(72), 373(12), 372(11), 345(63), 134 (11), 133(13), 107(9), 77(100), 47(24). Ir: 3112 cm^{-1}(NH). Anal. Calcd for $C_{21}H_{22}N_5OS$: C, 62.05; H, 5.46; N, 20.67. Found: C, 61.88; H, 5.29; N, 20.33.

1-[5-(3-Anilinopropylthio)-3-*p*-methoxyphenyl-1*H*-pyrazol-4-yl]-1,2,4-trizaole (**6'c**)
mp 138-140℃, yield 38%; ^{1}H-nmr ($CDCl_3$): δ 1.91(m, 2H, $SCH_2\underline{CH_2}CH_2N$), 2.93(t, 2H, J=6.9 Hz, SCH_2), 3.23 (t, 2H, J=6.3 Hz, NCH_2), 3.74 (s, 3H, OCH_3), 6.68-6.86 (m, 4H, ArH), 7.15-7.27(m, 5H, ArH), 8.15, 8.18 (2s, 2H, Tr); ms: (m/z) 406(M^+, 13%), 273(23), 272 (21), 134(13), 133(18), 132(25), 107(10), 106(100), 77(31). Ir 3145, 3119 cm^{-1}(PhNH, NH). Anal. Calcd for $C_{21}H_{22}N_6OS$: C, 62.05; H, 5.46; N, 20.67. Found: C, 61.88; H, 5.29; N, 20.33.

1-[5-(*N*-Phenyl-*N*-mercaptopropyl)amino-3-*p*-methylphenyl-1*H*-pyrazol-4-yl]-1,2,4-triazole (**6d**)
mp 128-130℃, yield 18%; ^{1}H-nmr($CDCl_3$): δ 1.90 (m, 2H, $NCH_2\underline{CH_2}CH_2SH$), 2.28 (s, 3H, CH_3), 2.54 (t, 2H, J=6.8 Hz, SCH_2), 3.73 (t, 2H, J=7.1 Hz, NCH_2), 6.83-7.25 (m, 9H, ArH), 7.69, 7.82 (2s, 2H, Tr), 9.00 (br, 2H, NH); ms: (m/z) 390 (M^+, 45%), 329 (100), 144 (12), 118 (39), 117 (18), 104 (20), 91 (54), 77 (65), 47 (42), 41 (42). Ir: 3087 cm^{-1} (NH). Anal. Calcd for $C_{21}H_{22}N_6S$: C, 64.59; H, 5.68; N, 21.52. Found: C, 64.31; H, 5.45; N, 21.34.

1-[5-(3-Anilinopropylthio)-3-*p*-methylphenyl-1*H*-pyrazol-4-yl]-1,2,4-triazole (**6'd**)
mp 101-103℃, yield 55%; ^{1}H-nmr($CDCl_3$): δ 1.88 (m, 2H, $SCH_2\underline{CH_2}CH_2N$), 2.31 (s, 3H, CH_3), 2.90 (t, 2H, J=6.4 Hz, SCH_2), 3.19 (t, 2H, J=6.2 Hz, NCH_2), 6.66-7.25 (m, 9H, ArH), 8.13, 8.18 (2s, 2H, Tr); ms: (m/z) 390 (M^+, 12%), 329 (15), 257 (28), 133 (12), 132 (23), 118 (13), 117 (9), 106 (100), 91 (13), 77 (30). Ir: 3147, 3105 cm^{-1} (PhNH, NH). Anal. Calcd for $C_{21}H_{22}N_6S$: C, 64.59; H, 5.68; N, 21.52. Found: C, 64.20; H, 5.29; N, 21.34.

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