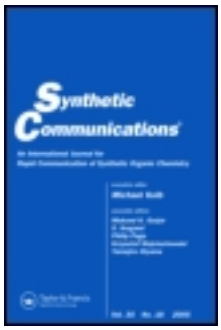

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Synthesis of Some Novel α-Cyanoketene-*N,S*-acetals Derived From Secondary Aliphatic Amines and Their Use in Pyrazole Synthesis

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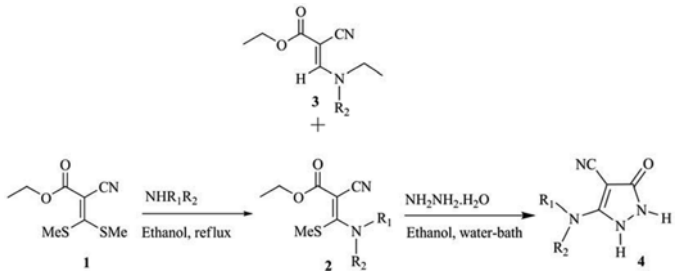
Abstract

New α-cyanoketene-*N,S*-acetals**2**(**a-g**) and β-dialkylamine-α-cyanoacrylates **3**(**g-i**) were synthesized in good to excellent yields by the reaction of ethyl 2-cyano-3,3-bis(methylthio)acrylate **1** with secondary aliphatic amines, i.e. *N*-methylalkyl- and *N*-ethylalkylamines, and pyrrolidine, in the presence of triethylamine, under reflux in ethanol, for 1–16 h, depending on the amine used. Five *N*-methylalkyl amines and pyrrolidine yielded exclusively mono-substituted *N*,*S*-acetals**2**(**a-f**) in high yields. On the other hand, *N*-ethylbenzylamine gave a mixture of mono-substituted products including *N*,*S*-acetal**2g** in 35% yield and the unexpected product ethyl 3-[benzyl(ethyl)amino]-2-cyanoacrylate **3g** in50% yield. *N*-ethylcyclohexylamine and *N*-ethylbutylamine did not produce *N*,*S*-acetals and gave only the unexpected products ethyl 2-cyano-3-[cyclohexyl(ethyl)amino]acrylate **3h** and ethyl 3-[butyl(ethyl)amino]-2-cyanoacrylate **3i** in good yields. The α-cyanoketene-*N*,*S*-acetals**2**(**a-f**), **2j**, and **2k** underwent cyclization with the binucleophile hydrazine in ethanol under reflux to afford substituted pyrazoles**4**(**a-f**), **4j**, and **4k** in high yields.

[Supplementary materials are available for this article. Go to the publisher's online edition of *Synthetic Communications*® for the following free supplemental resource(s): Full experimental and spectral details.]



KEYWORDS: α-Cyanoketene-*N,S*-acetals; secondary aliphatic amines; pyrazole derivatives.

INTRODUCTION

The synthesis of α-cyanoketene-*N*,*S*-acetals has been a subject of great interest because of their wide applications. For example, they are important and versatile reagents in organic synthesis, and have been used in particularfor the synthesis of polyfunctionalizedheterocycles.[1–9] The synthesis of α-cyanoketene-*N*,*S*-acetals has been reported by other research groups from α-cyanoketene-*S*,*S*-acetals through addition–elimination reactions with strong nucleophiles such as alkylamines or weaker nucleophiles such as arylamines, under gentle or powerful conditions, in various solvents.[10–15] However, the α-cyanoketene-*S*,*S*-acetals have received much more attention regarding their reaction with primary amines than regarding their reaction with secondary amines. In this paper we report the synthesis of new α-cyanoketene-*N*,*S*-acetals **2**(**a-g**) and an unexpected β-dialkylamine-α-cyanoacrylates **3**(**g-i**) derived from secondary

aliphatic amines of *N*-methylalkyl- and *N*-ethylalkylamines, and pyrrolidinefrom ethyl 2-cyano-3,3-bis(methylthio)acrylate **1** asa starting material (Scheme 1, Table 1). Furthermore, forseveral years, pyrazoles and their derivatives began to attract wide attention as one of the most active classes of compounds possessing a broad spectrum of biological activities and pharmacological properties including antibacterial[10], antifungal[11], and insecticidal activity[12]. As a result, many research groups have reported the synthesis of pyrazole derivatives from α-cyanoketene-*N*,*S*-acetals[16–19]. In our work, we used the α-cyanoketene-*N*,*S*-acetals**2**(**a-f**), **2j**, and **2k** to synthesize a new series of pyrazole derivatives **4**(**a-f**), **4j**, and **4k** by displacing both the methylthio and ethoxy groups in the α-cyanoketene-*N*,*S*-acetals with the hydrazine binucleophile (Scheme 2, Table 2). The structures of the obtained compounds were established on the basis of elemental analysis, FT-IR spectra, ^{1}H-NMR spectra, ^{13}C-NMR spectra, mass spectra, and X-ray crystallography.

RESULTS AND DISCUSSION

The method for preparing the α-cyanoketene-*N*,*S*-acetals**2**(**a-g**) and the β-dialkylamine-α-cyanoacrylates **3**(**g-i**) is presented in Scheme 1. The starting material ethyl-2-cyano-3,3-bis(methylthio)acrylate **1** was obtained easily in high yield, as reported in the literature.[23] It was prepared in onepot from the reaction ofethyl 2-cyanoacetate with carbon disulfide in the presence of potassium carbonate followed by alkylation with methyl iodide. Compound **1** (1.08 g, 5 mmol) was reacted with nine secondary aliphatic amines (5 mmol) in the presence of TEA in ethanol (20 mL) under reflux for a few hours, depending on the amine used. The solvent was evaporated in a vacuum to afford an oily

viscous crude product that was purified by performing column chromatography with an ethyl acetate and hexane (1:1) eluent. Five *N*-methylalkyl amines (entries 1–5) and pyrrolidine (entry 6) gave exclusively mono-substituted *N*,*S*-acetal products **2**(**a-f**) in high yields (78%–98%). The yields of these products are influenced by the alkyls in the *N*-methylalkyl amines. Compared to alkyls with secondary α-carbons, the alkyls with primary α-carbons (entries 1–4) have less steric crowding, making the *N*-methylalkyl amines react much faster with compound **1** (entry 5). This is clearly demonstrated by the fact that the *N*-methylalkyl amines in entries 1–4 gave higher yields of 86%–98% than did the amine in entry 5 (78%). However, pyrrolidine (entry 6), which has a dimethylene ring residue on two α-carbons, produced an excellent yield of 98% because it has less steric crowding around its nitrogen facing toward compound **1**. The formation of *N*,*S*-acetals**2**(**a-f**)begins with a nucleophilic attack by the –NH of the amines on the ethylenic double bond of compound **1** and concluded with the elimination of methanethiol. A similar reaction of compound **1** with the *N*-ethylalkylamine counterpart of *N*-ethylbenzylamine (entry 7) gave a mixture of *N*,*S*-acetal(2*Z*)-ethyl3-[benzyl(ethyl)amino]-2-cyano-3-(methylthio)acrylate **2g**, which was obtained in a relatively low yield (35%) because some of it was converted to the unexpected (2*E*)-ethyl 3-[benzyl(ethyl)amino]-2-cyanoacrylate product **3g** (50%). In contrast, the *N*-methylbenzylamine (entry 4), which is less crowded than the *N*-ethylbenzylamine (entry 7) gave the *N*,*S*-acetal of (2*Z*)-ethyl3-[benzyl(methyl)amino]-2-cyano-3-(methylthio)acrylate **2d** as the only product,with no unexpected products. The low yield of the *N*,*S*-acetal**2g** is due to the stronger steric push from the *N*-ethy in *N*-ethylbenzylamine than from the *N*-methyl in *N*-methylbenzylamine on the big sulfur of

the C–S bond. This steric push results in the expulsion of the methylthio group as a cation (CH_3S^+), where the incipient carbon ion abstracts a proton from ethanol to form compound **3g** in 50% yield. For *N*-ethylcyclohexylamine (entry 8) and *N*-ethylbutylamine (entry 9), the initially formed *N*,*S*-acetals are converted completely to (2*E*)-ethyl-2-cyano-3-[cyclohexyl(ethyl)amino]acrylate **3h** and (2*E*)-ethyl-3-[butyl(ethyl)amino]-2-cyanoacrylate **3i** in good yields of 77% and 69%, as shown in Table 1.

The structures of the α-cyanoketene-*N*,*S*-acetals**2**(**a-g**)andtheβ-dialkylamine-α-cyanoacrylates **3**(**g-i**) were established on the basis of their elemental analyses and spectral data. The experimental C, H, and N elemental analysis results were in good agreement with the theoretical values based on the suggested formulas. The characteristic absorption band in the IR spectra of α-cyanoketene-*N*,*S*-acetals**2**(**a-g**) is at ν = 1027–1099 cm^{-1} for C–N stretching vibrations. This means that the amine is attached to the carbon replaced with a methylthio group (SMe) of ketene-*S*,*S*-acetal**1** to form *N*,*S*-acetal**2**(**a-g**). Bands appeared at ν =911–938 cm^{-1} and851–898 cm^{-1} for the asymmetrical and symmetrical stretching vibrations of the =C–S group, respectively. These bands disappeared in compounds **3**(**g-i**), which means that they did not form the expected *N*,*S*-acetals. The absorption bands appearing in the range ν = 1664–1747 cm^{-1} for the C=O group of compounds **2(a-g)** and **3(a-g)** and in the range ν = 1514–1607 cm^{-1} for the C=C group are significantly shifted from the typical C=O and C=C absorption bands of esters (1750 cm^{-1}) and alkenes(1600-1660 cm^{-1}). These bands are shifted to lower frequencies because of the conjugation of the C=O bond with a C=C bond in the α,β-unsaturated esters. The ^{1}H NMR spectra showed quarter signals at δ 3.93–4.37 ppm corresponding to

the CH_2–O group for all the synthesized compounds. The singlet resonances appearing at δ 2.84–3.09 ppm are due to the methyl proton attached to the nitrogen (CH_3–N) in compounds **2**(**a-e**). The triplet signals appearing at δ 3.46–3.69 ppm represent CH_2–N groups in compounds **2b**, **c**,and **f**, whereas the corresponding CH_2–N group appeared as quarter signals at δ 3.40–3.69 ppm for the compounds **2a**, **2g**, and **3**(**g-i**). Triplet signals occur at δ 4.35 and δ 4.34 ppm for the CH–N groups of compounds **2e** and **3h**. The downfield shifts of these protons are due to the electron-withdrawing effect of the nitrogen, which reduces the electron density of the proton attached to the carbon and thus deshields the proton. Signals appeared in the region of δ 6.05–7.34 ppm represent aromatic protons of compounds **2d**, **2g**, and **3g**. Single signals occur at δ 2.40–2.67 ppm for the methylthio groups (MeS) of compounds **2**(**a-g**), and these signals disappeared for compounds **3**(**g-i**). Triplet and multiplet signals appearing between δ 0.66-1.33 and 1.08-1.89 ppm represent CH_2 and CH_3 groups. The ^{13}C spectra of all synthesized compounds showed the expected carbon signals for all types and numbers of carbons in the various groups. The signals appearing downfield in the region of δ 174.3–179.2ppm are due to the carbon attached to the sulfide atom (S–C–N) in compounds **2**(**a-g**), and this signal disappears for compounds **3**(**g-i**), which means that they did not form *N*,*S*-acetals. The most characteristicsignals were atδ 156.2, 153.9, and 153.7 ppm for compounds **3g**, **3h**,and **3i**, respectively, corresponding to the carbon attached to nitrogen (=CH–N). The signals appearing in the regions of δ 165.9–163.1 ppm and δ 118.4–120.3ppm are assignable to the carbons in the carbonyl (C=O) and cyano(C≡N) groups, respectively. The aromatic carbons for compounds **2d**, **2g**, and **3g** occur at δ 126.6–135.3ppm. The signals observed in the regions of δ67.6–71.8ppm, δ 59.2–61.8 ppm, and δ 43.0–59.0

ppm are due to the carbons attached to the cyano group (C–CN), oxygen (CH_2–O), and nitrogen (CH_2–N), respectively. The signals occurring at higher fields of δ 64.4 and δ 67.8 ppm are due to the carbon attached to nitrogen (CH–N) in compounds **2e** and **3h**. The chemical shifts of the carbons in CH_2 and CH_3 are observed in the ranges of δ 19.5–32.8ppm and δ 13.3–15.1 ppm, respectively. The structures of the isolated products were supported by their electrospray ionization mass spectrometry (ESIMS) and direct infusion mass spectrometry (DIMS) results, which showed molecular ions corresponding to the molecular formula. For example, the DIMS of compound **2e** showed a molecular ion at *m/z* = 282.40, which corresponds to the molecular formula $C_{14}H_{22}N_2O_2S$ (282.41). The stereochemistry of **3h** was established by performing a NOESY experiment (Scheme 2). The NOESY spectrum suggested a weak cross-peak between the hydrogen of the methyl Ha fragment and the vinylic hydrogen Hc, which indicated that Ha and Hc are located on the same side of the molecule, as in the *E* geometric isomer. Similar results were observed for **3g** and **3i**.

The structure of(2*Z*)-ethyl 2-cyano-3-(methylthio)-3-(pyrrolidin-1-yl)acrylate**2f** was further identified by performing X-ray diffraction analysis.[21] The crystal data and structure refinement results for compound **2f** are given in Table 2. The *ORTEP* plot of compound **2f** and the numbering scheme are presented in Figure 1. The compound adopted a *Z* configuration with respect to the C=C bond. Compound **2f**crystallized in an orthorhombic system with space group *P*21212. Selected bond distances, bond angles, and torsion angles are given in Table 3. The bond lengths and angles in the pyrrolidine ring of compound **2f** are within in the normal range Allen et al. 1987.[22] The C2–N3

bond length is 1.316(3) Å, which is shorter than normal for C–N bonds (1.47 Å). As a result, the C2=C8 bond length of 1.421(3) Å becomes longer than the normal value of 1.34 Å and closer to that of a C–C single bond (1.54 Å). This is due to the strength of the π-delocalization between the carbon atom C2 and the nitrogen atom N3.

The mean planes for compound **2f** were observed in the pyrrolidine ring N3/C4/C5/C6/C7, N10/C2/C8/C9/C11 fragment, and O12/O15/C8/C11/C13 fragment; the maximum deviation was 0.238(2)º at the C14 atom. The dihedral angle between the pyrrolidine ring and the N10/C2/C8/C9/C11 fragment is 57.58(11)°, and the pyrrolidine ring makes a dihedral angle of 62.36 (11)º with theO12/O15/C8/C11/C13 fragment. The methylthio group is twisted out of the mean planes, as can be seen in the value of the C16–S1–C2–N3 torsion angle, 153.02(14)º(see Electronic Supplementary Information[21]).

Our work was also extended to the synthesis of a series of pyrazole derivatives that contain *N*-methylalkyls, pyrrolidine, piperidine, and morpholine substituents, i.e., compounds **4**(**a-f**), **4j**, and **4k**. These pyrazoles were conveniently prepared by reacting the *N*,*S*-acetals**2**(**a-f**) synthesized here and *N*,*S*-acetals**2j** and **2k** (first prepared in 1965 by Yoshikata*et al*.[23]) with excess amounts of hydrazine (mole ratio 1:5) in ethanol under reflux, as shown in Scheme 3. These pyrazoles were obtained in good yields of 75–97% after solvent evaporation, washing with ethanol, and drying followed by recrystallization from methanol, as shown in Table 4.

The proposed mechanism for the formation of pyrazoles**4**(**a-f**), **4j**, and **4k** is assumed to proceed via a nucleophilic attack of the NH_2 of hydrazine on the ethylenic bond in acyclic α-cyanoketene-*N*,*S*-acetals **2**(**a-f**), **2j**, and **2k** to form an intermediate adduct A. This reaction is followed by elimination of methanethiol to give a neutral intermediate B. Then, subsequent intramolecularcyclizations occur to give an intermediate adduct C, followed by expulsion of ethanol to afford products **4**(**a-f**), **4j**, and **4k**, as shown in Scheme 4.

The structures of pyrazoles**4**(**a-f**), **4j**, and **4k** were proven by performing elemental analysis and obtaining spectral data. The elemental analysis and mass spectra for each compound correspond to the molecular formula. The most important bands in the IR spectra of the synthesized compounds **4**(**a-f**), **4j**, and **4k** appeared at υ= 3031–3275 cm^{-1}, from the stretching vibrations of NH groups. These bands are broad because of Fermi resonance overtones (overlapping with other fundamental vibrations of the NH bending band at 1550 cm^{-1}) and strong hydrogen bonding. In addition, the IR spectrum showed broad absorptions at υ = 1601–1674 cm^{-1} and at υ = 1504–1614 cm^{-1} arising from the stretching vibrations of C=O and C=C, respectively, and these bands overlap with the N–H bending bands. These bands appeared at lowfrequencies because of the formation of hydrogen bonds in the molecule. The ^1H NMR spectra of **4**(**a-f**), **4j**, and **4k** showed the disappearance of the methylthio group (MeS) and ethoxy group (OCH_2CH_3); this means that the methylthio group in the *N*,*S*-acetals was displaced with hydrazine hydrate and cyclization bonds to form pyrazoles, after which the ethoxy group was eliminated. For most of the pyrazoles, we were not able to reveal any clear signal of the NH group

because of the strength and symmetry of the intramolecular hydrogen bond, which resulted in a weak dipole and exchange with the solvent in the range at 3.76-4.31 ppm. In the case of pyrazoles**4c**, **4f**, and **4j**, the strongly deshielded signals of the amine proton appeared at δ 10.29, 10.07, and 10.97 ppm due to the intramolecular hydrogen bonding between NH and C=O. The ^{13}C NMR spectra showed characteristic peaks of the carbon attached to the nitrogen (C–NH) at δ 165.2–168.0 ppm and of the carbon of the carbonyl group (C=O) in the pyrazole rings at δ 155.9–157.4 ppm. Signals due to the carbon in the cyano groups (CN) also appeared at δ 116.9–117.9 ppm. The signals in the region of 60.8–62.2 ppm are due to the carbons attached to the cyano groups (C–CN).

The structure of 5-[butyl(methyl)amino]-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carbonitrile **4b** was further confirmed by performing X-ray diffraction analysis. Suitable crystals were grown during slow evaporation of a methanol solution of the compound. The molecular structure and numbering schemeforcompound **4b** are presented in Figure 2. The crystal data and structure refinement results for compound **2f** are given in Table 5 Compound **4b** crystallized in an orthorhombic crystal system with space group *P*212121.[24] Selected bond distances, bond angles, and torsion angles are given in Table 6. The bond lengths and angles in the *N*-ethylmethyl amino group in **4b** are in the normal ranges Allen et al. 1987[22]. In **4b**, the C5=C6 bond length is 1.406(2) Å, which is longer than the average (1.34 Å) and indicates single C–C bond character (1.45 Å).In addition, the C5–N9 [1.3330(19)Å], C5–N4 [1.3586(18) Å], and C2–N3 [1.3707(18)Å] bond lengths are shorter than normal (1.47 Å). These bond lengths confirm the partial double bond character arising from electron-donating effects of the amino groups. The mean plane of

the pyrazole**4b** O1/N9/N3/N8/C10/C5/C6/C2/C7 fragment is planar with a maximum deviation of -0.052(1)º for the C5 atom. The mean plane forms a dihedral angle of 88.25(17)º with the N1/C10/C11/C12/C14 fragment corresponding to the ethyl amino group (see Electronic Supplementary Information[24]).

EXPERIMENTAL

Melting points were determined using a hot stage Gallenkamp melting point apparatus. Infrared spectra were recorded onFT-IR 8300 Shimadzu spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on FT-NMR 400 MHz Joel, ECP, JNM-ECX 500 MHz, Joel and FT-NMR 600 MHz Bruker, AVANCE III spectrometer operating at 400 MHz, 500 MHz and 600 MHz for ^{1}H-NMR and 100, 125 and 150 MHz for^{13}C-NMR in $CDCl_3$, CD_3OD and DMSO-$d_6$as solvents and using TMS as internal standard; chemical shifts are reported in δ(ppm). ESIMS spectra were recorded on Dionex, Bruker, and MicroTof Q apparatus. DIMS spectra were recorded on QP5050A Shimadzu apparatus. Elemental analyses of all new compounds were performed on Thermo Finnigan EA1112. X-ray diffraction (XR-D) data were collected at room temperature with Bruker APEXII CCD a spectrometer. TLC analysis was carried out on silica gel of Merck No. 5545 to monitor completion of reactions, in which ethyl acetate-hexane (1:1) was used as eluent. Column chromatography was performed using silica gel of Merck No. 9385.

Synthesis Of Starting Material (1)

Ethyl-2-cyano-3,3-bis(methylthio)acrylate **1** was prepared in onepot from the reaction ofethyl 2-cyanoacetate with carbon disulfide in the presence of potassium carbonate followed by alkylation with methyl iodide, according to literature[20].

General Method For Synthesis Of A-Cyanoketene-*N,S*-Acetals 2(A-G) And Compounds 3(G-I)

A mixtureof ethyl 2-cyano-3,3-bis(methylthio)acrylate **1** (1.09 g, 5 mmol), secondary aliphatic amine (5 mmol), and 3 drops of triethylamine was dissolvedin ethanol (20 mL). The reaction mixture was reflux for several hours based on the amine used. The solvent was concentrated in vacuum to afford an oily viscous crude product which was purified by column chromatography using SiO_2 (Merck 9385). Elution with ethyl acetate and hexane (1:1) furnished compounds **2**(**a-g**)and **3**(**g-i**).

Supporting Information: Full experimental detail, IR, ^{1}H and ^{13}C NMR spectra, analytical data, HPLC traces, DIMS, ESIMS and X-ray data of new compounds. This material can be found via the “Supplementary Content” section of this article’s webpage.

Selected Data

(2*Z*)-Ethyl 3-[Ethyl(Methyl)Amino]-2-Cyano-3- (Methylthio)Acrylate (2a)

Yellow viscous liquid; IR (neat, cm^{-1}) *v*:2195 (CN), 1681 (C=O), 1532 (C=C), 1062, 1031 (C–N), 938, 861 (=C–S); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.06 (t, 3H, $NCH_2C\underline{H}_3$, J = 6.9 Hz), 1.08 (t, 3H, $OCH_2C\underline{H}_3$, J = 7.2 Hz), 2.43 (s, 3H, SCH_3), 2.95 (s, 3H, NCH_3), 3.54 (q, 2H, $NC\underline{H}_2CH_3$, J = 6.9 Hz), 3.94 (q, 2H, $OC\underline{H}_2CH_3$, J = 7.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 13.3 ($NCH_2\underline{C}H_3$), 14.4 ($OCH_2\underline{C}H_3$), 18.1 (SCH_3), 42.9 (NCH_3), 51.1

(NCH_2), 59.4 (OCH_2), 70.1 (C–CN), 119.8 (CN), 163.1 (C=O), 177.3 (S–C–N); ESIMS found $[M+H]^+$: 229.1063 (calc. for $C_{10}H_{16}N_2O_2S$, M^+ requires 228.3152); Anal. Calcd. for $C_{10}H_{16}N_2O_2S$: C 52.61, H 7.06, N 12.27%; Found: C 53.01, H 7.08, N 12.12%.

Synthesis Of (2*Z*)-Ethyl 2-Cyano-3-(Methylthio)-3-Morpholinoacrylate 2j And (2*Z*)-Ethyl 2-Cyano-3-(Methylthio)-3-(Piperidin-1-Yl)Acrylate 2k

These compounds **2j** and **2k**prepared according to Yoshikata et al.'s procedure[23] from the reaction of compound **1** withmorpholine and pipyridine under reflux in ethanol.

General Method For The Synthesis Of Pyrazoles 4(A-F), 4j And 4k

A suspension of α-cyanoketene-*N,S*-acetals **2**(**a-f**), **2j** and **2k** (4 mmol) in hydrazine hydrate (1g, 20 mmol) was refluxed on water-bath for 2 hours. Then ethanol (20 mL) was added and the reaction mixture was refluxed further for 2 hours. The solvent was evaporated and the product was collected, washed with ethanol, dried and recrystallize from methanol to give pure products of **4**(**a-f**), **4j** and **4k**.

Supporting Information: Full experimental detail, IR, ^1H and ^{13}C NMR spectra, analytical data, HPLC traces, DIMS, ESIMS and X-ray data of new all pyrazoles. This material can be found via the "Supplementary Content" section of this article's webpage

Spectral Data

5-[Ethyl(Methyl)Amino]-3-Oxo-2,3-Dihydro-1*H*-Pyrazole-4-Carbonitrile (4a).

Colorless peal crystal; FT-IR (KBr, cm^{-1}) *v*: 3150, 3068 (NH), 2210 (CN), 1607 (C=O), 1516 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.08 (t, 3H, $NCH_2C\underline{H}_3$, J = 7.0 Hz), 2.92 (s, 3H, NCH_3), 3.39 (q, 2H, NCH_2, J = 7.0 Hz), 3.85 (br s, 2H, 2NH,DMSO exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.6 ($NCH_2\underline{C}H_3$), 36.3 (NCH_3), 39.1 (NCH_2), 61.2 (<u>C</u>–CN), 117.2 (CN), 157.0 (C=O), 167.7 (C–NH); DIMS found *m/z*: 166.10 (calc. for $C_7H_{10}N_4O$ M^+ requires 166.18); Anal. Calcd. for $C_7H_{10}N_4O$: C 50.59, H 6.07, N 33.71%; Found: C 50.58, H 6.09, N 34.11%.

4. CONCLUSIONS

In summary, we have successfully demonstrated the synthesis of new α-cyanoketene-*N*,*S*-acetals derived only from secondary aliphatic amines. We further carried out their reactions with hydrazine to produce pyrazoles that have never been reported before. This method is highly appealing because of its simple procedure and mild conditions and because the reactions gave high yields and utilize readily available various secondary aliphatic amines as starting materials. A new feature arises in the preparation of the α-cyanoketene-*N*,*S*-acetals, where noncyclic *N*-ethylalkylamines yield products of types which are not obtained using noncyclic *N*-methylalkylamines. Finally, these α-cyanoketene-*N*,*S*-acetals can be used as intermediates for the synthesis of many other heterocyclic compounds.

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Table 1. Preparation of α-cyanoketene-*N,S*-acetals**2**(**a-g**)and compounds **3**(**g-i**).

Entry	NHR_1R_2	Time (h)	α-Cyanoketene-*N,S*-acetals 2a-g	β-dialkylamine-α-cyanoacrylates 3g-i	Yield %
1	R_1 = Me, R_2 = Et	1h	**2a**: R_1 = Me, R_2 = Et	-	92
2	R_1 = Me, R_2 = n-Bu	6h	**2b**:R_1 = Me, R_2 = n-Bu	-	86
3	R_1 = Me, R_2 = n-hexyl	4h	**2c**:R_1 = Me, R_2 = n-hexyl	-	86
4	R_1 = Me, R_2 = benzyl	6h	**2d**: R_1 = Me, R_2 = benzyl	-	98
5	R_1 = Me, R_2 = cyclohexyl	1h	**2e**:R_1 = Me, R_2 = cyclohexyl	-	78
6	R_1, R_2 = pyrrolidine	1h	**2f**: R_1, R_2 = pyrrolidine	-	98
7	R_1 = Et, R_2 = benzyl	11h	**2g**: R_1 = Et, R_2 = benzyl	**3g**: R_1 = Et, R_2 = benzyl	**2g**:35, **3g**:50
8	R_1 = Et, R_2 = cyclohexyl	1h	-	**3h**: R_1 = Et, R_2 = cyclohexyl	77
9	R_1 = Et, R_2 = n-Bu	16h	-	**3i**:R_1 = Et, R_2 = n-Bu	69

Table 2. Crystal data and structure refinement for compound **2f**.

Chemical formula	$C_{11}H_{16}N_2O_2S_1$	**Absorption coefficient**	2.338 mm^{-1}
Formula weight	240.33 g mol^{-1}	**F(000)**	512.0
Colour	Colorless	**Theta range for data collection**	5.0-71.2 (º)
Crystal shape	Prismatic	**Reflections collected / unique**	4425, 2240, R_{int} = 0.020
Size	0.10 x 0.18 x 0.23 mm	**Completeness to theta = 25.00**	0.991
Temperature	100 K	**Max. and min. transmission**	T_{min} = 0.837,T_{max} = 1.000
Wavelength	1.54180 Å	**Refinement method**	Full-matrix least-squares on F^2
Crystal system	orthorhombic	**Data/ restraints/ parameters**	2231/0/145
Space group	*P21212* (No. 19)	**Goodness-of-fit on F^2**	0.730
***a,b,c* (Å); α, β, γ ( )°**	6.7899(3), 9.9302(4), 17.5667(7); 90, 90, 90	**Final R indices [I>2 σ (I)]**	R = 0.0327,wR = 0.0841
Cell volume	1184.44(9)$Å^3$	**Largest diff. peak and hole**	-0.27 & 0.39 e $Å^{-3}$
Z	4	**Calculated density**	1.348 $g.cm^{-3}$

Table 3. Selected bond lengths (Å), angles and torsion angles (º) for **2f**.

Bond	Bond length (Å)	Bond	Bond angle (º)	Bond	torsion angles (º)
S(1)–C(2)	1.7646(19)	C(2)–S(1)–C(16)	103.86(10)	N(3)–C(2)–C(8)–C(9)	142.19(19)
S(1)–C(16)	1.807(2)	C(11)–O(12)–C(13)	115.73(16)	C(8)–C(2)–N(3)–C(4)	179.64(18)
O(12)–C(11)	1.362(2)	C(2)–N(3)–C(4)	123.66(17)	C(16)–S(1)–C(2)–C(8)	-29.85(18)
O(12)–C(13)	1.452(2)	S(1)–C(2)–N(3)	114.56(15)	C(2)–C(8)–C(11)–O(12)	175.06(17
O(15)–C(11)	1.212(2)	S(1) –C(2)–C(8)	121.24(15)	C(8)–C(2)–N(3)–C(7)	-13.9(3)
N(3)–C(2)	1.316(3)	C(2)–C(8)–C(9)	117.66(17)	S(1)–C(2)–C(8)–C(9)	(2) 34.7-
N(10)–C(9)	1.156(3)	C(2)–C(8)–C(11)	122.62(17)	C(9)–C(8)–C(11)–O(15)	169.64 (19)
C(2)–C(8)	1.421(3)	C(14)–C(13)–O(12)	110.78(17)	S(1)– C(2)–N(3)– C(7)	163.10(14)
C(8)–C(9)	1.424(3)	N(10)–(C9)–C(8)	177.4(2)	C(16)–S(1)–C(2)–N(3)	153.02(14)
C(8)–C(11)	1.453(3)	O(12)–C(11)–O(15)	123.33(18)	O(12)–C(11)–C(8)–C(9)	- 4.7(2)
C(5)–C(4)	1.527(3)	C(2)–N(3)–C(7)	124.47(17)	O(15)–C(11)–O(12)–C(13)	1.5 (3)

Table 4. The structures, yields and melting points of pyrazoles**4(a-f)**, **4j** and **4k**.

Entry	*N,S*-acetals 2a-f, 2j and 2k	Pyrazoles 4a-f, 4j and 4k	Yield %	Melting point (°C)
1	**2a**	**4a**:R_1 = Me, R_2 = Et	88	228-230
2	**2b**	**4b**:R_1 = Me, R_2 = n-Bu	75	197-198
3	**2c**	**4c**:R_1 = Me, R_2 = n-hexyl	95	176-178
4	**2d**	**4d**: R_1 = Me, R_2 = benzyl	97	230-231
5	**2e**	**4e**: R_1 = Me, R_2 = cyclohexyl	80	> 310
6	**2f**	**4f**: R_1, R_2 = pyrrolidine	91	> 300
7	**2j**	**4j**: R_1, R_2 = morpholine	94	181-183
8	**2k**	**4k**: R_1, R_2 = piperidine	88	> 350

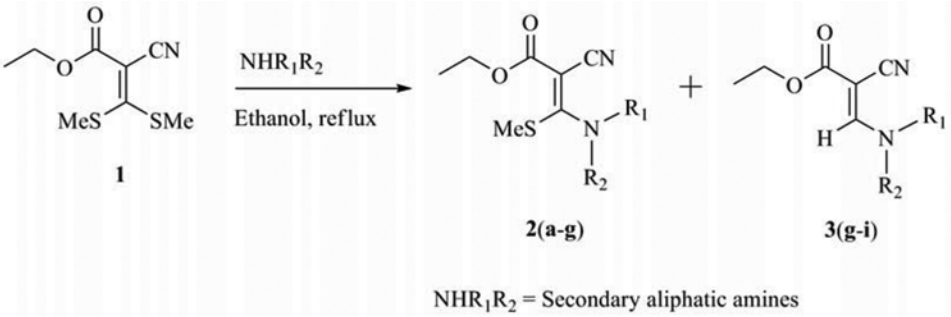
Table 5. Crystal data and structure refinement for **4b**.

Chemical formula	$C_9H_{14}N_4O$	**Absorption coefficient**	0.719mm^{-1}
Formula weight	194.24 g mol^{-1}	**F(000)**	416
Colour	Colorless	**Theta range for data collection**	5.4–71.2(°)
Crystal shape	Block	**Reflections collected / unique**	11181, 1929, R_{int} = 0.028
Size	0.13 x 0.17 x 0.26 mm	**Completeness to theta = 25.00**	1.66/0.99
Temperature	150 K	**Max. and min. transmission**	T_{min} = 0.885,T_{max} = 0.911
Wavelength	1.54184 Å	**Refinement method**	Full-matrix least-squares on F^2
Crystal system	Orthorhombic	**Data/ restraints/ parameters**	1921/0/128
Space group	*P212121 (No. 19)*	**Goodness-of-fit on F^2**	0.99
***a,b,c* (Å); α, β, γ ( )°**	7.52407(17),8.2298(2), 16.2919(4); 90, 90, 90	**Final R indices [I>2 σ (I)]**	R = 0.035,wR = 0.0874
Cell volume	1008.82(4) Å^3	**Largest diff. peak and hole**	-0.20 &, 0.15 (e Å^{-3})
Z	4	**Calculated density**	1.279 (g.cm^{-3})

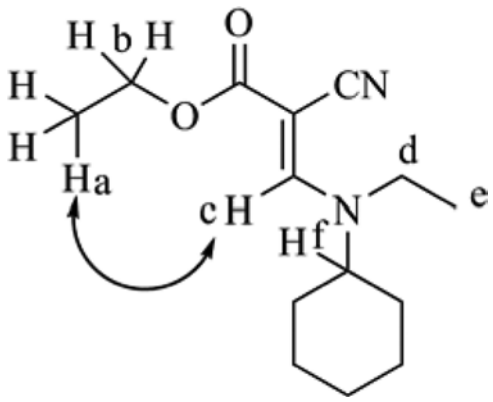
Table 6. Selected bond lengths [Å], angles [º] and torsion angles [º] for **4b**.

Bond	Bond length (Å)	Bond	Bond angle (º)	Bond	torsion angles (º)
O1–C2	1.2394(18)	C5—N4—N3	108.74(11)	C10–N9–C5–C6	-4.8(3)
C5—N9	1.3330(19)	C2—N3—N4	108.86(11)	C5–N4–N3–C2	10.42(16)
N9—C10	1.4660(18)	C5—N9—C10	121.90(1	N3–N4–C5–N9	171.24(13)
N9—C14	1.459(2)	C5—N4—N3	108.74(11)	N3–N4–C5–C6	-8.04(16)
C5—N4	1.3586(18)	C2—N3—N4	108.86(11)	N4–N3–C2–O1	171.81(13)
N4—N3	1.4053(17)	N9—C5—N4	120.16(13)	C5–C6–C2–O1	-176.69(15)
C2—N3	1.3707(18)	N9—C5—C6	132.01(13)	N4–N3–C2–C6	-8.27(15)
C11—C12	1.519(2)	N4—C5—C6	107.82(12)	N9–C5–C6–C2	-176.25(16)
C10—C11	1.523(2)	C7—C6—C5	130.33(13)	N9–C5–C6–C7	8.6(3)
C12—C13	1.523(2)	C7—C6—C2	122.00(13)	C7–C6–C2–O1	-1.1(2)
C5–C6	1.406(2)	C5—C6—C2	107.49(12)	C7–C6–C2–N3	179.02(13)

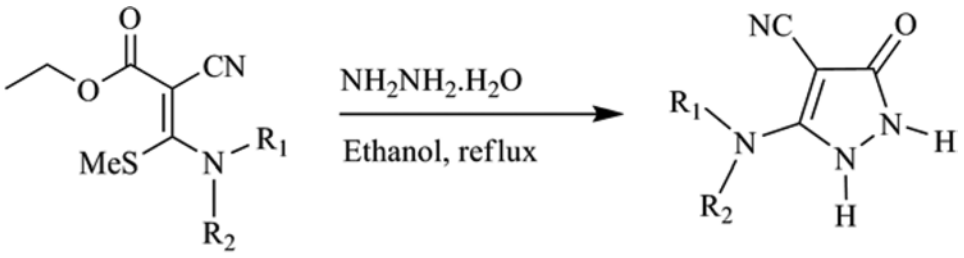
Scheme 1. Synthesis of α-cyanoketene-*N,S*-acetals **2**(**a-g**) and compounds **3**(**g-i**).



Scheme 2. Selected NOESY correlation for compound (**3h**).



Scheme 3. Synthesis of substituted pyrazoles **4**(**a-f**), **4j** and **4k**.



2(a-f), 2j and **2 k** **4(a-f), 4j** and **4k**

Scheme 4. Proposed mechanism for the formation of pyrazoles **4**(**a-f**), **4j** and **4k**.

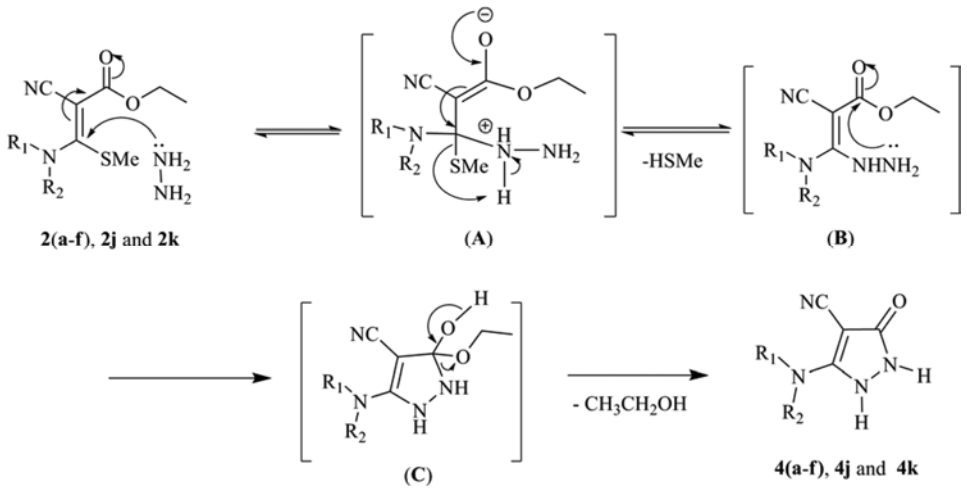


Figure 1. The structure of compound (**2f)** showing the atom numbering scheme with ellipsoids drawn at the 50% probability level.

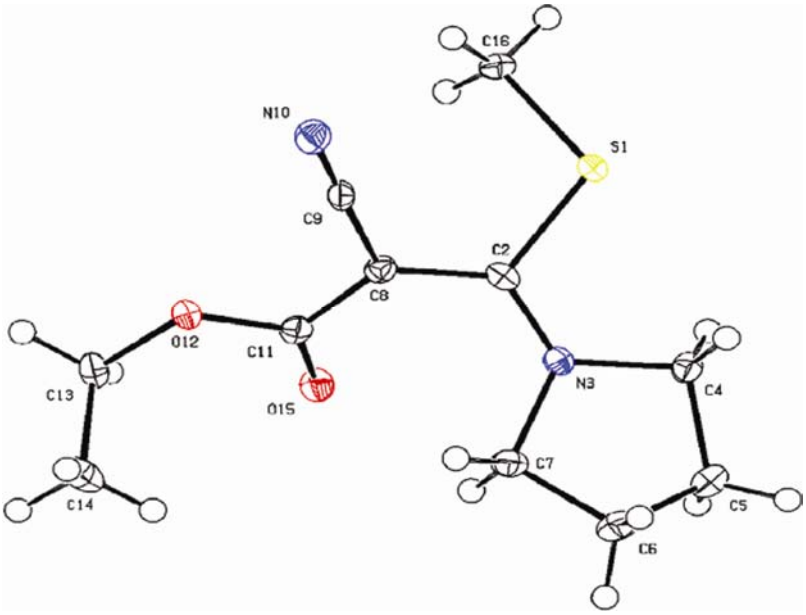


Figure 2. The structure of compound **4b** showing the atom numbering scheme with ellipsoids drawn at the 50% probability level.