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Nef-isocyanide-Perkow access to novel pyrazolone derivations containing a cyclic ketene dithioacetal moiety

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ABSTRACT

Alkyl (*E*)-2-(3-Alkyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)-5-(alkylamino)-1,3-dithiole-4-carboxylates have been obtained by condensation of 2-pyrazolin-5-ones with carbon disulfide followed by ring formation with phosphorylated hydroxyketenimines [generated *in situ* from Nef-isocyanide-Perkow reaction] in the presence of Et_3N. The structure of target compounds was confirmed by X-ray diffraction study. The good yields of the products, diastereoselectivity, and lack of activators or metal promoters are the main advantages of this method.

GRAPHICAL ABSTRACT

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KEYWORDS
Pyrazolone; Nef-isocyanide-Perkow reaction; cyclic ketene dithioacetal; carbon disulfide; polarized double bond

Introduction

Pyrazolone compounds are privileged scaffolds in organic synthesis by virtue of their potential biological activities and wide-ranging utility as synthetic intermediates. Bioactive compounds bearing a pyrazolone systems have attracted much interest in medicinal chemistry.[1–3] Recently, the construction of structurally diverse pyrazolone derivatives has attracted the research interests of synthetic chemists.[4–8] As part of our current studies on developments of new applications of pyrazolone derivatives in heterocyclic synthesis,[9–12] we now report the formation of novel cyclic ketene dithioacetals containing a pyrazolone motif from the reaction between 2-pyrazolin-5-ones-CS_2 adduct and phosphorylated hydroxyketenimines [generated *in situ* from Nef-isocyanide-Perkow reaction], in the presence of Et_3N, at room temperature. Ketene dithioacetals

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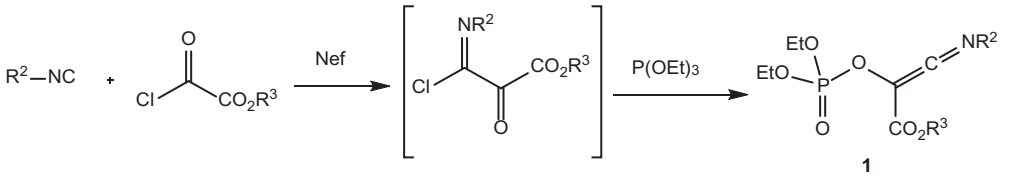
are versatile intermediates in organic synthesis,[13–15] and extensive research has given rise to new prospects in their chemistry.[16,17]

Recently, we reported on the synthesis of new types of ketene dithioacetals through the reaction between phosphorylated hydroxyketenimines, 1,3-dicarbonyl compounds, and carbon disulfide at room temperature.[18]

α-Ketoimidoyl chlorides, generated *in situ* from acyl chlorides and isocyanides,[19] are trapped by trialkyl phosphites via a Perkow-type reaction leading to phosphorylated hydroxyketenimine **1** (Scheme 1).[20] The Nef-isocyanide reaction is performed under solvent-free conditions, and the Perkow reaction is carried out at room temperature.[21]

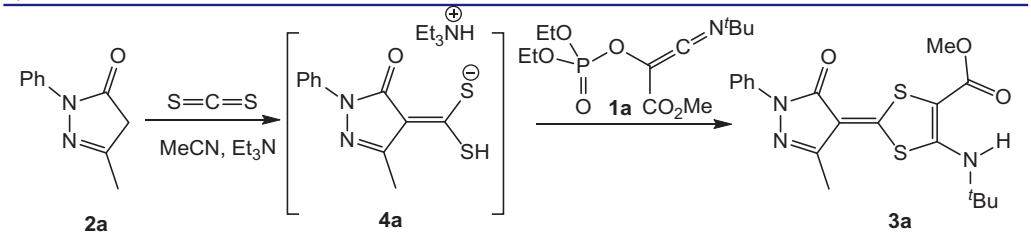
Results and discussion

Initially, adduct **4a**, obtained from methyl 2-(5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl) acetate (**2a**) and carbon disulfide, was treated with methyl 3-(*tert*-butylimino)-2-[(diethoxyphosphoryl)oxy]acrylate (**1a**) at room temperature in different solvents. As shown in Table 1 (Entry 1), the reaction proceeded in EtOH to afford methyl 5-(*tert*-butylamino)-2-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)-1,3-dithiole-4-carboxylate (**3a**) in 20% yield. Using CH_2Cl_2 or acetone (Entries 2 and 3) led to slightly better yields. The use of MeCN as solvent and Et_3N as a base, afforded product



Scheme 1. Formation of phosphorylated hydroxyketenimine **1** by a Nef-Perkow sequence.

Table 1. Optimization of reaction conditions for the formation of product **3a** from ketenimine **1a**, pyrazolone **2a**, and carbon disulfide[a].



Entry	Solvent	Base (x eq.)	Yield (%)[b]
1	EtOH	DBU (1)	20
2	CH_2Cl_2	DBU (1)	30
3	Acetone	DBU (1)	45
4	MeCN	NaH (1)	50
5	MeCN	DABCO (1)	73
6	MeCN	Et_3N (1)	80
7	MeCN	Et_3N (2)	87

[a]Reaction conditions: (i) **1a** (1.1 mmol); (ii) **2a** (1 mmol), CS_2 (1.2 mmol) and base at r.t., 12 h.
[b]Isolated yield.

3a in 80% yield (Entry 6). The conversion proceeded in an improved yield (87%) with 2 equivalents of Et_3N (Entry 7) in 12 h at room temperature.

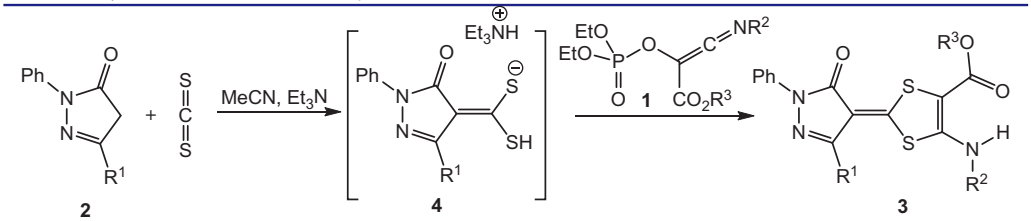
With the suitable reaction conditions in hand, we next explored the protocol with phosphorylated hydroxyketenimines **1**, pyrazolone derivatives **2**, and CS_2 in the presence of Et_3N. As shown in Table 2, these reactions led to the formation of alkyl 5-(alkylamino)-2-(3-alkyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)-1,3-dithiole-4-carboxylates **3a–j**, in 68–87% yields.

The structures of compounds **3a-j** were confirmed using IR, ^{1}H NMR, and ^{13}C NMR spectral data and single-crystal X-ray analyses. For example, the ^{1}H NMR spectrum of **3a** showed singlets at 1.53, 2.60, and 3.86 ppm for *tert*-Bu, Me, and MeO protons, respectively. The NH proton appears as a fairly broad singlet at 8.61 ppm. The ^{1}H-decoupled ^{13}C NMR spectrum of **3a** exhibited 18 signals in agreement with the proposed structure.

There is the possibility of geometrical isomerism about the central alkene linkage in compounds **3**. Thus, two geometrical isomers, namely (*E*)-**3** and (*Z*)-**3**, are possible. Unequivocal evidences for the structure and geometry of the central alkene linkage of compound **3f** were obtained from single-crystal X-ray analyses. According to the ORTEP diagram of **3f**, shown in Figure 1, the preferred geometry of the central alkene linkage is (*E*). The same structures were assumed for the other derivatives on the basis of their NMR spectroscopic similarities.

A mechanistic rationalization for the formation of products **3** is shown in Scheme 2. The Nef-isocyanide reaction leads to the formation of imidoyl chlorides, which can later be treated with triethyl phosphite to afford ketenimine **1** in a Perkow-type reaction. Subsequent reaction of triethyl ammonium salt of **4** with **1** afford intermediate **5**, which is converted to **6** by proton transfer reaction. Intermediate **6** undergoes elimination of

Table 2. Synthesis of products **3a–j**[a].



Entry	R^1	R^2	R^3	Product	Yield (%)[b]
1	Me	^{t}Bu	Me	**3a**	70
2	Me	^{t}Bu	Et	**3b**	77
3	Me	Cyclohexyl	Me	**3c**	75
4	Me	Cyclohexyl	Et	**3d**	73
5	CH_2CO_2Me	^{t}Bu	Me	**3e**	68
6	CH_2CO_2Me	^{t}Bu	Et	**3f**	87
7	CH_2CO_2Me	Cyclohexyl	Me	**3g**	80
8	CH_2CO_2Me	Cyclohexyl	Et	**3h**	86
9	CH_2CO_2Et	^{t}Bu	Et	**3i**	73
10	CH_2CO_2Et	Cyclohexyl	Et	**3j**	77

[a]Reaction conditions: (i) **1** (1.1 mmol); (ii) **2** (1 mmol), CS_2 (1.2 mmol), at r.t., 12 h.
[b]Isolated yield.

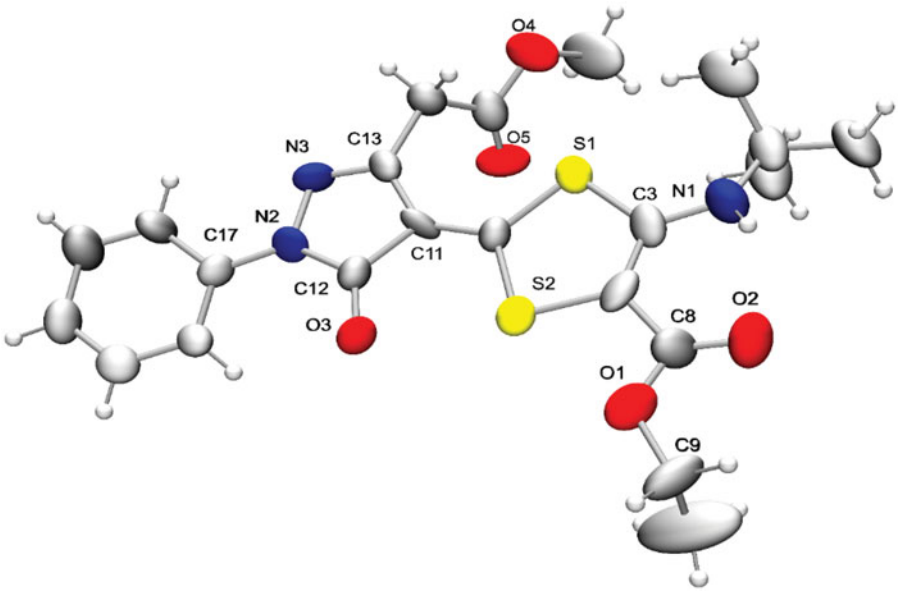
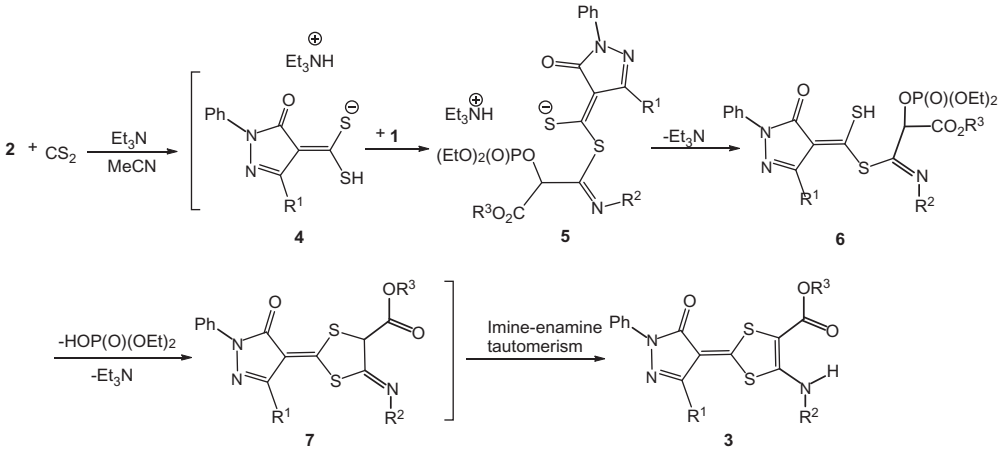


Figure 1. An ORTEP diagram of **3f**. The thermal ellipsoids are drawn at the 40% probability level.



Scheme 2. Proposed mechanism for the formation of products **3**.

diethyl hydrogen phosphate to afford intermediate **7**, which is converted to product **3** by imine-enamine tautomerization reaction.

In summary, we have developed a simple synthesis of novel pyrazolones containing a cyclic ketene dithioacetal moiety by condensation of 2-pyrazolin-5-ones-CS_2 adduct with phosphorylated hydroxyketenimines, in the presence of Et_3N, at room temperature. This protocol provides fast access to a variety of structurally diverse pyrazolones. The structure of a typical product was confirmed using X-ray crystallography. The mild and simple reaction conditions of this protocol make it suitable for the generation of such derivatives.

Experimental

Materials

All purchased solvents and chemicals were of analytical grade and used without further purification. Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a Shimadzu IR-460 spectrometer, respectively. The ^{1}H and ^{13}C NMR spectra were obtained with a BRUKER DRX-500 AVANCE instrument using $CDCl_3$ as applied solvent and TMS as internal standard at 500 or 300 and 125 or 75 MHz, respectively. The abbreviations used for NMR signals: s = singlet, d = doublet, t = triplet, and m = multiplet. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer.

General procedure for the synthesis of compounds 3

A mixture of 2-pyrazolin-5-ones (1 mmol) with carbon disulfide (0.091 g, 1.2 mmol) and Et_3N (0.202 g, 2 mmol) in MeCN (4 mL) was stirred for 30 min at room temperature. Then, a solution of the appropriate ketenimine **1** (1 mmol) in MeCN (2 mL) was added. After 12 h, the solvent was removed under reduced pressure and the residue was purified using preparative TLC (SiO_2; AcOEt/*n*-hexane 1:3).

*Ethyl (*E*)-5-(*tert*-butylamino)-2-(3-(2-methoxy-2-oxoethyl)-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-ylidene)-1,3-dithiole-4-carboxylate* **(3f):** Yellow crystals. Mp 160–162 °C; yield: 0.41 g (87%); IR (KBr)$\bar{\nu}$ cm^{-1}: 3451 (N–H), 1738 (C = O), 1654 (C = O), 1566, 1497, 1432, 1265 (C–O). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.32 (t, $J = 7.2$ Hz, 3H), 1.52 (s, 9H), 3.78 (s, 3H), 3.91 (s, 2H), 4.31 (q, $J = 7.2$ Hz, 2H), 7.16 (t, $J = 7.3$ Hz, 1H), 7.39 (t, $J = 7.4$ Hz, 2H), 8.01 (d, $J = 7.2$ Hz, 2H), 8.58 (br s, 1H). ^{13}C NMR ($CDCl_3$) 14.4 (Me), 29.3 ($C(Me)_3$), 36.1 (CH_2), 52.4 (MeO), 54.4 ($C(Me)_3$), 61.2 (CH_2O), 101.1 (C), 118.8 (2 CH), 123.1 (C), 124.6 (CH), 128.7 (2 CH), 133.7 (C), 138.7 (C), 142.5 (C), 155.3 (C), 162.5 (C = O), 167.3 (C = O), 169.2 (C = O). EI-MS: *m/z* (%) 475 (8, M^+), 306 (4), 279 (8), 246 (10), 215 (3), 187 (12), 169 (18), 149 (60), 111 (15), 83 (32), 57 (100), 41 (80). Anal. Calcd for $C_{22}H_{25}N_3O_5S_2$ (475.12.): C 55.56, H 5.30, N 8.84. Found: C 55.91, H 5.32, N 8.87%.

X-ray crystal-structure determination of 3f

The X-ray diffraction measurements were carried out on STOE IPDS 2T diffractometer with graphite-monochromated MoK_α radiation. All single crystals were obtained from DMF solution and mounted on a glass fiber and used for data collection. Cell constants and orientation matrixes for data collection were obtained by least-square refinement of the diffraction data from 7488 for compound **3f**. Diffraction data were collected in a series of ω scans in 1° oscillations and integrated using the Stoe X-AREA software package. The structures were solved by direct methods and subsequent difference Fourier maps and then refined on F^2 by a full-matrix least-squares procedure using anisotropic displacement parameters. Atomic factors are from the International Tables

for X-ray Crystallography. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. All refinements were performed using the X-STEP32, SHELXL-2014 and WinGX-2013.3 programs.[22–24] CCDC-1815485 contains the supplementary crystallographic data for compound **3f**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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