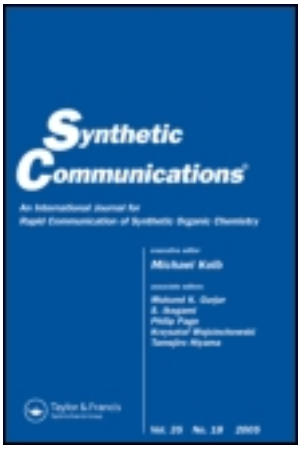

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An Easy Access to Variously Substituted Pyrroles Starting From Ketene Dithioacetals

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An Easy Access to Variously Substituted Pyrroles Starting From Ketene Dithioacetals

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Abstract: Variously substituted pyrroles **4** can easily be synthesized in two steps by reacting a primary or secondary amine and a ketene dithioacetal in a basic medium in moderate to good yield. Ketene dithioacetals **2** are readily prepared from acetylaceton or malononitrile, carbon disulfide, and methyl iodide.

Keywords: Ketene dithioacetals, amines, pyrroles, nucleophiles, addition-elimination

INTRODUCTION

Ketene dithioacetals are key intermediates for the preparation of a wide variety of heterocyclic structures.[1] Although their synthesis and reactions receive much attention, their corresponding N,S-acetals have been studied in only a few cases.[2] Various nucleophiles (thiols, hydrazines, organometallic reagents, etc.) can remove one of the methylsulfanyle group and cyclization of the intermediate can generally occur during the same stage. Several

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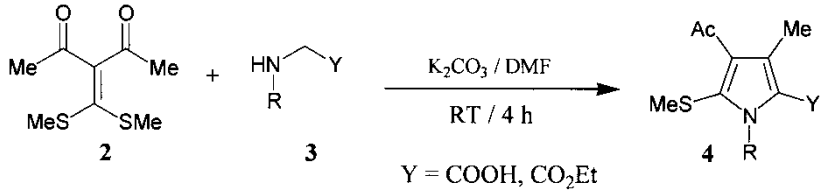
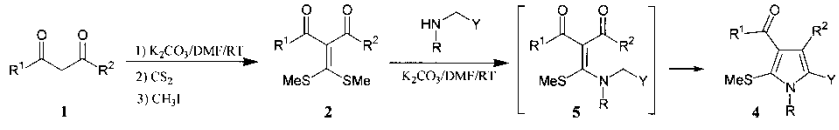


Scheme 1.

reports have appeared during these last years on the ability of an amine to displace a methylsulfanyle group on a ketene dithioacetal to synthesize oxazolidine,[3] pyrazole,[4] benzodiazepine,[5] or imidazolidine.[6] Amines used here (glycin, sarcosin, or ethyl sarcosinate) are well-known reagents used to prepare pyrrole in two steps via α-chloro-acrolein **2** obtained from a methyl keton by the Vilsmeier-Haack-Arnold reaction ($POCl_3$-DMF).[7]

A procedure was recently described that was used to obtain 5-methylsulfanyl-thiophenes and selenophenes and thieno[2,3-*b*]thiophenes in moderate to good yields,[10–15] by reacting ketene dithioacetals with sodium sulfide followed by a condensation with an activated methylene compound (such as alkyl bromoacetate, chloracetonitrile, chloraceton, or α-bromoacetophenone) and a Dieckman-type cyclization in the same step in a basic medium (K_2CO_3/DMF).

To the best of our knowledge, only one paper, which was written in 1988 by Liebscher,[16] deals with this kind of reaction. In an extension of our recent studies on the application of ketene dithioacetals in heterocyclic synthesis, the easy synthesis of pyrroles from ketene dithioacetals is reported here (Scheme 1). Different primary or secondary amines bearing an activated methylene are used to build the pyrrole ring in a one-pot reaction by a monosubstitution of a methylsulfanyle group. Liebscher describes a similar approach to this synthesis but surprisingly only one compound has been reported. The procedure cited therein, i.e., triethylamine in refluxing ethanol leading to the formation of a noncyclized intermediate **5** (Scheme 2). This is due to the soft conditions applied. A second step with a stronger base and harsher condition is then needed to afford pyrroles. The method we report here directly gives the pyrrole and no intermediate are observed. Potassium carbonate in dimethyl formamide (DMF) appears to be more convenient,



Scheme 2.

cheaper, and applicable to every ketene dithioacetal. Several pyrroles were synthesized from ketene dithioacetals and ethyl glycinate, sarcosin, ethyl sarcosinate, and glycin in moderate to good yield (Table 1).

The mechanism of this reaction seems to be similar to those observed previously,[10–15] namely, a Michael addition reaction, followed by elimination of one equivalent of a thiomethyl group and a Dieckman-type cyclization on the carbonyl group (or equivalent).

Pyrroles **4a-f** are obtained from symmetrical ketene dithioacetals in 49%–89% yield. A very interesting point is that unsymmetrical starting compounds give two different pyrroles in equivalent yield. Absolutely no regioselectivity is observed on this type of compound **2g**. Dieckman-type cyclization affords 3-hydroxy-pyrrole **4h** (ester site) and an 3-amino pyrrole **4g** (cyanide site) on a Thorpe-Ziegler-type reaction in 87% overall yield (Scheme 3).

To sum up, primary and secondary amines bearing an activated methylene react with ketene dithioacetals to afford the pyrrole ring in a one-pot reaction in moderate to good yields. Indeed, the method of synthesis of five-membered heterocycles starting from ketene dithioacetals, potassium carbonate in DMF is more convenient, cheaper, and generalized to a wider variety of heterocyclic syntheses.

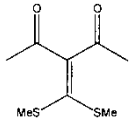
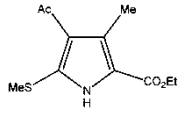
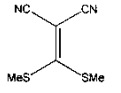
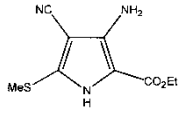
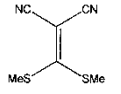
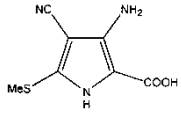
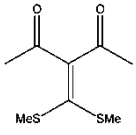
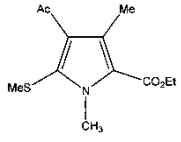
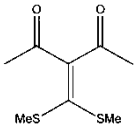
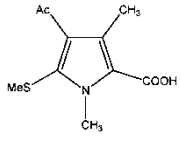
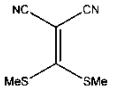
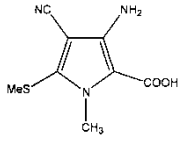
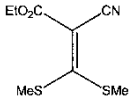
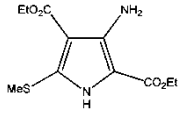
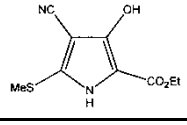
EXPERIMENTAL

All melting points were determined on a binocular apparatus from Stuart Scientific SMP3 and were uncorrected. Elemental analysis data were obtained by use of a Carlo Erba 1106. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 (250 MHz) spectrometer using tetramethylsilane (TMS) as an internal reference.

Ketene Dithioacetals: General Procedure

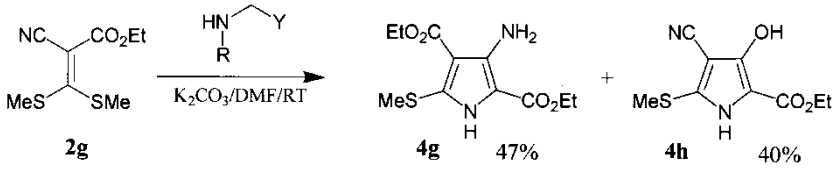
A 250 mL three-necked round-bottom flask equipped with magnetic stirrer, condenser, and septum was charged with a solution of 1,3-diketon (100 mmol) in DMF (100 mL). Dried K_2CO_3 (13.8 g, 100 mmol) was added and the mixture was stirred for 2 h at room temperature. CS_2 (18.0 mL, 300 mmol) was added and the mixture was stirred for an additional 2 h at room temperature. Methyl iodide (12.5 mL, 200 mmol) was then added and the mixture was stirred for 4 h before being poured onto water (400 mL). The precipitated crude product was purified by filtration followed by crystallization from EtOH. When the product was an oil, the organic phase was extracted with Et_2O (3×100 mL). The combined organic extracts were washed with H_2O (2×100 mL), dried ($MgSO_4$), and concentrated in vacuo to afford ketene dithioacetal directly used for the next step.

Table 1. Preparation of pyrroles **4** from dithioacetals **2**

Entry	Amine **3**	Dithioacetals **2**	Pyrroles **4**	Yield (%)
a	R = H Y = CO_2Et			**68**
b	R = H Y = CO_2Et			**87**
c	R = H Y = COOH			**89**
d	R = Me Y = CO_2Et			**84**
e	R = Me Y = COOH			**49**
f	R = Me Y = COOH			**67**
g	R = H Y = CO_2Et			**47**
h				**40**

Typical Procedure for the Preparation of Pyrroles 4

A 100 mL three-necked round-bottom flask equipped with magnetic stirrer, condenser, and septum was charged with a solution of ketene dithioacetals



Scheme 3.

(10.0 mmol) in DMF (30 mL). Dried K_2CO_3 (10.0 mmol) followed by the amine (10.0 mmol) was added and the mixture was stirred for 4 h at 60°C. The reaction mixture was then cooled down to room temperature, poured into ice water (100 mL), and stirred for 1 h before usual standard work-up. When the product was an oil, the organic phase was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with H_2O (2 × 100 mL), dried ($MgSO_4$), concentrated in vacuo, and purified on silica gel with dichloromethane as eluant. When precipitated, the product is filtered, washed with water, and purified by recrystallization from ethanol.

4-Acetyl-3-methyl-5-methylsulfanyl-1*H*-pyrrole-2-carboxylic acid ethyl ester **(4a)**

Mp: 128–130°C; δ_H (250 MHz, $CDCl_3$): 1.37 (t, 3H, $J = 7.1$ Hz), 2.48 (s, 3H), 2.51 (s, 3H), 2.58 (s,3H), 4.34 (q, 2H, $J = 7.1$ Hz), 8.96 (br s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$). 14.2 (CH_3), 14.4 (CH_3), 15.7 (CH_3), 30.5 (CH_3), 60.6 (CH_2), 117.5 (C_{ar}), 120.7 (C_{ar}), 125.1 (C_{ar}), 156.9 (C_{ar}), 161.4 (CO_2), 194.3 (CO); Anal. Calcd for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.80. Found: C, 54.57; H, 6.01, N, 5.48.

3-Amino-4-cyano-5-methylsulfanyl-1*H*-pyrrole-2-carboxylic acid ethyl ester **(4b)**[16]

Mp: 183–185°C; δ_H NMR (250 MHz, $CDCl_3$). 1.09 (t, 6H, $J = 7.2$ Hz), 2.26 (s, 6H), 4.34 (q, 4H, $J = 7.2$ Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) 12.2(CH_3), 14.0(CH_3), 61.6(CH_2), 75.3 (C_{ar}), 98.7 (C_{ar}), 114.9(CN), 167.8(CO_2), 174.1 (C_{ar}), 177.2 (C_{ar}); Anal. Calcd for $C_9H_{11}N_3O_2S$: C, 47.99; H, 4.92; N, 18.65. Found: C, 47.97; H, 4.78, N, 18.55.

3-Amino-4-cyano-5-methylsulfanyl-1*H*-pyrrole-2-carboxylic acid **(4c)**

Mp: 137–139°C; δ_H NMR (250 MHz, $CDCl_3$) 2.58 (s, 3H), 3.62 (sl, 1H), 4.26 (sl, 2H), 8.82 (sl, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) 19.3 (CH_3), 81.4 (C_{ar}), 115.6 (CN), 116.9(C_{ar}), 139.9 (C_{ar}), 160.8 (C_{ar}), 169.8 (COOH); Anal. Calcd for $C_7H_7N_3O_2S$: C, 42.63; H, 3.58; N, 21.31. Found: C, 42.58; H, 3.53, N, 21.22.

4-Acetyl-1,3-dimethyl-5-methylsulfanyl-1H-pyrrole-2-carboxylic acid ethyl ester **(4d)**

Yellow oil; δ_H NMR (250 MHz, $CDCl_3$) 1.35 (t, 3H, $J = 7.2$ Hz), 2.29 (s, 3H), 2.31 (s, 3H), 2.89 (s, 3H), 3.07 (s, 3H), 4.30 (q, 2H, $J = 7.2$ Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) 14.1 (CH_3), 14.3 (CH_3), 14.7 (CH_3), 18.8 (CH_3), 33.5 (CH_3), 59.2 (CH_2), 121.8 (C_{ar}), 129.2 (C_{ar}), 131.6 (C_{ar}), 151.8 (C_{ar}), 161.6 (CO_2), 192.8 (CO); Anal. Calcd for $C_{12}H_{17}NO_3S$: C, 56.45; H, 6.71; N, 5.49. Found: C, 56.54; H, 6.82, N, 5.42.

4-Acetyl-1,3-dimethyl-5-methylsulfanyl-1H-pyrrole-2-carboxylic acid **(4e)**

Orange oil; δ_H NMR (250 MHz, $CDCl_3$) 2.23 (s, 3H), 2.50 (s, 3H), 2.68 (s, 3H), 2.85 (s, 3H), 12.95 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) 19.3 ($2CH_3$), 28.2 (CH_3), 36.4 (CH_3), 102.1 (C_{ar}), 123.1 (C_{ar}), 135.6 (C_{ar}), 138.4 (C_{ar}), 173.1 (COOH), 191.5 (CO).; Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.85; H, 5.77; N, 6.16. Found: C, 52.66; H, 5.87, N, 6.02.

3-Amino-4-cyano-1-methyl-5-methylsulfanyl-1*H*-pyrrole-2-carboxylic acid **(4f)**

Brown oil; δ_H NMR (250 MHz, $CDCl_3$) 2.38 (s, 3H), 3.47 (s, 3H), 5.92 (sl, 2H), COOH nonvisible; ^{13}C NMR (62.5 MHz, $CDCl_3$) 16.8 (CH_3), 36.2 (CH_3), 88.1 (C_{ar}), 102.4 (C_{ar}), 112.1 (CN), 138.9 (C_{ar}), 153.9 (C_{ar}), 165.8 (COOH); Anal. Calcd for $C_8H_9N_3O_2S$: C, 45.49; H, 4.19; N, 19.89. Found: C, 45.82; H, 3.98, N, 19.53.

3-Amino-5-methylsulfanyl-1H-pyrrole-2,4-dicarboxylic acid diethyl ester **(4g)**

Mp: 69–71°C; δ_H NMR (250 MHz, $CDCl_3$) 1.26 (m, 6H), 2.28 (s, 3H), 4.22 (m, 4H), 9.74 (sl, 1H), NH_2 non visible.; ^{13}C NMR (62.5 MHz, $CDCl_3$) 13.0 (CH_3), 13.8 (CH_3), 15.0 (CH_3), 60.0 (CH_2), 61.6 (CH_2), 70.7 (C_{ar}), 117.7 (C_{ar}), 123.4 (C_{ar}), 168.2 (CO_2), 169.0 (CO_2), 171.3 (C_{ar}); Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29. Found: C, 48.66; H, 6.12, N, 10.04.

4-Cyano-3-hydroxy-5-methylsulfanyl-1H-pyrrole-2-carboxylic acid ethyl ester **(4h)**

Mp: 138–140°C; δ_H NMR (250 MHz, $CDCl_3$). 1.20 (t, 3H, $J = 7.2$ Hz), 2.20 (s, 3H), 3.70 (br s, 1H), 4.18 (q, 2H, $J = 7.2$ Hz), OH non visible; ^{13}C NMR (62.5 MHz, $CDCl_3$) 13.6 (CH_3), 15.5 (CH_3), 60.5 (CH_2), 80.7 (C_{ar}), 109.3 (C_{ar}), 117.7 (CN), 124.3 (C_{ar}), 168.6 (CO_2), 174.3 (C_{ar}); Anal. Calcd for $C_9H_{10}N_2O_3S$: C, 47.79; H, 4.42; N, 12.39. Found: C, 48.12; H, 4.12, N, 12.04.

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