A New Simple Synthesis of α-Substituted Acrylonitriles

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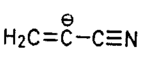
An efficient preparation of α-substituted acrylonitriles **6** based on the utilization of 4-cyano-3-ketothiolane enolate anion (**3**) as a synthetic equivalent to α-acrylonitrile anion (**1**) is described.

α-Substituted acrylonitriles are important intermediates in synthetic organic chemistry, being essential components in classical Michael and Diels-Alder reactions as well as starting materials for a wide variety of heterocycles. These compounds are not directly accessible by reaction of the anion **1** with electrophiles[1], therefore several round-about routes have been proposed for their preparation. Thus dehydration of cyanohydrins of methyl ketones[2] or oximes of α-alkylacroleins[3] was successfully applied, although the most general route[4] involves heating in dimethylformamide for 48 h at 80 °C of a quaternary salt of a Mannich base derivative of alkylated cyanoacetic esters. A synthetic equivalent of **1** was found[5] in the anion **2** of 2-cyano-5-norbornene, the Diels-Alder adduct between cyclopentadiene and acrylonitrile. Alkylation of **2**, generated by the action of sodium amide in tetrahydrofuran, with suitable electrophiles, followed by pyrolysis (350–380 °C) of the alkylated products, gave rise to the corresponding α-alkylated acrylonitriles in unspecified yield through a retro Diels-Alder reaction.



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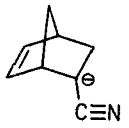

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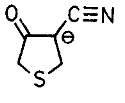

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We wish to describe in this paper a new method of preparation of α-substituted acrylonitriles **6** featured by the use of the heterocyclic anion **3** as a new synthetic equivalent for **1**, which circumvented the drastic conditions associated with the retro Diels-Alder reaction.

The required 4-cyano-3-oxotetrahydrothiophene (**4**) was prepared in 50% overall yield through Dieckmann cyclization of the Michael adduct between acrylonitrile and methyl thioglycolate in the presence of sodium methoxide in refluxing methanol, in a one-pot reaction described in the patent literature[6]. Treatment of **4** in acetone with a variety of alkyl halides in the presence of anhydrous potassium carbonate gave the corresponding *C*-alkylated products **5a–h**, which were isolated by simple filtration of the inorganic salts followed by solvent evaporation in vacuo.

The alkylation of the *β*-ketonitrile moiety[7] with primary alkyl halides in the cases of **6f–h** formed variable amounts (5–10%) of *O*-alkylated products, which could be easily removed by flash-chromatography. However this operation was unnecessary, the final products being more easily purified by bulb-to-bulb distillation.

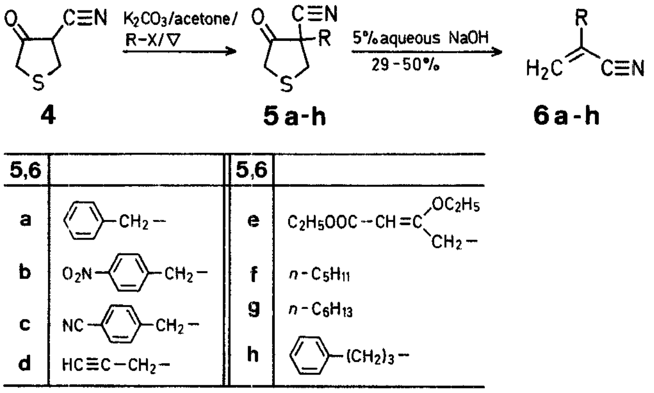

Table. Acrylonitriles **6a–h** prepared

Product	Yield[a] [%]	b.p. [°C]/torr or m.p. [°C]	Molecular formula[b] or Lit. data	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]
6a	49	105–106°/15	110–111°/20[5]	3.52 (s, 2H); 5.68 (m, 1H); 5.87 (s, 1H); 7.1–7.55 (m, 5H)
6b	50	44–46°[d]	$C_{10}H_8N_2O_2$ (188.2)	3.7 (s, 2H); 5.85 (m, 1H); 6.0 (m, 1H); 7.45 (d, *J* = 9 Hz, 2H); 8.2 (d, *J* = 9 Hz, 2H)
6c	47	149–150°/15	$C_{11}H_8N_2$ (168.2)	3.65 (s, 2H); 5.8 (m, 1H); 5.97 (s, 1H); 7.4 (d, *J* = 9 Hz, 2H); 7.7 (d, *J* = 9 Hz, 2H)
6d	29	120°/760	C_6H_5N (91.1)	2.3 (m, 1H); 3.2 (m, 2H); 6.05 (m, 1H); 6.15 (m, 1H)
6e	31	131–133°/50	$C_{11}H_{15}O_3N$ (209.3)	1.3 (t, *J* = 7 Hz, 3H); 1.35 (t, *J* = 7 Hz, 3H); 3.75 (m, 2H); 3.9 (q, *J* = 7 Hz, 2H); 4.15 (q, *J* = 7 Hz, 2H); 5.15 (s, 1H); 5.9 (s, 1H); 5.95 (s, 1H)
6f	43	110–112°/50	77–78°/25[3]	0.9 (t, 3H); 1.1–1.7 (m, 6H); 2.15 (m, 2H); 5.65 (m, 1H); 5.8 (s, 1H)
6g	41	114–116°/50	–[e]	0.9 (t, 3H); 1.1–1.8 (m, 8H); 2.2 (m, 2H); 5.68 (m, 1H); 5.8 (s, 1H)
6h	39	118–119°/15	$C_{12}H_{13}N$ (171.2)	1.9 (m, 2H); 2.2 (m, 2H); 2.65 (t, *J* = 7 Hz, 2H); 5.65 (s, 1H); 5.8 (s, 1H); 7.1–7.4 (m, 5H)

[a] Yields are not optimized and are given for isolated products after bulb-to-bulb distillation or crystallization.

[b] Satisfactory microanalyses obtained: C ± 0.29, H ± 0.28, N ± 0.3.

[c] Recorded at 80 MHz.

[d] Recrystallized from *n*-pentane.

[e] Ref.[4], not reported.

The crude **5a–h** on exposure to 5% aqueous sodium hydroxide in a two phase water/ether system at room temperature underwent a hydroxide ion-promoted fragmentation which proceeded through a series of inverse Dieckmann-Michael reactions, resulting in a clean formation of the α-substituted acrylonitriles **6a–h** (Table).

The mild conditions involved and the good overall yields make this sequence a novel and convenient route to α-substituted acrylonitriles **6**, a class of extremely useful compounds. These findings confirm and further extend the versatility of this strategy, which we have already applied to the synthesis of α-alkyl-α,β-unsaturated esters[8,9] and to α-alkyl-α,β-unsaturated cyclic ketones[10].

4-Cyano-3-oxotetrahydrothiophene (4):

To a solution of sodium methoxide prepared from sodium metal (13.2 g, 0.57 mol) in methanol (200 ml), methyl thioglycolate (21.6 g, 0.41 mol) is added dropwise at 0 °C. Then neat, freshly distilled acrylonitrile (43 g, 0.41 mol) is added and the mixture is heated at reflux for 1 h. Most of the solvent is removed in vacuo (15 torr), the mixture is diluted with water (100 ml) and extracted with ether (1 × 25 ml). The aqueous phase is acidified with 10% hydrochloric acid and extracted with ether (4 × 25 ml). Evaporation of the dried (magnesium sulfate) extracts gives **4** as a solid; yield: 12.8 g (50%); m.p. 71–72 °C (ether) (Lit.[6], m.p. 72 °C; yield: 58%).

I.R. ($CHCl_3$): $\nu = 2260, 1760\,cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$/TMS): $\delta = 3.5$ ppm (m, 5H).

Acrylonitriles 6; General Procedure:

To a suspension of anhydrous potassium carbonate (30 mmol) and compound **4** (10 mmol) in dry acetone (20 ml), is added the alkyl halide (10 mmol) and the mixture is refluxed for the appropriate time (T.L.C. control, eluent: diethyl ether/hexane, 1/2). After cooling the mixture is filtered and the solvent removed at 25 torr. The residue is dissolved in ether (30 ml) and vigorously stirred with 5% aqueous sodium hydroxide (50 ml) at room temperature until complete fragmentation (T.L.C. control, eluent: diethyl ether/petroleum ether, 1/4). The organic phase is separated and dried with sodium sulfate. Removal of the solvent leaves a residue which is distilled or crystallized.

Received: March 5, 1985

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