The Electrophilic Addition of Chlorosulfonyl Isocyanate to Ketones. A General Synthesis of β-Keto-nitriles

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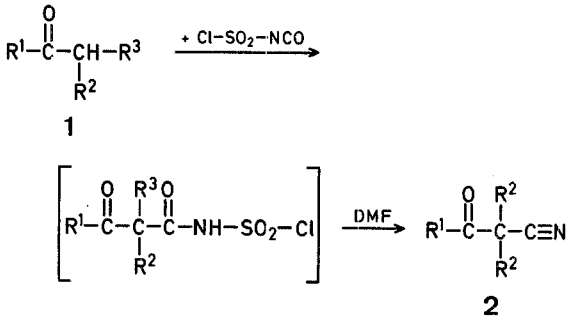
β-Keto-nitriles (α-cyano-ketones) are important intermediates for the synthesis of many heterocyclic compounds, including pyrimidines[1] and pyridones[2]. The simplest method for their preparation appears to be the acylation of nitriles with esters by means of sodium amide in liquid ammonia[3]. The addition of cyanogen chloride to cyclic enamines has been used to prepare cyclic β-keto-nitriles[4]. We wish to report an extremely facile, one-pot synthesis of β-keto-nitriles from simple ketones.

N-Chlorosulfonylcarboxamides are known to be converted into nitriles by treatment with dimethylformamide[5]. Recently we reported[6] a reaction of simple ketones with excess chlorosulfonyl isocyanate (CSI) in which *N*-chlorosulfonyl-β-keto-amides were implicated as intermediates. We have now found that reaction of CSI with a two equivalents of ketones **1** (excess ketone was necessary to decrease polymer formation), followed by treatment with dimethylformamide, gives β-ketonitriles **2** in good yield (Table). Excess starting material **1** can be easily separted from product **2**.



1

2

The β-keto-nitriles **2** were identified by their I.R., ^{1}H-N.M.R., and mass spectra, and by comparison with properties reported in the literature (Table). This new procedure for the preparation of **2** appears to be quite general, and allows the preparation of nitriles inaccessible by the acylation method (e.g. **2c**)[3]. In contrast to the introduction of the cyano group at C-6 of 2-methylcyclohexanone (**1i**) (by the enamine route)[4], our method leads exclusively to the α-cyano-ketone **2i**, which is difficultly accessible in several steps[7].

Reaction of Chlorosulfonyl Isocyanate with Ketones (1a–i); General Procedure:

To a stirred solution of ketone (20 mmol) in dry dichloromethane (10 ml) was added chlorosulfonylisocyanate (10 mmol). The reaction was continued at room temperature or at reflux, and followed by ^{1}H-N.M.R. Upon completion of the reaction, dimethylformamide (22 mmol) was added dropwise and the resulting solution stirred at room temperature for 30 min, then poured into water. The organic layer was separated, washed three times with water, dried (Na_2SO_4), and evaporated in vacuo to give the crude product. Starting ketone **1** and nitrile **2** were separated by distillation (Method A) or by column chromatography on neutral alumina (Method B). Here, separation was achieved by eluting with ether, or ether followed by 1:1 methanol/ether. The products **2** were obtained in > 95% purity as established by ^{1}H-N.M.R.

Table. β-Keto-nitriles (**2**) from Ketones (**1**) and Chlorosulfonyl Isocyanate

	R^1	R^2	R^3	Yield	Method[a]	References
a	C_6H_5	CH_3	H	90	B	[b]
b	C_6H_5	C_2H_5	H	82	B	[c]
c	C_6H_5	CH_3	CH_3	80	A	[d]
d	C_2H_5	CH_3	H	71	B	[b]
e	CH_3	CH_3	CH_3	87	A	[e]
f	CH_3	CH_3	H	63	B	[b]
g	CH_3	—CO—CH_3	H	70	C[f]	[g]
h	—$(CH_2)_3$—		H	54	A	[h]
i	—$(CH_2)_4$—		CH_3	69	B	[i]

[a] See experimental procedure.
[b] Ref.[3].
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[g] Ref.[4].
[h] Ref.[7].

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