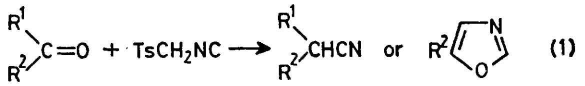
Conversion of Aldehydes and Ketones into Nitriles Containing an Additional Carbon Atom

By Daniel M. Orere and Colin B. Reese*
(*Department of Chemistry, King's College, Strand, London* WC2R 2LS)

Summary Reaction between aldehyde and ketone 2,4,6-tri-isopropylbenzenesulphonyl hydrazones (**6c**) with potassium cyanide in boiling methanol solution gives good yields of the corresponding nitriles (**3**), containing an additional carbon atom.

Apparently no general procedure for the direct conversion of both aldehydes and ketones into nitriles containing an additional carbon atom has been described in the literature. The dehydration of cyanohydrins and the hydrogenation of the resulting unsaturated nitriles constitutes a feasible procedure only in the absence of certain other functions. Recently Oldenziel and van Leusen reported[1] that when ketones (**1**; $R^1,R^2 \neq H$) are treated with tosylmethyl isocyanide (**2**) and an excess of potassium t-butoxide in t-butyl alcohol–1,2-dimethoxyethane solution [reaction (1)], the corresponding nitriles (**3**) are obtained and usually in good yields. If aldehydes (**1**; $R^1 = H$) are treated with (**2**) in the presence of base, oxazole derivatives (**4**) are obtained[2] instead of nitriles.

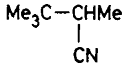


(1) (2) (3) (4)
(from ketones) (from aldehydes)

$$\underset{}{(1)} + \underset{(5)}{ArSO_2NHNH_2} \rightarrow \underset{(6)}{R^1R^2C{=}NNHSO_2Ar} \xrightarrow[MeOH]{KCN} (3) \qquad (2)$$

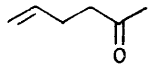
a; Ar = $4\text{-}MeC_6H_4$
b; Ar = $2,4,6\text{-}Me_3C_6H_2$
c; Ar = $2,4,6\text{-}(Me_2CH)_3C_6H_2$

We now report that when aldehydes and ketones are allowed to react with 2,4,6-tri-isopropylbenzenesulphonyl hydrazide[3] (TPSH, **5c**) in tetrahydrofuran or methanol solution at room temperature for 1—2 h and the resulting hydrazone derivatives (**6c**) are heated, under reflux, with an excess of potassium cyanide in methanol solution for 1—2 h, the corresponding nitriles (**3**) are obtained† and may usually be isolated in good yields [reaction (2) and Table]. It is noteworthy that a satisfactory yield of the nitrile (**7**) is obtained from the comparatively hindered ketone pinacolone‡ (expt. 3). Experiments 7 and 8 are of particular interest in that an unsaturated ketone (**8**) and a steroidal keto-alcohol (**10**) may both be converted into the corresponding nitriles [(**9**) and (**11**), respectively] in good yields. Clearly, if the latter two transformations were to be effected *via* cyanohydrin intermediates, the additional functions would need to be protected.

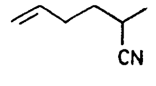


$Me_3C{-}\underset{CN}{\underset{|}{C}}HMe$

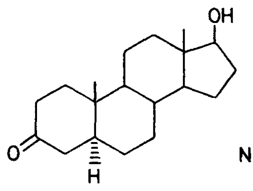
(7)



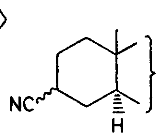
(8)



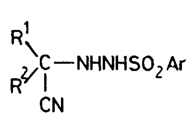
(9)



(10)



(11)



(12)

Table

Exp.	Substrate	Product[a]	B.p./°C at 15 mmHg	Yield[b] (%)
1	Cyclopentanone	C_5H_9CN[c]	62—63	47
2	Cyclohexanone	$C_6H_{11}CN$	69—70	71[d]
3	Pinacolone	(**7**)	38—40	60
4	Heptan-4-one	Pr_2CHCN	65—68	74
5	n-Heptaldehyde	$Me[CH_2]_6CN$	78—80	72
6	n-Octaldehyde	$Me[CH_2]_7CN$	98—100	65
7	(**8**)	(**9**)	48—50	70
8	(**10**)	(**11**)	(m.p. 139—141 °C)	70

[a] All products except (**11**) were shown by g.l.c. to be > 95% pure; they were characterized on the basis of spectroscopic (^1H and ^{13}C n.m.r., i.r., and m.s.) data. [b] This represents, for liquids, the isolated yield after distillation. [c] In this experiment, the hydrazone derivative (**6c**; $R^1,R^2 = -[CH_2]_4-$) was heated with potassium cyanide in *ethanol* solution, under reflux, for 7 h. [d] The isolated yield was 73% starting from pure hydrazone derivative (**6c**; $R^1,R^2 = -[CH_2]_5-$).

The present procedure is related to that described previously by Cacchi *et al.*[4] These workers converted cyclohexanone and heptan-4-one tosyl hydrazones (**6a**; $R^1,R^2 = -[CH_2]_5-$ and $R^1 = R^2 = Pr^n$, respectively) into their hydrogen cyanide adducts (**12**; Ar = $4\text{-}MeC_6H_4$) and

---

† In a typical experiment (see Table, expt. 4), heptan-4-one (**1**; $R^1 = R^2 = Pr^n$; 20 mmol) and TPSH (**5c**; 25 mmol) were stirred together in tetrahydrofuran (30 ml) solution at room temperature. After 2 h, the products were evaporated under reduced pressure and the residue [crude (**6c**; $R^1 = R^2 = Pr^n$)] redissolved in methanol (30 ml). Potassium cyanide (60 mmol) was then added, and the mixture was heated, under reflux, for 2 h and then cooled. Water (20 ml) and dichloromethane (60 ml) were added. The bottom layer was separated and extracted in turn with aqueous sodium hydrogen carbonate, dilute hydrochloric acid and water. The dried ($MgSO_4$) organic layer was concentrated under reduced pressure at room temperature and then distilled to give the product (**3**; $R^1 = R^2 = Pr^n$).

‡ The nitrile synthesis involving $TsCH_2NC$ (**2**) [reaction (1)] leads (ref. 1) to a much poorer yield of (**7**) from pinacolone.

heated the latter at 180 °C in decalin solution to give the corresponding nitriles (**3**). However, in a later paper, they reported[5] that, under these vigorous conditions, elimination of hydrogen cyanide to regenerate the tosyl hydrazones (**6a**) competes with nitrile formation. In devising the present nitrile synthesis, we decided that it would be undesirable to attempt to isolate the hydrogen cyanide adducts (**12**) which might, in any case, be in equilibrium with the hydrazone derivatives (**6**) in solution. Thus, we find that when cyclohexanone tosyl hydrazone (**6a**; $R^1,R^2 = -[CH_2]_5-$) is heated with an excess of potassium cyanide in boiling ethanol solution for 24 h, the corresponding nitrile (**3**; $R^1,R^2 = -[CH_2]_5-$) may be isolated from the products in 61% yield. As TPSH (**5c**) undergoes thermal decomposition[3] at a rate *ca.* 380 times that of tosyl hydrazide (**5a**), the hydrogen cyanide adducts of 2,4,6-tri-isopropylbenzenesulphonyl hydrazones [**12**; Ar = 2,4,6-$(Me_2CH)_3$-C_6H_2] would be expected to decompose much more readily than the corresponding tosyl hydrazone adducts (**12**; Ar = 4-MeC_6H_4). As anticipated,[3] the conversion of cyclohexanone 2,4,6-trimethylbenzenesulphonyl hydrazone (**6b**; $R^1,R^2 = -[CH_2]_5-$) into (**3**; $R^1,R^2 = -[CH_2]_5-$) occurs at an intermediate rate: the latter compound may be isolated from the products in 61% yield when (**6b**; $R^1,R^2 = -[CH_2]_5-$) is heated with an excess of potassium cyanide in boiling ethanol solution for 7 h.

Finally, it is hoped that a systematic study, now in progress, of the reaction between nucleophiles other than cyanide ion with 2,4,6-tri-isopropylbenzenesulphonyl hydrazones (**6c**) will lead to the development of a number of other valuable synthetic methods.

(*Received*, 17*th January* 1977; *Com.* 038.)

---

[1] O. H. Oldenziel and A. M. van Leusen, *Tetrahedron Letters*, 1973, 1357.

[2] A. M. van Leusen, B. E. Hoogenboom, and H. Siderius, *Tetrahedron Letters*, 1972, 2369.

[3] N. J. Cusack, C. B. Reese, and B. Roozpeikar, *J.C.S. Chem. Comm.*, 1972, 1132; N. J. Cusack, C. B. Reese, A. C. Risius, and B. Roozpeikar, *Tetrahedron*, 1976, **32**, 2157.

[4] S. Cacchi, L. Caglioti, and G. Paolucci, *Chem. and Ind.*, 1972, 213.

[5] S. Cacchi, L. Caglioti, and G. Paolucci, *Synthesis*, 1975, 120.