Cuprous Cyanide Catalysis for Alkylations of Ethyl *s*-Butylidenecyanoacetate

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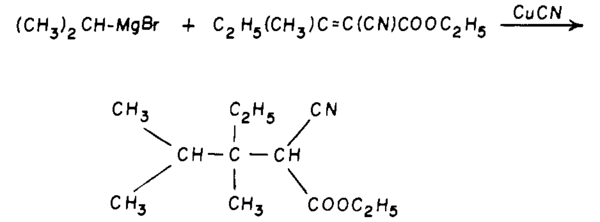
Cuprous cyanide has proved to be a most effective catalyst for the promotion of 1,4-addition of Grignard reagents to ethyl *s*-butylidenecyanoacetate.

THE UNCATALYZED ADDITION of small Grignard reagents to ethyl *s*-butylidenecyanoacetate (and similar substrates) has been reported (*1-4*). Rabjohn, Phillips, and DeFeo (*5*) obtained better yields of addition product when cuprous iodide as catalyst and inverse addition were employed.

Table I. Grignard Additions to Ethyl *s*-Butylidenecyanoacetate[a]

Run	Method[b]	Catalyst (3.75 G.)	Product B.P., ° C. (mm. Hg)	Grams	%
1	PN	None	130-34(8)[c]	44.4	28.1[d]
2	PI	None	118-35(9)	63.5	40.1
3	PN	CuCl	120-30(7)	46.6	29.4
4	PI	CuCl	115-31(10-9)	75.9	47.9
5	PI	CuBr	142-45(19-17)	72.7	45.9[e]
6	PI	CuI	120-27.5(5)	88.4	55.8[e]
7	PI	CuCN	127-30(6)	103.7	65.5[f]
8	PI	$FeCl_3$	111-27(6)	49.1	31.0[g]
9	PI	Hg_2I_2	116-37(12)	65.6	41.5[g]
10	PI	$CoCO_3$	105-20(3)	65.8	41.6[g]
11	PI	AgCN	107-29(7)	66.8	42.2[g]
12	PI	KCN	107-32(10-8)	69.8	44.1[g]
13	BI	CuCN	100-10(8-9)	52.3	31.0[h]
14	AI	CuCN	149-51(9-10)	145.1	80.7[i]

[a] Grignard reagent from 0.90 mole of halide added to 0.75 mole of ethyl *s*-butylidenecyanoacetate. Product distilled through 60-cm., heated Vigreux column. [b] P isopropyl bromide, B isobutyl bromide, A isoamyl bromide, N normal addition, I inverse addition. [c] Reported (*2*) b.p. 147-52° (21 mm.), n_D^{25} 1.4497. [d] 33.5% yield obtained following Prout (*2*). [e] Better of two runs. [f] Three other runs in range 63.6 to 65.5%. [g] Runs 8 to 12 are single runs, showing inertness for these salts. [h] Prout (*2*) reported b.p. 148-50° (15 mm.), n_D^{25} 1.4449, and 8.5% yield. [i] Virginia N. Aguilar using Prout's procedure (*2*) reported a 41% yield b.p. 157° (15 mm.), n_D^{25} 1.4445. Anal. Calcd. for $C_{14}H_{25}O_2N$: C, 70.25; H, 10.53. Found: C, 70.21; H, 10.66.



$$(CH_3)_2CH\text{-}MgBr + C_2H_5(CH_3)C{=}C(CN)COOC_2H_5 \xrightarrow{CuCN} (CH_3)_2CH\text{-}C(C_2H_5)(CH_3)\text{-}CH(CN)COOC_2H_5$$

We have reinvestigated the reaction of isopropylmagnesium bromide with ethyl *s*-butylidenecyanoacetate employing catalytic amounts of several salts. Yield was improved only with cuprous salts. The increase in yield was accompanied by decreases in the reduction product (ethyl 2-cyano-3-methylpentanoate) and in polymer formation (residue after distillation).

In general, the Grignard reagent from 0.90 mole of isopropyl bromide was added to an ethereal solution of 0.75 mole of ethyl *s*-butylidenecyanoacetate (*3*) and 3.75 grams of catalyst below 20° C. This procedure was substantially that of Rabjohn, Phillips, and DeFeo (*5*). Selected results are incorporated in Table I.

Because many results were based on only one run, the yields should be considered as having a precision of about ±5%. However, four runs using cuprous cyanide under optimum conditions ranged between 63.6 and 65.5%. The lower efficiency of other cuprous salts is apparently related to solubility or dissociation in ether. The other catalysts (except ferric chloride) seemed completely neutral and the average of yields from runs 1, 9, 10, 11, and 12 (41.9%) represents the average for noncatalyzed runs.

Cuprous cyanide catalysis resulted in yield improvement from 8.5 to 31% with isobutylmagnesium bromide (run 13, Table I) and from 41 to 81% with isoamylmagnesium bromide (run 14, Table I).

Table II. Acids from Hydrolysis of Ethyl *tert*-Alkylcyanoacetates

$$R\text{-}C(C_2H_5)(CH_3)\text{-}CH(CN)(COOC_2H_5) \xrightarrow{KOH} R\text{-}C(C_2H_5)(CH_3)\text{-}CH_2COOH$$

Acid[a] R-	B.P., ° C. (Mm.Hg)	n_D^{25}	Yield, %	Neutralization Equivalent Calcd.	Found
$(CH_3)_2CH$-	133-34(14)[b]	1.4463[b]	94.1	. . .	
$(CH_3)_2CH$-CH_2	133-34(10)	1.4415	92.9	172.3	174.8[c]
$(CH_3)_2CH$-CH_2CH_2-	145-45(10)	1.4418	92.4	186.3	185.1[d]

[a] Cyanoester (0.25 mole) heated under reflux for 50 hours with 1.8 moles potassium hydroxide in 350 ml. ethylene glycol to effect hydrolysis and decarboxylation. Products fractionated through 60-cm., heated Vigreux column. [b] Prout (*2*) has reported b.p. 138-40° (15 mm.), n_D^{25} 1.4460. [c] Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 70.09; H, 11.60. [d] Calcd. for $C_{11}H_{22}O_2$: C, 70.90; H, 11.91. Found: C, 70.80; H, 12.12.

Hydrolysis of the three *tert*-alkylcyanoacetate esters by long heating with potassium hydroxide in ethylene glycol resulted in high yields of the anticipated quaternary acids (Table II).

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The Preparation of 2,2-Dialkyl-3-nitropropionic Acids

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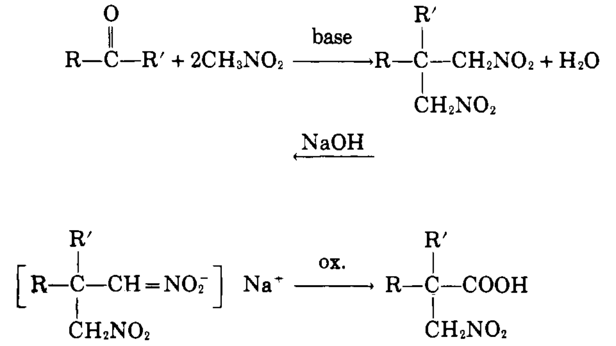
Several 2,2-dialkyl-3-nitropropionic acids were prepared by the nitric acid oxidation of the monoalkali salts of 2,2-dialkyl-1,3-dinitropropanes. The dinitro compounds were obtained conveniently by the base-catalyzed condensation of aliphatic ketones with nitromethane.

NITROPIVALIC ACID, 2,2-dimethyl-3-nitropropionic acid, has been reported in the literature once (*9*), but there appears to be no mention of any other 2,2-dialkylnitropropionic acid. The preparation noted for nitropivalic acid (*9*) consisted of the addition of hydrogen cyanide to 2-methyl-1-nitropropene followed by hydrolysis of the nitronitrile. No experimental details were given nor was there any mention of yields or physical properties.

Since nitro acids of this type were needed, consideration was given to alternate routes which might be more convenient or more general. Among these were the liquid-phase nitration of pivalic acid and the reaction of iodo- or bromopivalic esters with silver nitrite or sodium nitrite (*5*), but both were rejected as being infeasible, the first because of the known difficulty of nitrating neopentane (*4*) and aliphatic acids (*10*), and the second because of the reported inability to obtain nitro compounds from the reaction of neopentyl iodide with silver nitrite (*6*).

The method finally chosen was the oxidation of monosalts of 2,2-dialkyl-1,3-dinitropropanes:



$$R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}R' + 2CH_3NO_2 \xrightarrow{\text{base}} R{-}\underset{\underset{\displaystyle CH_2NO_2}{|}}{\overset{\overset{\displaystyle R'}{|}}{C}}{-}CH_2NO_2 + H_2O$$

$$\xleftarrow{\text{NaOH}}$$

$$\left[R{-}\underset{\underset{\displaystyle CH_2NO_2}{|}}{\overset{\overset{\displaystyle R'}{|}}{C}}{-}CH{=}NO_2^-\right] Na^+ \xrightarrow{\text{ox.}} R{-}\underset{\underset{\displaystyle CH_2NO_2}{|}}{\overset{\overset{\displaystyle R'}{|}}{C}}{-}COOH$$

Many 2,2-dialkyl-1,3-dinitropropanes can be obtained readily by the reaction of ketones with nitromethane (*1, 2, 7, 8*). Preparation of the monosalts is relatively straightforward using stoichiometric amounts of sodium hydroxide. The authors thought, at first, that Nef reaction (*11, 13*) on the salts might lead to nitroaldehydes which then could be oxidized further to the acids. However, treatment of the nitrosalts with hydrochloric or sulfuric acid, under a variety of conditions, invariably led to regeneration of the dinitro compounds as the principal reaction. This result is clearly in agreement with the mechanism of the Nef reaction postulated by van Tamelen (*17*) and by Hawthorne (*3*) where the slow step in the reaction is attack by water on the carbon bonded to a protonated acinitro group. In the case of a neopentyl nitro compound, isomerization of the acinitro to the nitro would be expected to be much faster than a sterically hindered nucleophilic attack by solvent.

Since Shechter has studied the effect of many oxidizing agents on salts of mononitro compounds (*15, 16*), and has reported that such salts can be oxidized with potassium permanganate to acids (*16*), then, the use of strong oxidizing agents was considered. A brief investigation of potassium permanganate led only to inconclusive results. However, when nitric acid was used as the oxidant, the nitrosalts were converted smoothly into the desired acids. Table I lists the melting points and analyses of the compounds isolated. The oxidation appears to be general and probably can be used to convert any primary nitroparaffin containing no other readily oxidizable groups to the corresponding acid.

The reaction of cyclohexanone with nitromethane is reported (*7*) to give a very low yield of 1,1-bis(nitromethyl)-cyclohexane with the principal product being a condensed product (*12*), which has recently been identified by Noland and Sundberg (*14*). The use of diethylamine as the condensing agent and long reaction times at room temperature made it possible to obtain a crude material which gave an infrared spectrum consistent with 1,1-bis(nitromethyl)-cyclohexane, but all attempts to obtain a pure dinitro compound failed. However, the conversion of the crude material to a salt, followed by oxidation, gave a low yield of 1-nitromethylcyclohexane carboxylic acid.

EXPERIMENTAL

Condensation of Ketones with Nitromethane. In a typical preparation, 2 moles of nitromethane, 1 mole of ketone, and 1 mole of diethylamine were mixed together and allowed to stand for a week or more over magnesium sulfate in a

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