[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

THE PREPARATION OF β-KETO ESTERS FROM NITRILES AND α-BROMOESTERS[1]

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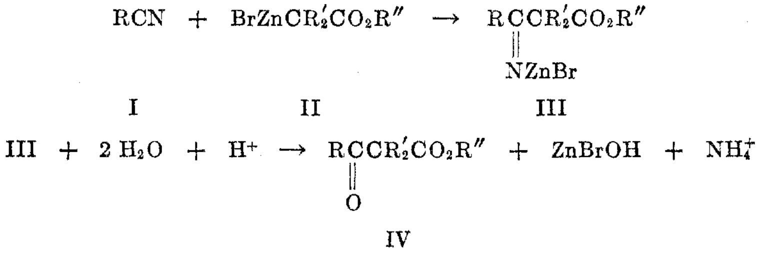
The reaction of a nitrile with the zinc reagent from an α-bromoester to give a β-keto ester was reported by Blaise (1–3) more than fifty years ago; however, there appears to be only one subsequent report (4) of the utilization of this reaction. Since the method constitutes a one-step synthesis of higher aliphatic β-keto esters from stable and accessible starting materials, the present investigation has been directed towards delineation of its scope and applicability as a synthetic tool.

The reaction is considered to proceed by a mechanism (1) analogous to that of the Reformatsky reaction (5), involving an initial condensation of the nitrile (I) with the bromozinc reagent (II) formed from the reaction of zinc with an α-bromoester. The intermediate bromozincimino ester (III) is finally hydrolyzed in acidic solution to give a β-keto ester (IV) as the product.



$$\underset{\text{I}}{\mathrm{RCN}} + \underset{\text{II}}{\mathrm{BrZnCR'_2CO_2R''}} \rightarrow \underset{\text{III}}{\mathrm{R}\underset{\underset{\mathrm{NZnBr}}{\|}}{\mathrm{C}}\mathrm{CR'_2CO_2R''}}$$

$$\text{III} + 2\,\mathrm{H_2O} + \mathrm{H^+} \rightarrow \underset{\text{IV}}{\mathrm{R}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{CR'_2CO_2R''}} + \mathrm{ZnBrOH} + \mathrm{NH_4^+}$$

The present study has been concerned with determining optimum conditions and with the effects of structure on the course of the reaction. Results obtained by varying the groups R, R′, and R″ are assembled in Table I.

Esters of bromoacetic acid gave no isolable yield of β-keto ester, whereas esters of α-bromopropionic acid and α-bromoisobutyric acid gave β-keto esters in yields varying from 30 to 60%. In condensations with like nitriles, ethyl α-bromoisobutyrate gave somewhat better yields than ethyl α-bromopropionate. Thus, the presence of one alkyl group in the *alpha* position of the bromoester seems to be a requisite for successful condensation with nitriles under the most favorable conditions discovered. A second substitution improves the yield to a smaller extent.

Since hindrance in the ester appears to favor the desired condensation, reactions were carried out with esters of secondary and tertiary alcohols. Although the tertiary esters proved to be too unstable to permit satisfactory fractional dis-

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tillation, yields were improved significantly by use of esters of 2-butanol or 3-pentanol. These esters gave yields of 45–58% in instances where yields of ethyl esters were 30–35%. Yields obtainable with the *sec*-butyl esters make the reaction of considerable synthetic interest.

TABLE I

PREPARATION OF β-KETO ESTERS

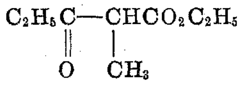
β-KETO ESTER	B.p., °C./mm. n_D^{25}	REACTANT RATIO[a]	ONDITIONS[b]	YIELD,[c] %
Ethyl α-acetylpropionate[d]	68–75/12	1:1.5:1	40 (5)	16
Ethyl α-benzoylisobutyrate[e]	132–135/13	1:1.5:1	40 (5)	50
		1:1.5:1.5	45 (45)	57
Ethyl α-benzoylpropionate[f]	140–143/12	1:1.5:1	40 (5)	40
Ethyl benzoylacetate[g]		1:1.5:1	40 (5)	0
Ethyl α-isocaproylisobutyrate[h]	115–120/13	1:1.5:1	40 (5)	49
	1.4307			
Ethyl α-isocaproylpropionate[i]	113–115/12	1:1.5:1	40 (5)	38
	1.4288			
Ethyl α-*n*-caproylpropionate[j]	118–120/12	1:1.5:1.5	45 (45)	33
	1.4312	1:3:3	20 (50)	36
		1:1:1.8[k]	45 (45)	30
sec-Butyl α-*n*-caproylpropionate[l]	133–134/11.5	1:1.5:1.5	45 (45)	52
	1.4302	2:1:1	45 (45)	37
3-Pentyl α-*n*-caproylpropionate[m]	125–127/3.9	1:1.5:1.5	45 (45)	57
	1.4333			
3-Pentyl α,γ-dimethyl-β-oxocaprate[n]	138–139/1.6	1:1.5:1.5	45 (45)	29
	1.4381			
3-Pentyl 2,5-dimethyl-3-oxohendecanoate[o]	134–136/0.6	1:1.5:1.5	45 (1140)[p]	38
	1.4403			
3-Pentyl α-*n*-caproylacetate		1:1.5:1.5	45 (45)	0

[a] Ratio indicated is nitrile:bromoester:zinc. [b] The first quantity is time of reaction in mins.; the second quantity (in parentheses) is time of hydrolysis in mins. [c] Some of the yields are the average of several runs. The yield is based on the limiting reagent. [d] Literature b.p. 75.5–76.5°/12 mm., von Auwers, *Ber.*, **46,** 504 (1913). [e] Literature b.p. 152°/20 mm., Ref. (3). [f] Literature b.p. 162–163°/18 mm., Hope and Perkin, *J. Chem. Soc.*, **95,** 2045 (1909). [g] Meyer and Tögel, *Ann.*, **347,** 78 (1906), reported for this compound b.p. 148–149°/12 mm., n_D^{18} 1.5317. [h] Literature b.p. 121–124°/20–22 mm., Ref. (1). [i] Literature b.p. 117–118°/13 mm., Locquin, *Bull. soc. chim.*, [3] **31,** 599 (1904). [j] Literature b.p. 128–129°/12 mm., Locquin, *Bull. soc. chim.*, [3] **31,** 596 (1904). [k] The bromoester was added dropwise over 30 minutes. [l] Calc'd for $C_{13}H_{24}O_3$: C, 68.39; H, 10.59. Found: C, 68.15; H, 10.75. [m] Calc'd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.11; H, 10.58. [n] Calc'd for $C_{17}H_{32}O_3$: C, 71.78; H, 11.34. Found: C, 72.03; H, 11.69. [o] Calc'd for $C_{18}H_{34}O_3$: C, 72.44; H, 11.48. Found: C, 72.55; H, 11.66. [p] The yield was 3% when hydrolysis was continued for only 45 minutes.

The chief limitation of the use of *sec*-butyl esters for this condensation appears to be their thermal instability at distillation temperatures above about 140°. Efforts to *trans*-esterify these esters with ethanol were unsuccessful. Without catalyst, reaction was excessively slow, and with acid catalysis the yield was poor. Although Bader and Vogel (6) have reported the very rapid, uncatalyzed *trans*-esterification of β-keto esters, this occurred in presence of excess keto ester. The very slow *trans*-esterification observed by us, in presence of excess alcohol, is consistent with the report by Carroll (7) that this *trans*-esterification is first order with respect to ester and zero order with respect to alcohol.

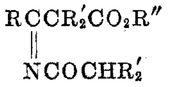
Although aromatic and normal aliphatic nitriles give comparable yields (*Cf.* benzonitrile and capronitrile), acetonitrile gave poor yields. This suggests that self-condensation of the nitrile becomes a serious side reaction in the latter instance, as is the case in the Grignard reaction with this nitrile (8). Since hindrance in the ester moiety improves the yield of condensation with nitrile, hindrance in the nitrile would be expected to be unfavorable. The data on 3-methylnonanoic nitrile and 2-methyloctanoic nitrile fulfill this expectation.

Although the nature of the by-products in this reaction renders difficult a complete separation and characterization of them, evidence has been obtained that side reactions are those that would be expected from studies of other reactions involving organometallic intermediates, especially the Reformatsky reaction (5). The only evidence of self-condensation of the nitrile moiety is the lower yield obtained with acetonitrile, and estimates of material balance indicate that this side reaction is not important in other cases, unless an excess of nitrile be used. In most runs, some nitrile was recovered, although an excess of bromoester and zinc was used. Self-condensation of the ester appears to be an important side reaction. This is indicated by the improved yields obtained with hindered esters, also by the isolation of ethyl α-propionylpropionate (V) and of *sec*-butyl α-propionylpropionate.



$C_2H_5\underset{\underset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle CH_3}{|}}{C}HCO_2C_2H_5$

V



$R\underset{\underset{\displaystyle NCOCHR'_2}{\|}}{C}CR'_2CO_2R''$

VI

No evidence has been secured for condensation of the bromoester in a Wurtz type of reaction (*cf.* Ref. 5). Horeau and Jacques (4) have reported that further condensation of the bromozincimino ester is an important side reaction, and have formulated the product as in VI. Although their evidence for this specific type of structure seems hardly conclusive, some type of further condensation appears to be the major side reaction, for there is always a large distillation residue which cracks to ill-defined products on heating. Hydrolysis with boiling 18 *N* sulfuric acid of the residue from distillation of *sec*-butyl caproylpropionate gave a relatively good recovery of ethyl *n*-amyl ketone. This indicates that further condensation does not occur primarily *via trans*-metalation of the imino ester.

Experiments designed to determine the optimum reaction conditions and ratio of reactants gave results consistent with expectations based on the side reactions found to occur. An excess of zinc and bromoester are advantageous, and a rather brief reaction time discourages further condensation of the product. The latter was emphasized by Horeau and Jacques (4). Except when a β-methylnitrile was used, cleavage of the imino ester was accomplished by stirring for 45 minutes at room temperature the two-phase solution resulting after addition of dilute sulfuric acid to the reaction mixture. Stirring for much longer periods under these conditions did not appreciably hydrolyze the β-keto ester, and a 19-hour period was used for the hydrolysis when 3-methylnonanoic nitrile was used. Hindrance exerted by a β-methyl substituent has been observed in other connections (9).

EXPERIMENTAL[3]

Preparation of β-keto esters. An illustration of the procedure regarded as most favorable is described. Cupric bromide (0.1 g.) and 9.7 g. (0.15 mole) of freshly-sandpapered zinc foil were added to a three-necked flask, followed by 300 ml. of dried benzene. To dry the apparatus and contents, 75 ml. of benzene was slowly distilled from the flask. To the flask were then added rapidly 0.10 mole of nitrile and 0.15 mole of bromoester. The reactants were heated at reflux for 45 minutes, after which the solution was cooled for 15 minutes in an ice-bath, 100 ml. of ice-cold 12 *N* sulfuric acid was added, and stirring was continued for 45 minutes at room temperature. After separation of the two phases, the aqueous layer was diluted with water and extracted with benzene. The two benzene solutions were then washed separately with water, saturated sodium bicarbonate solution, and again with water, then combined and dried over sodium sulfate. After the solvent had been removed by flash-distillation, the material was fractionated. The usual fractions consisted of small amounts of reduced ester (corresponding to bromoester), recovered nitrile, and the β-keto ester from condensation of the reduced ester, in addition to the desired β-keto ester.

The various other procedures employed differed from that described only in the reactant ratios and in the reaction and hydrolysis times; this is further described in Table I.

The recovered nitrile fraction was identified by comparison of its boiling point with that of the starting material and by the characteristic odor. Reduced bromo esters were isolated only for the higher-boiling esters of secondary alcohols. *3-Pentyl*[4] *acetate* boiled at 49–52°/30 mm. [Lit. (10) b.p. 133°], *3-pentyl propionate* at 44–46°/12 mm., n_D^{25} 1.4029. The keto ester condensation products of the reduced bromo esters were identified by their boiling points, and by the characteristic blue-violet color imparted by ferric chloride (11). The boiling point of *ethyl α-propionylpropionate* was 85–88°/12 mm. [Lit. (12) b.p. 88–90°/12 mm.]. *sec-Butyl α-propionylpropionate* boiled at 80–92°/4.5 mm.

Characterization of the β-keto esters. The products isolated from the reaction of esters of α-bromopropionic acid gave in all cases tested the blue-violet color with ferric chloride described by Henecka (11) as typical for α-alkyl-β-keto esters. Copper chelates of these keto esters could not be isolated although color change indicated their formation. With both ethyl α-*n*-caproylpropionate and *sec*-butyl α-*n*-caproylpropionate the corresponding 5-pyrazolone, *3-n-amyl-4-methyl-1-phenyl-5-pyrazolone*, was prepared by the method of von Auwers (13). *sec*-Butyl α-*n*-caproylpropionate (4.56 g.) was heated with 2.16 g. of phenylhydrazine for two hours on a steam-bath, then for six hours in an oil-bath at 180°. Distillation gave 3.2 g. (66%) of pyrazolone, b.p. 187–189°/1.6 mm. It crystallized slowly from hexane, m.p. 80.4–82.9°. Similarly, 4.00 g. of ethyl α-*n*-caproylpropionate and 2.16 g. of phenylhydrazine gave, after 4 hours heating at 180°, 4.06 g. (83%) of the 5-pyrazolone.

Anal. Calc'd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47.
Found: C, 73.65; H, 8.27; N, 11.53.

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[3] All melting points are corrected. All boiling points are uncorrected; pressures above 5 mm. were measured with a Zimmerli gage, those below 5 mm. with a tilting McLeod gage. Unless otherwise specified, all distillations were through an 18″ Podbielniak type column with simple tantalum wire spiral, heated jacket, and partial reflux head. Microanalyses were by the Microanalytical Division, Department of Chemistry and Chemical Engineering, University of Calif.

[4] For convenience, the 1-ethylpropyl radical is referred to as "3-pentyl" throughout this paper.

Acid decomposition of distillation residue from keto ester isolation. The residue (10 g.) from the distillation of the product in the synthesis of *sec*-butyl α-*n*-caproylpropionate was refluxed for two hours with 35 ml. of 18 *N* sulfuric acid. The cooled reaction mixture was diluted with water and extracted with benzene. The benzene solution was washed with water, saturated sodium bicarbonate solution, and water, then dried over sodium sulfate. Fractionation yielded 3.3 g. of *n*-amyl ethyl ketone, b.p. 59–61°/14 mm., n_{D}^{25} 1.4142 [Lit. (14) b.p. 170°, n_{D}^{20} 1.4156]. The *semicarbazone*, prepared according to Shriner and Fuson (15), melted at 111.0–112.0° [Lit. (16) m.p. 112°].

tert-Butyl α-isocaproylpropionate. A solution of 9.6 g. of isocapronitrile, 30.4 g. of *tert*-butyl α-bromopropionate, and 6.5 g. of zinc in 210 ml. of benzene was heated at reflux for 25 minutes, then cooled in an ice-bath. After 100 ml. of 6 *N* sulfuric acid had been added with stirring, the two layers were treated as in the above-described preparation of β-keto esters. Upon fractional distillation, 2.1 g. of unreacted nitrile and 5.1 g. of starting bromoester were recovered, together with 5.2 g. (23%) of *tert*-butyl isocaproylpropionate; b.p. 110–113°/7 mm., n_{D}^{25} 1.4266.

Anal. Calc'd for $C_{13}H_{24}O_3$: C, 68.39; H, 10.59.

Found: C, 68.43; H, 10.66.

tert-Butyl α-bromopropionate. This bromo ester was prepared by a modification of the method of Hauser (17). To 175.9 g. of dried propionic acid was added with stirring 225.7 g. of phophorus tribromide. After the resultant solution had been heated for 30 minutes at 50–60°, 399 g. of bromine was slowly added while the temperature was kept at 60–70°. After all the bromine had been added the temperature was raised to 90–100° for 30 minutes. Decantation and distillation of the upper layer in a Claisen flask gave 370 g. (72%) of crude α-bromopropionyl bromide, b.p. 55–70°/20 mm. To the stirred acyl bromide was added 206.4 g. of dimethylaniline, then 127.2 g. of *tert*-butyl alcohol during 20 minutes, while the solution was cooled in an ice-bath. After standing overnight at room temperature the liquid was decanted and the precipitated salt was dissolved in 1000 ml. of water, which was extracted with benzene. The ester and benzene solution were combined and washed four times with ice-cold sulfuric acid, once with saturated sodium bicarbonate, and once with water. After it had been dried over sodium sulfate, the benzene was removed by flash distillation and the product was fractionated to give 191.8 g. (39%, over-all) of *tert*-butyl α-bromopropionate; b.p. 80.3–83°/30 mm., n_{D}^{25} 1.4370.

Anal. Calc'd for $C_7H_{13}BrO_2$: C, 40.21; H, 6.27.

Found: C, 40.66; H, 6.35.

sec-Butyl α-bromopropionate. A mixture of 145 g. of ethyl α-bromopropionate, 177.5 g. of *sec*-butyl alcohol, and 4.8 ml. of concentrated sulfuric acid was heated beneath a fractionating column; the temperature of the head was regulated to 80–83°. After *ca.* 65 ml. of distillate had been collected the reaction mixture was poured while warm into 800 ml. of water and was extracted twice with benzene. The combined extracts were washed with portions of water, saturated sodium bicarbonate solution, and again water, then dried over sodium sulfate. Fractionation of the product gave 136.6 g. (82%) of *sec*-butyl α-bromopropionate; b.p. 97.0–98.3°/39 mm., n_{D}^{25} 1.4420.

Anal. Calc'd for $C_7H_{13}BrO_2$: C, 40.21; H, 6.27.

Found: C, 40.01; H, 6.12.

3-Pentyl α-bromopropionate. A mixture of 72.4 g. of ethyl α-bromopropionate, 105.7 g. of synthetic 3-pentanol, and 2.4 ml. of concentrated sulfuric acid was treated as in the preparation of *sec*-butyl α-bromopropionate. Ether was used in extractions to aid in the recovery of 3-pentanol, which was collected in a Dry Ice trap. The yield of 3-pentyl α-bromopropionate was 69.0 g. (77%), b.p. 98–100°/30 mm., n_{D}^{25} 1.4453.

Anal. Calc'd for $C_8H_{15}BrO_2$: C, 43.06; H, 6.78.

Found: C, 42.92; H, 6.82.

3-Pentyl bromoacetate was prepared from 83.5 g. of ethyl bromoacetate, 124.1 g. of 3-

pentanol, and 3.0 ml. of concentrated sulfuric acid by the procedure described for preparation of 3-pentyl α-bromopropionate; yield 93.2 g. (89%), b.p. 98–100°/28 mm., n_D^{25} 1.4489.

Anal. Calc'd for $C_7H_{13}BrO_2$: C, 40.28; H, 6.27.

Found: C, 40.05; H, 6.17.

α-Methylcaprylic acid was prepared *via* the usual malonic ester synthesis (18) from 24.2 g. of sodium, 191.4 g. of diethyl methylmalonate, and 165.1 g. of *n*-hexyl bromide. The yield of *diethyl n-hexylmethylmalonate* was 175.4 g. (68%), b.p. 132–133°/6.5 mm., n_D^{25} 1.4280.

Anal. Calc'd for $C_{14}H_{26}O_4$: C, 65.07; H, 10.14.

Found: C, 65.14; H, 10.28.

Saponification and decarboxylation gave 93% yield of α-methylcaprylic acid, b.p. 137–139°/14 mm., n_D^{25} 1.4281 [Lit. (19), b.p. 136°/17 mm.]

α-Methylcaprylamide was prepared by the method of Bishop (20) from 94.8 g. of α-methylcaprylic acid; yield of unrecrystallized amide, 89.5 g. (95%), m.p. 76.5–77.3° [Lit. (21), m.p. 80–81°].

α-Methylcaprylonitrile was prepared by a previously described method (22) from 88.9 g. of α-methylcaprylamide and 260 g. of phosphorus oxychloride; yield 60.3 g. (77%), b.p. 95–97°/17.5 mm., n_D^{25} 1.4186 [Lit. (23), b.p. 206°].

3-Methylnonanamide was prepared from 3-methylnonanoic acid (24) by the procedure used for α-methylcaprylamide; yield of crude amide, 96%. A sample crystallized three times from acetone-water had m.p. 88.0–88.8°.

Anal. Calc'd for $C_{10}H_{21}NO$: C, 70.10; H, 12.35.

Found: C, 70.55; H, 12.12.

3-Methylnonanoic nitrile was prepared by the procedure employed in the synthesis of α-methylcaprylonitrile; yield 97%, b.p. 101–103°/10 mm., n_D^{25} 1.4277.

Anal. Calc'd for $C_{10}H_{19}N$: C, 78.36; H, 12.50.

Found: C, 78.36; H, 12.51.

Trans-esterification of β-keto esters. A. When 11.4 g. of *sec*-butyl α-*n*-caproylpropionate and 48 g. of methanol were heated under reflux without catalyst for 44 hours, no methyl ester could be detected by fractional distillation.

B. When the above quantities of material and 1 ml. of concentrated sulfuric acid were heated under reflux for 24 hours, work-up and distillation yielded 2.1 g. (18%) of recovered *sec*-butyl ester and 3.8 g. (41%) of *methyl α-n-caproylpropionate,* b.p. 114–115°/12 mm., n_D^{25} 1.4302.

Anal. Calc'd for $C_{10}H_{18}O_3$: C, 64.48; H, 9.74.

Found: C, 64.77; H, 9.95.

C. When an acid-catalyzed reaction, using *sec*-butyl α-isocaproylpropionate, was allowed to stand for 69 hours at room temperature, there was recovered 49% of *sec*-butyl ester and 23% of *methyl α-isocaproylpropionate,* b.p. 114–115°/17 mm., n_D^{25} 1.4298.

Anal. Calc'd for $C_{10}H_{18}O_3$: C, 64.48; H, 9.74.

Found: C, 64.01; H, 9.66.

SUMMARY

The synthetic utility of the reaction of a nitrile with the zinc reagent of an α-bromoester has been investigated. The reaction appears useful for the synthesis of α-substituted β-keto esters. It proceeds best with aromatic nitriles and unhindered aliphatic nitriles, somewhat less well with α- or β-alkyl nitriles. The use of bromoesters of secondary alcohols gives substantially better yields than obtained with *n*-alkyl esters.

The *trans*-esterification of β-keto esters has been found to proceed very slowly in the presence of excess alcohol.

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