[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Reformatsky Reaction: Effect of Alkyl Group in Alkyl α-Bromopropionates

BY MELVIN S. NEWMAN AND F. JAMES EVANS, JR.[1]

RECEIVED AUGUST 12, 1954

The reactions of methyl, ethyl, propyl, isopropyl, isobutyl, *t*-butyl and neopentyl α-bromopropionates with zinc in benzene–ether solvent in the presence and absence of benzophenone are herein described.

Certain yield-diminishing side reactions of bromo esters in the Reformatsky reaction have been discussed previously.[2] When ethyl α-bromopropionate and ethyl α-bromoisobutyrate were used ethyl α-propionylpropionate and ethyl α-isobutyroylisobutyrate were formed in approximately 35 and 69% yields, respectively. When the above bromo esters were allowed to react with zinc alone in benzene the yields of keto esters were 39 and 65%, respectively. The present study was undertaken to see what effect the alkyl group in alkyl α-bromopropionates might have on the rate of self condensation and other side reactions. The reaction of methyl, ethyl, propyl, isopropyl, isobutyl, *t*-butyl and neopentyl α-bromopropionates with zinc in benzene–ether solvent in the presence and absence of benzophenone are herein described.

TABLE I

PROPERTIES AND ANALYSES FOR ALKYL α-BROMOPROPIONATES USED

Alkyl	Method[e]	Yield,[a] %	B.p. (10 mm.), °C.	n^{t}_{D}	*t*, °C.	Bromine, % Calcd.	Bromine, % Found
Methyl[b]	B	70	37	1.4468	31	47.9	48.2
Ethyl[b]	..[c]		46	1.4422	29		
Propyl	A	56	61–61.5	1.4424	31	41.0	41.2
i-Propyl[b]	B	83	50–50.5	1.4361	30	41.0	40.9
i-Butyl	A	58	67–69	1.4405	31		
	B	84	68–69	1.4428	25	38.2	38.4
t-Butyl	A[d]	48	51–52	1.4326	27	38.2	37.9
Neopentyl	B	87	73–74	1.4398	30	35.8	35.9

[a] Yield represents pure product used in study. [b] O. Burkard and L. Kahovec, *Monatsh.*, **71**, 333 (1938). [c] Commercial sample was rectified. [d] Triethylamine used, see Experimental for unsuccessful attempts. [e] Preparation of α-bromo esters: method A, α-bromopropionyl chloride, b.p. 35–45° at 20–30 mm., was treated with the alcohol in the cold. The mixture was then warmed for four hours, cooled and treated with water. The bromo ester was finally fractionated under reduced pressure. Fractions of almost identical indices of refraction were combined and a representative sample taken for measurement of index of refraction and analysis. Method B, α-bromopropionic acid was refluxed with the alcohol in benzene solution, the water being removed as formed. The benzene was distilled and the ester obtained by vacuum rectification as in method A.

Experimental

***t*-Butyl α-Bromopropionate.**—The procedure described below was successful when others failed. The failures included: maintaining α-bromopropionic acid and *t*-butyl alcohol at room temperature for three hours (heating caused evolution of a gas, presumably isobutene, which decolorized bromine in carbon tetrachloride); reaction of α-bromopropionyl chloride and *t*-butyl alcohol in the presence of dimethylaniline[3]; reaction of ethyl chloroformate with α-bromopropionic acid in triethylamine followed by addition of *t*-butyl alcohol.[4]

To a solution of 151 g. (3 moles) of pure triethylamine and 148 g. (2 moles) of *t*-butyl alcohol in 200 cc. of dry ether at 0–5° was added during 90 minutes 171 g. (1 mole) of α-bromopropionyl chloride. After stirring for 20 hours at 20–25°, 175 cc. of water was added to dissolve the solid. The organic layer was separated and washed. After drying and solvent removal there was obtained 100 g. (48%) of *t*-butyl α-bromopropionate.

Zinc.—About 250 g. of 20-mesh zinc was covered with 300 cc. of 5% hydrochloric acid and stirred vigorously for three minutes. The zinc was washed by decantation three times with 300 cc. of distilled water, twice with 200 cc. of acetone and twice with 200 cc. of ether. The zinc then was dried rapidly in a vacuum desiccator. Five pounds of zinc was processed, combined to ensure uniformity, and kept in a stoppered bottle in a desiccator. Zinc prepared in this way[5] retained its bright luster for the duration of the research.

Procedure.—Using ethyl α-bromopropionate, experiments were carried out to determine reproducibility of results and optimum conditions for reaction with zinc in the absence of ketone. All reactions were run in a 1-l. three-necked flask fitted with a mercury-sealed stirrer, dropping funnel, and take-off reflux condenser. Thirty cc. more than the desired amount of pure benzene was placed in the flask and 15 cc. was distilled to remove any moisture. A few cc. of acetone were used to rinse down any droplets of water which adhered to the walls of the condenser and another 15 cc. of benzene was distilled. After cooling somewhat the zinc and bromoester were added; when ether was used, this was added at the same time. The reaction mixture then was refluxed for the desired time, cooled, and dilute hydrochloric acid was added until clear solutions resulted. Tests showed that a negligible amount of zinc reacted with dilute acid under these conditions. The zinc was separated, washed, dried and weighed. The combined organic layer and ether extracts of the aqueous layer were washed with saturated salt solution, dried over anhydrous sodium sulfate, and distilled through a small column. The fraction b.p. 35–80° was collected and the residue was held at about 25° at 10 mm. for two hours, volatile material being caught in a Dry Ice cooled trap. The amount of reduced ester (*e.g.*, alkyl propionate) in the combined distillate and trapped fraction was determined by saponification equivalent. The remaining material was distilled at 10 mm. and the amount of unreacted bromoester and/or β-keto ester determined by the weights of appropriate distillates. Bromo esters were characterized by b.p. and index of refraction, while the β-keto ester was identified by reaction with phenylhydrazine to form 1-phenyl-3-ethyl-4-methyl-5-pyrazolone,[6] m.p. 111–112°. The dark viscous residue in the flask remaining after the β-keto ester had been distilled was weighed. These weights are listed in the Tables II and III as residue.

The experiments listed in Table II were run using ethyl ester to determine the best conditions for comparative experiments. Most of these experiments were checked, the values obtained being reproducible to ±1%. The analyses of the reaction products obtained in typical runs (average of experiments 8 and 9; 10 and 11) were: % zinc reacted 89.5 and 85.5; % reduced ester, ethyl propionate, formed, 19.5 and 19.2; % β-keto ester formed, 38.2 and 30.7. The weights of residue formed were 6.9, 14.8, 16.9, and 16.7 g., respectively. Since the structure of the products in the

---

(1) Taken from the Ph.D. thesis of F. J. E., The Ohio State University, 1952.

(2) (a) M. S. Newman, THIS JOURNAL, **64**, 2131 (1942); (b) A. S. Hussey and M. S. Newman, *ibid.*, **70**, 3024 (1948).

(3) B. Abramovitch, J. C. Shivers, B. E. Hudson and C. R. Hauser, *ibid.*, **65**, 986 (1943).

(4) T. Wieland, W. Schäfer and E. Bokelmann, *Ann.*, **573**, 102 (1951).

(5) W. E. Bachman, W. Cole and A. L. Wilds, THIS JOURNAL, **62**, 832 (1940).

(6) O. Emmerling and L. Kristeller, *Ber.*, **39**, 2450 (1906).

TABLE II

REACTIONS OF ETHYL α-BROMOPROPIONATE WITH ZINC; SOLVENT, CONCENTRATION AND OTHER EFFECTS

Expt.	Solvent (300 cc.)	Zn used, mole	Ester, mole	Reflux, hours	Zn re-acted,[a] %
1	Benzene	1.0	0.5	0.5	58
2	Benzene	1.0	.5	3.0	79
3	Benzene	1.0	.5	3.0	79
4	Benzene	1.0[b]	.5	3.5	79
5	Benzene	0.56[c]	.5	3.25	83
6	Benzene[d]	1.0	.25	3.0	83
7	Benzene	0.5	.25	3.0	55
8	Benzene–ether[e]	0.5	.25	3.0	89
9	Benzene–ether	1.0	.5	3.0	90
10	Benzene–ether	0.55	.5	4.0	86
11	Benzene–ether	0.55	.5	6.0	85

[a] The percentage Zn reacted is calculated from the weight of zinc recovered by assuming that one mole of zinc would be consumed for every mole of bromoester used originally. [b] One-half of zinc added initially, one half after 30 min. [c] Freshly sandpapered zinc foil was used in place of granulated zinc. [d] Only 150 cc. of benzene was used. [e] 1:1.

TABLE III

REACTION OF ALKYL α-BROMOPROPIONATES WITH ZINC IN BENZENE–ETHER[a]

Expt.	Ester (alkyl)	Zn re-acted,[b] %	Reduced ester, %	β-Keto ester, %	α-Bromo ester recov-ered, %	Resi-due, g.
12	Methyl	71.0	25.6	16.4	5.6	17.5
13	Methyl	73.0	25.8	15.3	5.2	18.1
14	Ethyl	89.0	19.2	37.7	0	13.8
15	Ethyl	89.2	19.5	37.2	0	14.0
16	*n*-Propyl	82.8	16.2	39.4	0	14.6
17	*n*-Propyl	84.6	16.8	39.8	0	15.2
18	*i*-Propyl	3.6	2.8	0	92.2	1.5
19	*i*-Propyl	4.0	3.0	0	92.7	0.5
20	*i*-Butyl	29.0	11.8	0	60.9	10.9
21	*i*-Butyl	27.7	10.0	0	64.5	10.2
22	*t*-Butyl	1.6	0	0	86.7	0
23	Neopentyl	3.6	2.8	0	90.6	3.2
24	Neopentyl	3.0	2.5	0	93.8	0.5
25	Ethyl[c]	91.6	44.5	9.8	0	12.2

[a] In all experiments 0.5 mole of ester, 1.0 mole of zinc, 150 cc. of benzene and 150 cc. of ether were allowed to react for three hours at reflux. [b] Zinc from the same batch was used in all experiments. [c] Ethyl α-bromoacetate.

residue is unknown, no percentage yield can be calculated. Since the reaction proceeded more smoothly and completely in benzene–ether, 1:1, the conditions of expt. 9, Table II, were chosen as standard.[7]

The results of a number of experiments conducted under standard conditions and in which the alkyl group of the bromo ester was varied are listed in Table III. These runs were all made without added ketone. In Table IV are listed runs in which ketone was present.

TABLE IV

CONDENSATIONS OF ALKYL α-BROMOPROPIONATES WITH BENZOPHENONE

Expt.[a]	Ester	Zn reacted, %	Re-formatsky product, %	Reduced ester, %	Recov-ered bromo-ester, %
26	Ethyl[b]	98.8	86.8[c]	3.7	..
27	*i*-Propyl	3.0	..	..	86.7
28	*i*-Butyl	99.4	87.2[d]	1.0	..
29	*t*-Butyl	1.6	...	..	86.7
30	Neopentyl	3.4	...	..	87.8

[a] In all of these experiments the solvent was 150 cc. of ether and 150 cc. of benzene; one mole of zinc and one-half mole each of bromoester and ketone. [b] In a similar experiment, except that 5,8-dimethyl-1-tetralone replaced the benzophenone, the corresponding figures were 97.8, 72.7, 3.2 and —. Compare M. S. Newman and A. S. Hussey, THIS JOURNAL, **69**, 3023 (1947). [c] M.p. 101–102°, see H. Rupe, H. Steiger and F. Fiedler, *Ber.*, **47**, 63 (1914). [d] M.p. 85–87°.

Discussion

Inspection of the results listed in Table II shows that ethyl α-bromopropionate reacts more completely in benzene–ether than in benzene alone and that the reaction is somewhat better when a 100% excess of zinc rather than a 10% excess is used (experiments 9 and 10). Experiments 8 and 9 show that the concentration of bromoester has little effect on the completeness of reaction. As a result of these experiments, standard conditions similar to those in experiment 9 were used for all subsequent reactions unless otherwise noted.

The variation in reactivity of various alkyl α-bromopropionates with zinc is shown in Table III. It is striking that small variations in alkyl structure can so markedly affect reactivity. Note particularly that isopropyl α-bromopropionate (experiments 18, 19) is almost entirely inert, as are also the *t*-butyl and neopentyl esters (experiments 22, 23, 24). The isobutyl ester is noteworthy because it stands alone regarding reactivity (experiments 20, 21). Furthermore, when one considers the yields of Reformatsky product listed in Table IV, the isobutyl ester is seen to afford as high a yield as the ethyl ester (note experiments 26 and 28), whereas the other alkyl α-bromopropionates, isopropyl, *t*-butyl and neopentyl, which were inert to zinc alone, are also inert to zinc in the presence of benzophenone.

As a result of this work one can recommend that in cases where ethyl α-bromopropionate gives a poor yield in a Reformatsky reaction due to self condensation or other side reactions the use of isobutyl α-bromopropionate be studied. This recommendation is based upon the fact that isobutyl α-bromopropionate shows little tendency to engage in side reactions with itself whereas it still seems capable of reacting well with ketones to yield the desired Reformatsky product.

COLUMBUS 10, OHIO

---

[7] In previous work, it was reported that ethyl α-bromoacetate in benzene reacted very slowly with zinc in the absence of carbonyl compounds.[2a] Interestingly in benzene–ether this reaction was so vigorous that external cooling was needed and 91.6% of the theoretical amount of zinc was consumed. See Table III, exp. 25, for analysis of products.