tated solid collected on a filter; yield 2.5 g. (90%), and crystallized from glacial acetic acid.

Summary

1. 1-(o-Nitrophenyl)-3,4-dimethyl-1,2,5-triazole as well as the p-isomer was obtained in the nitration of 1-phenyl-3,4-dimethyl-1,2,5-triazole.

2. Arsonation by the Bart reaction has been effected from the amines obtained from the above nitro compounds.

3. Several new derivatives have been obtained by reactions of nitration, oxidation, reduction, and esterification on 1-(4-arsonophenyl)-3,4-dimethyl-1,2,5-triazole.

LINCOLN, NEBRASKA RECEIVED APRIL 15, 1946

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF OBERLIN COLLEGE]

A Study of Alternate Methods for the Alkylation of Acetoacetic Esters

BY W. B. RENFROW AND ANTOINETTE RENFROW

Evidence reported[1] earlier indicates that potassium t-amyloxide in t-amyl alcohol is superior in some cases to sodium ethoxide in ethanol as a reagent in the alkylation of acetoacetic esters. Further work has shown that t-butyl alcohol is a more satisfactory reagent than t-amyl alcohol. Inability to reproduce earlier results satisfactorily led us to discover that the method used to purify t-amyl alcohol (refluxing with sodium) did not give a uniform product from different batches of alcohol. Since no convenient method for obtaining reliable t-amyl alcohol was apparent, we investigated t-butyl alcohol. Practically pure t-butyl alcohol is available commercially and its quality can be confirmed readily by melting point. Potassium t-butoxide in t-butyl alcohol has given 5–10% higher yields of alkylation products than were obtained with potassium t-amyloxide in t-amyl alcohol.

In order to evaluate the potassium t-butoxide method for alkylating acetoacetic esters, we have compared it with the following alternative procedures[2]: sodium ethoxide[3] or potassium ethoxide in ethanol, sodium[4] or potassium metals in dioxane, sodium metal in toluene,[5] sodium amide in dioxane and sodium hydride in dioxane.

The butyl halides were selected as alkylating reagents because they are representative of the main types of alkyl halides and produce alkylation products of convenient boiling range. All runs were made with 120 ml. of solvent and 0.200 g.-equiv. of sodium, potassium, sodium amide, or sodium hydride. Equivalent amounts[6] (0.200

mole) of β-keto esters were used in all runs except those with sodium or potassium metals in dioxane or toluene. A 10% excess of ester (0.22 mole) was used in the latter cases to facilitate reaction with the metal. An excess of alkyl halide (0.22 mole) was used in all cases.

Whenever feasible, the times required for one-half of the alkalinity to disappear were determined at the temperatures of the refluxing solutions. The primary reason for obtaining the data on reaction rates was to determine how long the solutions should be refluxed and not to study the kinetics of the reactions. Values for reaction half-times could be satisfactorily reproduced for the reactions which yielded 70% or better of alkylation products, and these reactions appeared to follow the second-order rate of reaction equation. For those reactions that gave less than about 60% yields of alkylation products, duplicate values for the reaction half-times varied considerably.

Reaction mixtures were generally refluxed for a period equalling ten times the half-time or until 95% of the alkalinity had disappeared. When the alkylation was very slow, however, better yields were sometimes obtained by terminating the reactions earlier. For example, the alkylation of acetoacetic ester with sodium ethoxide and i-butyl bromide gave a 19% yield of alkylation product if the reaction was stopped after 70% of the alkalinity had reacted, but only a 7% yield after 95% of the alkalinity had reacted.

The data are listed in Table I.

Alkyl iodides are generally recognized as superior to bromides for the alkylation of acetoacetic esters[7] but the degree of superiority is difficult to estimate from data in the literature. We have found that iodides react from two to six times faster than bromides (compare experiments 2–7,

(1) Renfrow, THIS JOURNAL, 66, 144 (1944).

(2) To facilitate presentation, names of metallating reagents or of metallating reagents and solvents will be used to refer to the entire alkylation process using the specified reagents. See equation at top of Table 1.

(3) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 248.

(4) Finkelstein and Elderfield, J. Org. Chem., 4, 370 (1939), used relatively more dioxane than we have used, and isolated the reaction product by a somewhat different method.

(5) Hope and Perkin, J. Chem. Soc., 95, 2046 (1909).

(6) Preliminary experiments on the alkylation of ethyl n-butyl-acetoacetate with sodium ethoxide and n-butyl iodide demonstrated that the use of 0.204 g.-atom of sodium to 0.200 mole of ester and 0.22 mole of iodide gave consistently about 3% lower yields of alkylation product than were obtained when equivalent amounts of sodium

and ester were employed. Runs using 0.200 g.-atom of sodium and 0.208 mole of ester gave the same yields of alkylation product as were obtained when equivalent amounts of sodium and ester were used. Decreasing the volume of ethanol from 120 to 50 ml. did not affect the yield of alkylation product from ethyl n-butylacetoacetate (0.200 mole), potassium ethoxide (0.200 mole) and n-butyl bromide (0.22 mole). The optimum amount of ethanol for runs with potassium is about two-thirds of the quantity used in our standard procedure.

(7) Locquin, Bull. soc. chim., 31, 758 (1904).

TABLE I

RESULTS OBTAINED FROM THE REACTIONS

$$CH_3-\overset{O}{\underset{}{C}}-\overset{H}{\underset{R}{C}}-\overset{O}{\underset{}{C}}-OC_2H_5 \xrightarrow[\text{Reagent}]{\text{Metallating}} Na \text{ or } K(CH_3COCRCO_2C_2H_5) \xrightarrow{R'X} CH_3\overset{O}{\underset{R}{C}}-\overset{R'}{\underset{}{C}}-\overset{O}{\underset{}{C}}\cdot OC_2H_5$$

Expt.	R	Metallating reagent	R'X	Reaction half-time,[a] minutes	Yield, %	Alkylation product B. r., °C	Min.	Alkalinity reacted %
1	H	t-BuOK	n-BuI	7	79	111–113	17	96
2	H	Na/Dioxane	n-BuI	22	76	110–112	15	97
3	H	EtOK	n-BuI	4	75	109–112	15	99
4	H	EtONa	n-BuI	8	73	112–115	16	94
5	H	EtOK	n-BuBr	22	72	113–115	16	95
6	H	EtONa	n-BuBr	44	69	113–115	16	88
7	H	Na/Dioxane	n-BuBr	140	59	111–113	15	97
8	H	Na/Toluene	n-BuI	..	46	112–116	15	[b]
9	H	Na/Toluene	n-BuBr	..	36	113–116	16	[c]
10	H	t-BuOK	i-BuI	70	66	97–102	13	97
11	H	EtOK	i-BuI	35	61	100–103	13	95
12	H	Na/Dioxane	i-BuI	197	56	98–101	13	95
13	H	EtONa	i-BuI	68	54	99–102	13	95
14	H	NaH	i-BuI	260	49	99–101	13	93
15	H	NaNH₂	i-BuI	..	39	99–101	13	..
16	H	NaH	i-BuI	..	39	99–102	13	[d]
17	H	EtONa	i-BuBr	395	17	99–101	13	70
18	H	t-BuOK	s-BuI	126	62	107–109	18.5	90
19	H	Na/Dioxane	s-BuI	400	55	108–110	19.5	88
20	H	EtOK	s-BuI	41	55	108–110	19	95
21	H	EtONa	s-BuI	98	55	109–110	19	96
22	H	NaH	s-BuI	..	50	108–111	19	[d]
23	H	NaNH₂	s-BuI	266	45	107–110	20	..
24	H	K/Dioxane	s-BuI	140	44	108–109	19.5	95
25	H	EtONa	s-BuBr	596	39	107–110	20	86
26	H	EtOK	s-BuBr	248	38	108–110	20	80
27	n-Bu	t-BuOK	n-BuI	6	80	132–135	10.5	95
28	n-Bu	t-BuOK	n-BuBr	21	77	146–149	18	95
29	n-Bu	NaH	n-BuI	24	73	129–131	9	96
30	n-Bu	EtOK	n-BuI	2	73	132–133	10.5	96
31	n-Bu	EtONa	n-BuI	5	63	133–135	11	97
32	n-Bu	Na/Dioxane	n-BuI	26	60	130–132	9	95
33	n-Bu	EtOK	n-BuBr	7	50	145–148	18	95
34	n-Bu	Na/Dioxane	n-BuBr	117	46	145–148	18	88
35	n-Bu	Na/Toluene	n-BuI	..	5	124–131	9	[b]
36	n-Bu	t-BuOK	i-BuI	42	62	135–138[e]	15	98
37	n-Bu	EtOK	i-BuI	7	50	135–138	15	95
38	n-Bu	t-BuOK	s-BuI	110	54	142–145[f]	20	91
39	n-Bu	Na/Dioxane	s-BuI	500	25	142–146	20	63
40	n-Bu	EtOK	s-BuI	13	14	143–144	19.5	96
41	i-Bu	t-BuOK	n-BuI	7	73	139–142	18	97
42	i-Bu	NaNH₂	n-BuI	40	66	135–138	15	92
43	i-Bu	t-BuOK	i-BuI	80	66	124–127	12	90
44[g]	i-Bu	t-BuOK	i-BuBr	150	46	123–128	12	88
45	s-Bu	t-BuOK	n-BuI	40	60	144–147	20.5	94
46	s-Bu	t-BuOK	s-BuI	165	10	120–129	17.5	90
47	s-Bu	NaNH₂	s-BuI	1000	13	120–129	17.5	87
48	s-Bu	NaH	s-BuI	[d]	10	120–126	17	..

[a] Temperatures of refluxing solutions: ethanol, 80–83°; t-butanol, 84–87°; dioxane, 101–105°; toluene, 111–113°. [b] Refluxed for five hours. [c] Refluxed for nine hours. [d] These reactions were carried out under pressure at 150° for five hours. [e,f] Apparently new compounds. *Anal.* Calcd. for C₁₄H₂₆O₃: C, 69.37; H, 10.81. Found: [e] C, 69.06; H, 10.86. [f] C 68.98; H, 10.85. [g] This run was made by Mr. Harry Rindfleisch at Occidental College, Los Angeles, California

3–5, 4–6, 13–17, 20–26, 21–25, 27–28, 30–33, 32–34, 43–44). The rates of alkylations with i-butyl

and s-butyl iodides are inconveniently slow and, consequently, few experiments were done with

the corresponding bromides. When we shortened the reaction time for a slow alkylation by operating under pressure at a higher temperature, the yield of alkylation product decreased (experiments 14–16). For some reactions the yields of alkylation products were practically the same from bromides as from iodides (experiments 3–5, 4–6, 27–28) while in other reactions iodides gave significantly better yields (experiments 2–7, 13–17, 20–26, 21–25, 30–33, 32–34, 43–44).

An attempt was made to alkylate ethyl acetoacetate with n-butyl chloride by the sodium ethoxide method, but the reaction was so slow (70% of the alkalinity remained after sixteen hours refluxing) that it was abandoned. The addition of 0.1 mole of sodium iodide to another run with n-butyl chloride (0.22 mole) increased the speed of the reaction (half-time was about 430 minutes) but gave only a 10% yield of ethyl n-butylacetoacetate.

We were unable to alkylate ethyl acetoacetate with either t-butyl chloride or iodide by the potassium t-butoxide method. The alkalinity disappeared rapidly but no alkylated ester was isolated.

The best yields of alkylation products were obtained with potassium t-butoxide in t-butanol as the metallating agent. These results may be attributed to the greater reactivity of potassio acetoacetic esters as compared with sodio acetoacetic esters (experiments 3–4, 5–6, 11–13, 19–24, 20–21, 25–26, 30–31); to less alcoholysis of the alkylation products in t-butanol as compared with ethanol; and to more quantitative isolation of the reaction products from t-butanol than from the higher-boiling dioxane. Rates of alkylations by the potassium t-butoxide method were about the same as by the sodium ethoxide method. Potassium t-butoxide was particularly good for the alkylation of α-substituted acetoacetic esters and affords a practical method for a variety of alkylations of this type (experiments 27, 28, 36, 38, 41, 43, 44, 45). Attempts to alkylate ethyl s-butylacetoacetate with s-butyl iodide were not successful (experiments 46, 47, 48). Some material was obtained that boiled in the range expected for ethyl di-s-butylacetoacetate, but the yields were so small that the material was not positively identified.

We found no report of the previous use of potassium ethoxide in the alkylation of acetoacetic esters. Rates of alkylations with this reagent were about twice as fast as with sodium ethoxide (experiments 3–4, 5–6, 11–13, 20–21, 25–26, 30–31), but approximately the same yields of alkylation products were obtained in most cases. The relatively fast rates of reactions make the potassium ethoxide method attractive for introducing an i-butyl or s-butyl group into ethyl acetoacetate. Potassium ethoxide was inferior to potassium t-butoxide for alkylating ethyl n-butylacetoacetate (experiments 27–30, 28–33, 36–37, 38–40).

Sodium metal in dioxane gave about the same

yields of alkylation products as sodium ethoxide (experiments 2–4, 12–13, 19–21, 31–32), but rates of reactions were slower and the method was less convenient. The isolation of very high-boiling products from runs using sodium metal in dioxane or toluene and α-substituted acetoacetic esters indicates that these esters reacted partially with sodium to form products of the acyloin type. Sodium in dioxane probably is the best reagent for preparing the sodio derivative of ethyl acetoacetate in a non-hydroxylic solvent. Potassium in dioxane was not thoroughly investigated because the method gave a slightly poorer yield of ethyl s-butylacetoacetate than did sodium in dioxane. Sodium metal in toluene was inferior to all of the other reagents for the alkylations that we studied.

Sodium amide and sodium hydride were investigated as reagents for preparing sodio acetoacetic esters because it seemed likely that these reagents would permit dioxane to be used as solvent and would avoid the reduction that sometimes occurs with use of sodium metal. Sodio acetoacetic esters are soluble in dioxane, and this solvent eliminates the possibility of alcoholysis of the ester or of the alkylating reagent. Sodium amide reacted with ethyl acetoacetate to give products other than the sodio acetoacetic ester, as was evidenced by formation of dioxane-insoluble material and low yields of alkylation products, but the sodium amide method was good for the alkylation of ethyl i-butylacetoacetate with n-butyl iodide. Sodium hydride in dioxane apparently reacted with both acetoacetic and n-butylacetoacetic esters to give mainly the sodio esters, and is probably the best reagent for preparing the sodio derivatives of α-substituted acetoacetic esters in a non-hydroxylic solvent. The failure to obtain consistently better yields from alkylations using dioxane instead of alcohol as solvent is probably due to a decrease in rates of alkylations without a corresponding decrease in rates of competing side reactions. Impurities in the sodium amide[8] and sodium hydride[9] may have reduced the yields of alkylation products.

Experimental

Commercial absolute alcohol was dried with sodium and diethyl phthalate.[10]

A good grade of t-butyl alcohol (freezing point 24.7°) was refluxed with 1% of its weight of thinly sliced sodium until most of the sodium had dissolved. After distillation, the alcohol froze at 25.2–25.5°.

Dioxane and toluene were purified by refluxing with sodium followed by fractional distillation.

Alkyl halides were extracted with concentrated sulfuric acid (for bromides) or 85% phosphoric acid (for iodides), washed with bicarbonate solution, dried (calcium chloride) and fractionated.

Acetoacetic esters were carefully fractionated through

(8) Sodium amide was prepared by the method of Vaughn, Vogt and Nieuwland, THIS JOURNAL, 56, 2120 (1934).

(9) Sodium hydride was courteously supplied by E. I. du Pont de Nemours and Company.

(10) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., 1941, p. 359.

25 cm. of glass helices. Fractions boiling within a 2°-range were used for alkylation experiments.

The procedure for experiments with ethanol or t-butyl alcohol was as follows: The alcohol (120 ml.) was placed in a 500-ml. three-necked flask fitted with an efficient stirrer, a reflux condenser and a thermometer. Sodium or potassium metal (0.200 g.-atom) was added and the mixture stirred and refluxed from an oil-bath until the metal had reacted. Potassium t-butoxide began to precipitate before all the metal had reacted, but the ethoxides were soluble. The solutions were cooled to about 50°, the β-keto esters (0.200 mole) added and the solutions stirred for two minutes (potassium t-butoxide dissolved). The alkyl halides (0.22 mole) were then added, the solutions stirred for one minute and a 2.00-ml. aliquot removed. The alcohol solutions were stirred and refluxed from an oil-bath and additional aliquots removed from time to time. To terminate the reactions, the reflux condenser was replaced by a short fractionating column and the mixture stirred and distilled until 100 ml. of distillate had been collected. The material in the reaction flask was worked up by addition of water (sufficient to dissolve the salt present) and ether. The ether layers were washed once with water and the water layers were extracted three times with ether. The combined ether layers were dried (sodium sulfate) and carefully fractionated through 18 cm. of glass helices.

The rate at which the alkali disappeared was determined as follows: aliquots (2.00 ml.) were run into 25.00 ml. of 0.1 N standard hydrochloric acid, 3 drops of "Nitrazine" indicator solution added and the excess hydrochloric acid titrated with standard sodium hydroxide solution.

The values listed in Table I under "Reaction Half-time" are based upon titrations of one or two aliquots which were removed as close as possible to the times at which one-half of the alkalinity had reacted. Discrepancies between the times of withdrawal of the aliquots and the actual times at which one-half of the alkalinity had reacted were corrected by use of the second-order rate of reaction equation,[11] but such corrections were generally of small magnitude.

Essentially the same apparatus was used in experiments with dioxane. Sodium or potassium metal (0.200 g.-atom) was melted by heating the dioxane (120 ml.) and the solution vigorously stirred (wire stirrer) to obtain the metal in a finely divided state. The mixture was maintained at 40–50° while the β-keto ester (0.22 mole) was added slowly from a dropping funnel, and then refluxed to dissolve the last particles of metal. The alkyl halides (0.22 mole) were added and an aliquot removed. The solutions were stirred and refluxed from an oil-bath and finally worked up as described above for experiments with ethanol and t-butyl alcohol.

Sodium hydride (0.20 mole) was weighed in an atmosphere of dry nitrogen and immediately transferred to a three-necked flask containing dioxane (120 ml.). The mixture was stirred while the acetoacetic ester (0.20 mole) was dropped in, and was finally refluxed to hasten reaction of the last traces of sodium hydride. The solution was cooled to about 50°, the alkyl halide (0.22 mole) added, an aliquot removed and the reaction completed as described above.

(11) See, for example, Taylor, "Elementary Physical Chemistry," D. Van Nostrand Company, New York, N. Y., 1927, pp. 165–166.

More dioxane (130 ml.) was used in runs with sodium amide (0.20 mole). After the sodio acetoacetic esters had been formed in the manner described for sodium hydride, dioxane (10 ml.) was distilled from the solution to sweep out ammonia. The alkyl halide was then added and the reaction completed in the usual way.

The procedure for runs with toluene was almost the same as described for dioxane. Sodio acetoacetic ester (but not sodio n-butylacetoacetic ester) was insoluble in toluene and formed a thick paste which could not be pipeted satisfactorily. After some reaction with an alkyl halide had occurred the mixture became more fluid and samples containing suspended salt and sodio acetoacetic ester could be removed and titrated to give some indication of the completion of the reactions. The products were worked up by extraction with water followed by fractional distillation.

Summary

Sodio and potassio acetoacetic esters were prepared with the following reagents: potassium t-butoxide in t-butanol, sodium ethoxide and potassium ethoxide in ethanol, sodium and potassium metals in dioxane, sodium hydride and sodium amide in dioxane, and sodium metal in toluene. · The sodio and potassio acetoacetic esters were alkylated with n-butyl, i-butyl and s-butyl bromides and iodides. The rates of the reactions and the yields of alkylation products were determined.

Alkyl iodides reacted faster than the corresponding bromides, but did not always give appreciably better yields of alkylation products. Optimum yields of alkylation products were 80% from n-butyl halides and 55–65% from i-butyl and s-butyl iodides. Attempts to use n-butyl chloride and t-butyl chloride or iodide as alklyating reagents were unsuccessful.

The potassium t-butoxide method was generally the best, but for any particular alkylation several alternate procedures gave almost as good yields. In general, we recommend the sodium ethoxide method for alkylating ethyl acetoacetate with n-butyl halides; the potassium ethoxide method for alkylating ethyl acetoacetate with i-butyl and s-butyl iodides; and the potassium t-butoxide method for alkylating α-substituted acetoacetic esters. Sodium in dioxane with ethyl acetoacetate and sodium hydride or sodium amide in dioxane with α-substituted acetoacetic esters would probably be useful in certain cases.

Attempts to prepare ethyl di-s-butylacetoacetate were not successful.