[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

The Acylation of Ketones with Aliphatic Anhydrides by Means of Boron Trifluoride. Synthesis of β-Diketones[1]

BY JOE T. ADAMS AND CHARLES R. HAUSER

Various ketones have previously been acetylated with acetic anhydride by means of boron trifluoride to form β-diketones.[2,3] The present paper reports the acylation of ketones, by means of this reagent, with higher aliphatic anhydrides including propionic, *n*-butyric, isobutyric and *n*-caproic anhydrides; also, certain new acetylations are described. Our results, including the previously reported[3] acetylations of methyl ethyl, methyl *n*-amyl and methyl isobutyl ketones, are summarized in Table I. We have obtained lower yields for the acetylations of acetophenone and especially of cyclohexanone than those reported by Meerwein and Vossen.[2]

It can be seen from Table I that the yields obtained on acylations vary considerably with various ketone anhydride combinations. At present any relationship between the yield and the structure of the ketone or anhydride is not apparent. Acetone and acetic anhydride have given the highest yield (80–86%)[4] for this type of reaction; in this case, the β-diketone, acetylacetone, may result not only from the acetylation of the ketone but also from the self-condensation of the anhydride.[2] The second highest yield is with methyl ethyl ketone and *n*-caproic anhydride (Table I). Since these reactions can be effected conveniently on a relatively large scale, yields of even 30% may be considered satisfactory. It appears that this type of reaction is quite general with purely aliphatic anhydrides. However, the reaction has failed with phenylacetic anhydride and acetone, and with succinic or phthalic anhydride and acetophenone. With acetic anhydride, di-isopropyl ketone gave a product not yet identified. Attempts to acylate acetophenone with benzoyl chloride[5] or methyl ethyl ketone with ethyl oxalate were unsuccessful. Ethyl levulinate failed to cyclize to form cyclopentanedione.

This boron trifluoride method of acylation of ketones is useful for the synthesis of a number of β-diketones certain of which have not been prepared satisfactorily by the more common basic reagent method.[6] In comparing these two methods it is convenient to consider the ketones in two groups. With a symmetrical ketone or with an unsymmetrical ketone having α, but no α′-hydrogen (such as acetophenone), acylation may generally be effected by either method to form the same β-diketone. The acylation of acetone, for example, may be represented by the scheme

$$\left.\begin{array}{l}(RCO)_2O + CH_3COCH_3 \xrightarrow{BF_3} \\ RCO_2C_2H_5 + CH_3COCH_3 \xrightarrow{Base}\end{array}\right\rangle \longrightarrow RCOCH_2COCH_3.$$

Although the basic reagent method has given better yields in certain cases, for example, in the butyrylation of acetophenone,[7] only the boron trifluoride method has been satisfactory for the propionylation or butyrylation of cyclohexanone[8] and for the acetylation of di-isobutyl ketone.[9]

With a methyl-methylene ketone, which has both α- and α′-hydrogen, two different β-diketones generally result on acylation by the two methods. On acylation of methyl benzyl, methyl ethyl, and higher methyl *n*-alkyl ketones, the methylene derivative is mainly (or entirely) formed by the boron trifluoride method, whereas the methyl derivative is mainly (or entirely) formed by the basic reagent method.[6]

$$RCOX + CH_3COCH_2R' \left\{\begin{array}{ll} \xrightarrow[X\,=\,RCOO]{BF_3} RCOCH(R')COCH_3 & \text{Type II} \\ \xrightarrow[X\,=\,OC_2H_5]{Base} RCOCH_2COCH_2R' & \text{Type I}\end{array}\right.$$

Thus, the basic reagent method is of value for the synthesis of β-diketones of Type I, whereas the boron trifluoride method is of value for the direct synthesis of β-diketones of Type II. The latter have generally been prepared by the alkylation of "unsubstituted"[1] β-diketones (Type I), but the direct synthesis from ketones by the boron trifluoride method is usually to be preferred. This method should be of particular value with methyl benzyl ketone, since such β-diketones as α-phenylacetylacetone cannot be prepared by the arylation of acetylacetone. Although small amounts of the methyl derivatives are also formed with methyl *n*-alkyl ketones higher than methyl ethyl ketone, the methylene derivatives

(1) Paper XXIX on "Condensations"; paper XXVIII, THIS JOURNAL, **66**, 1768 (1944).

(2) Meerwein and Vossen, *J. prakt. Chem.*, **141**, 149 (1934).

(3) Hauser and Adams, THIS JOURNAL, **66**, 345 (1944).

(4) Ref. 2 and "Organic Syntheses," Vol. 20, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 6.

(5) Meerwein and Vossen[2] have reported that the acylation fails with benzoic anhydride and acetophenone.

(6) See Adams and Hauser, THIS JOURNAL, **66**, 1220 (1944).

(7) Using ethyl *n*-butyrate and sodium amide, a yield of 42% has been obtained by J. A. Conroy in this Laboratory, compared to the 15% yield given in Table I.

(8) Yields of only 4–12% have been obtained by the basic reagent method even using sodium amide. Unpublished results of J. A. Conroy.

(9) An attempt to acetylate di-isobutyl ketone with ethyl acetate resulted in the self-condensation of the ester, even though the sodium derivative of the ketone was first prepared using sodium triphenylmethide or sodium amide. Unpublished results of Robert Levine.

TABLE I

ACYLATION OF KETONES WITH ANHYDRIDES BY MEANS OF BORON TRIFLUORIDE

Ketone	Anhydride	β-Diketone[a]	B. p. °C.	B. p. Mm.	Yield, %
Acetone	Propionic	Propionylacetone[b]	155–157	754	46
Acetone	*n*-Butyric	Butyrylacetone[c]	71–73	20	48
Cyclohexanone	Acetic	2-Acetylcyclohexanone	96–97	10	35 (56)[d]
Cyclohexanone	Propionic	2-Propionylcyclohexanone[e]	123–125	20	35
Cyclohexanone	*n*-Butyric	2-Butyrylcyclohexanone[f]	133–134	20	34
Acetophenone	Acetic	ω-Acetylacetophenone	140–141	18	50[g] (57)[d]
Acetophenone	Propionic	ω-Propionylacetophenone[h]	149–152	10	30
Acetophenone	*n*-Butyric	ω-Butyrylacetophenone[i]	159–161	10	15
Methyl *t*-butyl	Acetic	Pivaloylacetone[j]	70–71	20	45
Diethyl	*n*-Butyric	Methylpropionylbutyrylmethane[k]	106–108	20	46
Diisobutyl	Acetic	Isopropyl isobutyrylacetone[l]	113–115	20	45
Methyl ethyl	Acetic	Methyl acetylacetone	77–79	30	32
Methyl ethyl	Propionic	Methyl propionylacetone[m]	88–91	30	31
Methyl ethyl	*n*-Butyric	Methyl butyrylacetone[n]	93–96	20	44
Methyl ethyl	*n*-Caproic	Methyl caproylacetone[o]	120–123	20	64
Methyl *n*-amyl	Acetic	*n*-Butyl acetylacetone	105–106	20	53
		n-Hexoylacetone	102–103	20	6
Methyl *n*-amyl	Propionic	*n*-Butyl propionylacetone[p]	117–118	20	47
		Propionyl-*n*-hexoylmethane[q]	113–116	20	4
Methyl *n*-amyl	*n*-Butyric	*n*-Butyl butyrylacetone[r]	127–129	20	38
		Butyryl-*n*-hexoylmethane[s]	130–131	20	4
Methyl *n*-amyl	Isobutyric	*n*-Butyl isobutyrylacetone[t]	125–128	20	29
		Isobutyryl-*n*-hexoylacetone[u]	128–130	20	3
Methyl isobutyl	Acetic	Isovalerylacetone	78–79	20	25
		Isopropyl acetylacetone	183–185	750	16
Methyl isobutyl	Propionic	Propionylisovalerylmethane[v]	92–93	20	26
		Isopropyl propionylacetone[w]	95–97	20	17
Methyl isobutyl	*n*-Butyric	Butyrylisovalerylmethane[x]	107–108	20	26
		Isopropyl butyrylacetone[y]	104–107	20	18
Methyl benzyl	Acetic	3-Phenylacetylacetone[z]	132–134	20	41

[a] β-Diketones of the type $RCOCH_2COR$ gave a red enol test; those of the type RCOCHR'COR gave a purple enol test (except when R' was isopropyl, which gave no enol test). [b] Forms a blue copper salt, m. p. 198–199° [Griner, *Ann. chim. phys.*, [6] **26**, 362 (1892)]. [c] Forms a blue copper salt, m. p. 164–165° [Morgan, Drew and Porter, *J. Chem. Soc.*, **125**, 737 (1924)]. [d] See ref. 2. [e] *Anal.* Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.69; H, 8.59. Forms a gray copper salt, m. p. 184–185°. [f] *Anal.* Calcd. for $C_{10}H_{16}O_2$: C, 71.41; H, 9.59. Found: C, 71.61; H, 9.33. Forms a gray copper salt, m. p. 156–157°. [g] Obtained by J. A. Conroy; see also Breslow and Hauser, THIS JOURNAL, **62**, 2385 (1940). [h] Forms a greenish copper salt, m. p. 152–153° [Andre, *Ann. chim.*, [8] **29**, 579 (1913)]. [i] Forms a greenish copper salt, m. p. 137–138° [Moureu and Brachin, *Compt. rend.*, **139**, 209 (1904)]. [j] Forms a purple copper salt, m. p. 191–192° [Morgan and Drew, *J. Chem. Soc.*, 121, 922 (1922)]. [k] Forms a gray copper salt, m. p. 150–152°. [l] *Anal.* Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.27; H, 10.61. Thirty grams of the product was shaken intermittently for several hours with 100 cc. of 20% sodium hydroxide solution, then extracted with ether. On distillation the ether solution yielded small amounts of methyl isobutyl ketone (m. p. of 2,4-dinitrophenylhydrazone, 93–95°) and diisobutyl ketone (m. p. of semicarbazone, 120–121°). Most (72%) of the β-diketone was recovered unchanged. [m] Forms a gray copper salt, m. p. 176–177° [Morgan, Drew and Ackerman, *J. Chem. Soc.*, **125**, 745 (1924)]. [n] Forms a gray copper salt, m. p. 162–163° [Bouveault and Bongert, *Bull. Soc. Chim.*, [3] **27**, 1086 (1902)]. [o] *Anal.* Calcd. for $C_{10}H_{18}O_2$: C, 70.56; H, 10.66. Found: C, 70.91; H, 10.42. Forms a gray copper salt, m. p. 122–124°. [p] Forms a gray copper salt, m. p. 155–156° [Morgan and Holmes, *J. Chem. Soc.*, **125**, 760 (1924)]. [q] *Anal.* Calcd. for $C_{10}H_{18}O_2$: C, 70.56; H, 10.66. Found: C, 71.39; H, 10.08. Forms a blue copper salt, m. p. 111–112°. [r] *Anal.* Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.73; H, 10.48. Forms a gray copper salt, m. p. 152–153°. [s] *Anal.* Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 72.37; H, 10.40. Forms a blue copper salt, m. p. 107–108°. [t] *Anal.* Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.63; H, 10.16. Forms a gray copper salt, m. p. 141–142°. [u] This compound was not fully identified. [v] *Anal.* Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.27; H, 10.04. Forms a blue copper salt, m. p. 129–130°. [w] *Anal.* Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.34; H, 10.03. Does not form a copper salt [Morgan and Corly, *J. Chem. Soc.*, **127**, 2616 (1925)]. [x] *Anal.* Calcd. for $C_{10}H_{18}O_2$: C, 70.56; H, 10.66. Found: C, 70.10; H, 10.30. Forms a blue copper salt, m. p. 136–137°. [y] *Anal.* Calcd. for $C_{10}H_{18}O_2$: C, 70.56; H, 10.66. Found: C, 69.89; H, 9.96. Does not form a copper salt. [z] Melting point 58–60°. Forms a greenish copper salt, m. p. 222–224° [Morgan, Drew and Porter, *Ber.*, **58**, 333 (1925)].

readily may be obtained in an essentially pure condition. The boron trifluoride method is not of much value with methyl isobutyl ketone, since the methylene derivative is formed to a smaller extent than the methyl derivative and the latter is better prepared by the basic reagent method.[4]

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Experimental[10]

The acylation of ketones with various anhydrides was carried out according to the general procedure described previously[3] for the acetylation of ketones with acetic anhydride, using 0.5 mole of the ketone and 1.0 mole of the anhydride, except with methyl ethyl ketone and *n*-caproic anhydride which were used in one-half these quantities. The methyl and methylene derivatives obtained from methyl-methylene ketones were separated by the alkali extraction method described previously.[3] The yields and other data for the β-diketones are given in Table I.

With acetic anhydride (1.0 mole) and di-isopropyl ketone (0.5 mole) there was obtained 20 g. of product, b. p. 107–108 at 25 mm., which did not give the correct analysis for the corresponding β-diketone, dimethyl isobutyrylacetone. *Anal.* Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 62.29, 62.04; H, 9.85, 9.88.

(10) Boiling points and melting points are uncorrected. Analyses are by Dr. T. S. Ma, Microchemical Laboratory, University of Chicago, Chicago, Illinois.

Summary

1. The acylation of ketones with anhydrides by means of boron trifluoride to form β-diketones has been shown to be quite general with purely aliphatic anhydrides and various ketones having α-hydrogen.

2. The reaction is of particular value for the synthesis of a number of β-diketones, for certain of which the more common basic reagent method is not suitable.

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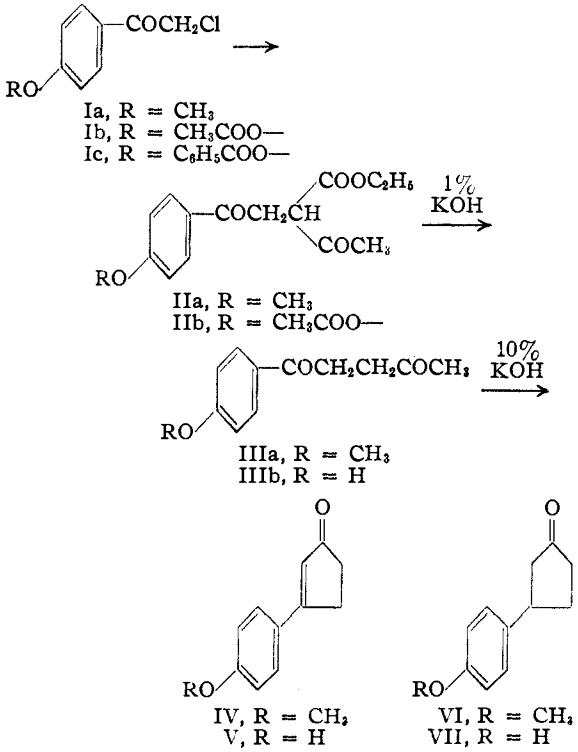
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Synthesis of 3-(*p*-Hydroxyphenyl)-cyclopentanone-1 and Related Compounds

BY A. L. WILDS AND THOMAS L. JOHNSON

As intermediate compounds in a projected synthesis, we were interested in preparing 3-(*p*-hydroxyphenyl)-cyclopenten-2-one-1 (V) and its reduction product 3-(*p*-hydroxyphenyl)-cyclopentanone-1 (VII). For this purpose we have employed the method which Borsche and co-workers[1] used a number of years ago for the synthesis of the corresponding compounds lacking the hydroxyl group.

p-Methoxyphenacyl chloride (Ia) was condensed with the sodio derivative of ethyl acetoacetate, giving the intermediate IIa, which upon treatment with aqueous potassium hydroxide underwent cyclization with loss of the carbethoxyl group to form the substituted cyclopentenone IV. This method of Borsche has been used in recent years by Robinson[2] and Weidlich[3] and their coworkers to prepare naphthylcyclopentenones and by Wilds[4] for the synthesis of an analogous ketocyclopentenophenanthrene derivative. In the present case considerable attention was devoted to finding the most favorable conditions for effecting the transformation of IIa into IV. Ultimately this was accomplished by warming the keto ester IIa with 1% potassium hydroxide for one and one-half hours, a process which resulted in the formation of the diketone IIIa, followed by refluxing with 10% alkali to effect the cyclization. In this manner, without isolation of intermediates, the cyclopentenone derivative IV was obtained in 65% over-all yield from *p*-methoxyphenacyl chloride. When the reaction was stopped after the action of 1% alkali, the crystalline diketone IIIa could be isolated. The latter was converted



to IV in 93% yield when heated for two hours with stronger alkali.

Selective hydrogenation of the carbon–carbon double bond of IV, using a palladium–charcoal catalyst, gave the crystalline cyclopentanone derivative VI in 63% yield. It was possible to demethylate the reduction product VI by the action of hydrobromic and acetic acids, although the yield of the phenol VII was rather low (39%), due to condensation. The unsaturated ketone IV was even more sensitive toward this demethyl-

(1) (a) Borsche and Menz, *Ber.*, **41**, 190 (1908); (b) Borsche and Fels, *ibid.*, **39**, 1809 (1906).

(2) Koebner and Robinson, *J. Chem. Soc.*, 566 (1941).

(3) Weidlich and Daniels, *Ber.*, **72**, 1590 (1939); Weidlich and Meyer-Delius, *ibid.*, **72**, 1941 (1939).

(4) Wilds, THIS JOURNAL, **64**, 1421 (1942).