[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

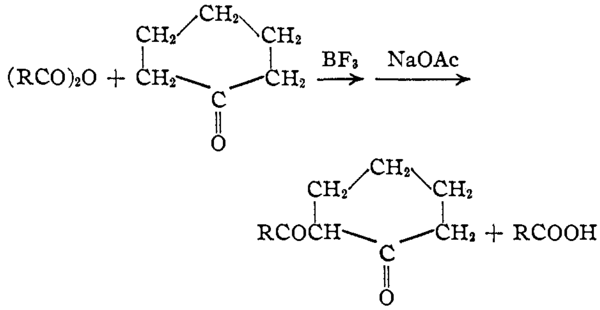
Improvement of Boron Fluoride Method of Acylation of Ketones to Form β-Diketones. Ring Opening of 2-Acyl Cyclic Ketones to Form Keto Acids[1]

BY ROBERT M. MANYIK,[2] FREDERICK C. FROSTICK, JR.,[3] JAMES J. SANDERSON[4] AND CHARLES R. HAUSER

RECEIVED JUNE 15, 1953

The success of the useful boron fluoride method of acylation of ketones with aliphatic anhydrides is now found to be dependent on the control of the temperature and the rate of mixing of the reactants. Two new procedures are described for preparing many β-diketones in much higher yields than those reported previously. Ring openings of 2-*n*-butyrylcyclopentanone and 2-*n*-butyrylcyclohexanone were effected with alkali to form δ-butyrylvaleric acid and ε-butyrylcaproic acid.

Various methyl and methylene ketones have been acylated with aliphatic anhydrides by means of boron fluoride to form β-diketones.[5–8] The method is particularly useful for the acylation of methylene ketones such as cyclohexanone for which the more common Claisen type of acylation employing basic reagents has usually not been very satisfactory.



However, even the boron fluoride method has generally given yields of only 35% for such acylations,[7] although a 56% yield has been reported for the acetylation.[5]

In the present investigation a study was first made of the acetylation of cyclohexanone with acetic anhydride to form 2-acetylcyclohexanone under various conditions. The yield was 45% when an ice-cooled mixture of 0.6 mole of the anhydride and 0.3 mole of the ketone was saturated with gaseous boron fluoride during two to three hours in accordance with the usual procedure.[6–8] The yield was not changed appreciably by allowing the reaction mixture to stand for as long as 18 hours after the slow saturation, by increasing the anhydride–ketone ratio to four to one, or by carrying out the reaction in the presence of ligroin, ethylene chloride or ether, although the yield was improved slightly (to 50–53%) by effecting the reaction in the presence of acetic acid (67–200 mole per cent.) or even wet ethylene chloride.[9] The yield was decreased slightly (to 42%) and a considerable amount of colored high-boiling material was produced when the anhydride–ketone mixture was saturated with the reagent within 25 minutes employing ice-bath cooling, in which case the temperature of the reaction mixture rose to 40°. However, the yield was improved considerably (to 73%) with correspondingly less high boiling material when saturation with the reagent was accomplished within 20 minutes, while maintaining the temperature of the reaction mixture at 0–10° by means of a Dry Ice–acetone bath. Moreover, the yield was improved still further (to 86%) when the anhydride–ketone mixture was added within five minutes to a boron fluoride–acetic acid complex, and the yield was 76% when the anhydride–ketone mixture was added similarly to a boron fluoride–ethyl acetate complex. In these inverse addition procedures, only ice-bath cooling is required. The boron fluoride complexes were prepared readily by adding the gaseous reagent to appropriate amounts of the acid or ester at 0° until the mixture solidified.

The "Fast Saturation" and "Inverse Addition" procedures described above for the acetylation of cyclohexanone were then applied to various acylations of cyclohexanone, cyclopentanone, diisobutyl ketone and acetophenone employing the usual two to one molar ratio of anhydride to ketone.[10] The results are summarized in Table I, there also being given for comparison the yields reported previously employing Slow Saturation procedures. It can be seen that with the exception of the acetylation of acetophenone,[11] the various acylations listed in Table I were realized in considerably better yields by one or both of the new procedures than by older ones. In general the inverse addition procedure would be chosen since it not only usually produced the best yields but it also is considered

---

[1] Paper LII on Condensations.

[2] Carbide and Carbon Chemicals Company Fellow, 1952–1953.

[3] Carbide and Carbon Chemicals Company Fellow, 1949–1950.

[4] Carbide and Carbon Chemicals Company Fellow, 1946–1947.

[5] H. Meerwein and D. Vossen, *J. prakt. Chem.*, **141**, 149 (1934).

[6] C. R. Hauser and J. T. Adams, THIS JOURNAL, **66**, 345 (1944).

[7] J. T. Adams and C. R. Hauser, *ibid.*, **67**, 284 (1945).

[8] *Org. Syntheses*, **20**, 6 (1940).

[9] The slight improvement in yield in this case was apparently due to the acetic acid formed by the hydrolysis of some of the excess acetic anhydride. Even when 25 mole per cent. of water was added to the anhydride and ketone and the resulting mixture saturated with the reagent, a 48% yield of the β-diketone was obtained, although none of the β-diketone could be isolated when 100 mole per cent. of water was used.

[10] As in the earlier slow saturation procedures (ref. 5, 6, 7), the yields of the β-diketones in the present procedures appear to be improved generally as the ratio of anhydride to ketone is increased. For example, in the propionylation of cyclohexanone, the yields were, respectively, 25, 38 and 63%, when the ratio was 1:2, 1:1 and 2:1 in the rapid saturation procedure, and 51 and 79% when the ratio was 1:1 and 2:1 in the inverse addition procedure.

[11] This acetylation and also that of tetralone have been reported in 83% yield in relatively small scale runs employing only ice-bath cooling (ref. 5). Since the acetylation of acetophenone has been realized in only 50% yield by slowly saturating the reaction mixture at 0° (ref. 7), the higher yield reported earlier apparently resulted from rapid addition of the reagent. We obtained a 73% yield for this acetylation on adding the reagent rapidly with ice-bath cooling but the temperature of the reaction mixture rose to 40° producing more high boiling material than usual. Yields of 80–86% of acetylacetone are obtained from acetic anhydride and acetone by a slow saturation procedure at 0° (ref. 8) but this β-diketone may arise not only from the acetylation of the ketone but also from self-condensation of the anhydride (ref. 5).

TABLE I

YIELDS OF β-DIKETONES FROM ANHYDRIDES AND KETONES BY BORON FLUORIDE EMPLOYING RAPID SATURATION, INVERSE ADDITION AND SLOW SATURATION PROCEDURES

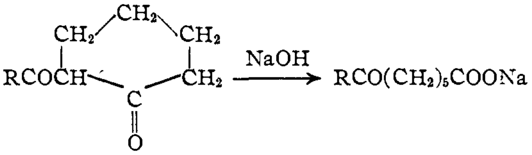
Anhydride	Ketone	β-Diketone	B.p. °C.	Mm.	Rapid saturation	Yield, % inverse addition[a]	Slow saturation
Acetic	Cyclohexanone	2-Acetylcyclohexanone	95–98	10	73	86, 75[b]	35,[c] 56[d]
Propionic	Cyclohexanone	2-Propionylcyclohexanone	123–125	20	63	79	35[c]
n-Butyric	Cyclohexanone	2-*n*-Butyrylcyclohexanone	133–135	20	74	83	34[c]
Caproic	Cyclohexanone	2-Caproylcyclohexanone[e]	140–145	9.5	37[f]	66, 68[b]	
2-Ethylbutyric	Cyclohexanone	2-(2-Ethylbutyryl)-cyclohexanone[g]	143–146	20.5	68[h]		
2-Ethylhexoic	Cyclohexanone	2-(2-Ethylhexoyl)-cyclohexanone[i]	135–138	5	56		
Acetic	Cyclopentanone	2-Acetylcyclopentanone	72–75	8	59	76	35[j]
n-Butyric	Cyclopentanone	2-*n*-Butyrylcyclopentanone[k]	99–101	10	54	88[b]	
Acetic	Diisobutyl	3-Isopropyl-6-methylheptanedione-2,4	112–115	20	23, 47[l]	78	45
Acetic	Acetophenone	1-Phenylbutanedione-1,3	142–145	19	83[m], 67[n]	70	50,[c] 83[d]
Propionic	Acetophenone	1-Phenylpentanedione-1,3	153–154	16	54	67	30[c]
n-Butyric	Acetophenone	1-Phenylhexanedione-1,3	165–166	14	63	81[o]	15[c]

[a] Acetic acid used unless otherwise stated. [b] Ethyl acetate used. [c] Reference 7. [d] Reference 5. [e] *Anal.* Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.70; H, 10.02. Gray-green copper enolate, m.p. 105–106°. [f] Anhydride–ketone ratio 1:2. [g] *Anal.* Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.40; H, 10.40. Dark green copper enolate, m.p. 114–115°. [h] When the anhydride–ketone ratio was 1:1, the yield was 14%; when it was 1:2, no product could be isolated. [i] *Anal.* Calcd. for $C_{14}H_{24}O_2$: C, 74.97; H, 10.78. Found: C, 74.93; H, 10.52. An attempt to prepare the copper enolate failed. [j] Reference 14. [k] *Anal.* Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.81; H, 9.11. Purple enol test. [l] Saturated in presence of acetic acid. [m] Saturated at 5 to 12°. [n] Saturated at −5 to 0°. [o] Butyric acid used.

more convenient. For acetylations by this procedure, the complex of boron fluoride with acetic acid[12] is recommended but, for acylations with higher anhydrides, the complex with ethyl acetate is probably preferable since that with acetic acid appeared to produce small amounts of the acetyl derivatives. These impurities arose presumably from exchange between the higher anhydride and acetic acid, followed by acetylation of the ketone by the resulting acetic anhydride or mixed acetic anhydride. There was no indication of such impurities in the acylations with higher anhydrides in the presence of ethyl acetate. In the butyrylation of acetopheneone, the formation of the acetyl derivative was avoided entirely by the use of the complex of boron fluoride with butyric acid, but the separation of butyric acid from the β-diketone was somewhat tedious. It should be pointed out that neither the carboxylic acid nor the ethyl acetate appeared to effect any acylation of the ketone[13]; the ethyl acetate being largely recovered.

Since the anhydrides higher than butyric anhydride were not available commercially, attempts were made to obtain satisfactory yields in the acylation of cyclohexanone employing less of the anhydride than usual. Some success was achieved with caproic anhydride with which a 37% yield based on the anhydride was obtained employing only a 1:2 ratio of anhydride to ketone. Although a 66–68% yield based on the ketone was obtained employing the usual two to one ratio of anhydride to ketone, this yield would correspond only to 33–34% if based on the less available anhydride. However the acylation of cyclohexanone with 2-ethylbutyric anhydride could be realized in an acceptable yield only by the use of excess of the anhydride (see note *h* of Table I).

The acylations of cyclopentanone and cyclohexanone are of particular interest since the resulting 2-acyl derivatives are useful in connection with the synthesis of δ- and ε-acyl acids. Thus, the acyl derivatives of cyclopentanone and cyclohexanone undergo, on alkaline cleavage, mainly ring openings to form these acids. Previously, 2-acetylcyclopentanone and 2-acetyl- and 2-propionylcyclohexanones were cleaved to form the corresponding keto acids in yields of 56–60%.[14] We have similarly cleaved 2-*n*-butyrylcyclopentanone and 2-*n*-butyrylcyclohexanone to form δ-acylvaleric and ε-acylcaproic acids in yields of 78–90% and 65%, respectively. The over-all yields from cyclopentanone and cyclohexanone were 69–79% and 54%, respectively. The cleavage may be illustrated with 2-acylcyclohexanones.



Experimental

Diketones (Table I). (A) Rapid Saturation Procedure.—A mixture of the anhydride (0.6 mole) and the ketone (0.3 mole) was placed in a three-necked flask fitted with an efficient, sealed stirrer, a gas inlet tube reaching to within 1–2 cm. of the surface of the liquid, and (in the third neck) a calcium chloride outlet tube and a thermometer immersed in the liquid. The flask was immersed in a Dry Ice–acetone-bath, the mixture stirred vigorously, and commercial boron fluoride (bubbled first through 95% sulfuric acid) passed in as fast as possible (10–20 minutes) until the mixture, kept at 0–10° (for the methylene ketones) or at 5–15° (for acetophenone) was saturated (copious evolution of white fumes). The Dry Ice–acetone-bath was then replaced by an ice-bath and the reagent passed in at a slower rate for 15 minutes to ensure maximum absorption. The stirring was continued until the total reaction time was 4

---

[12] The use of the complex of boron fluoride with ethyl ether in the acetylation of acetophenone with acetic anhydride gave a considerably lower yield than that obtained with the acetic acid complex.

[13] Even phenyl acetate, which is a more reactive ester than ethyl acetate, failed to acetylate acetophenone or methyl isobutyl ketone in the presence of boron fluoride at 0–10°, although a little of the phenyl ester underwent the Fries reaction.

[14] C. R. Hauser, F. W. Swamer and B. I. Ringler, THIS JOURNAL, **70**, 4023 (1948).

hours, while the ice-bath was allowed to come slowly to room temperature. The reaction mixture was poured into a solution of sodium acetate (two moles per mole of anhydride), refluxed for 30 minutes to one hour (until the boron fluoride complexes were hydrolyzed), chilled and extracted with ether or ligroin (b.p. 30–60°).[15] When the product was soluble in the hydrolysis mixture, the solution was partly neutralized with solid sodium bicarbonate before extraction. The extracts were washed free of acid with saturated sodium bicarbonate solution and dried over Drierite. The β-diketones were isolated by distillation.

In experiments in which the reaction mixtures became difficult to stir because of the formation of solid boron fluoride complexes, ethylene chloride was used as solvent. After the reaction mixture was treated with the sodium acetate solution, the ethylene chloride was removed by distillation until the vapor temperature rose above 90°. The residue was then refluxed and worked up as described above.

(B) Inverse Addition Procedure.—Acetic acid[16] (0.8 mole) or ethyl acetate (0.6 mole) was placed in a three-necked flask fitted with an efficient, sealed stirrer, a gas inlet tube and an outlet tube loosely closed with a cotton plug. The flask was immersed in an ice-bath and, with vigorous stirring, boron fluoride passed in as rapidly as it was absorbed. Addition was continued (at a reduced rate as saturation was approached) until the contents of the flask became a powdery solid.[17] At this point, the acid had absorbed 75–85 mole per cent. of the reagent,[18] and the ester, 100 mole per cent. A dropping funnel was then substituted for the gas inlet tube, and a mixture of the ketone (0.2 mole) and anhydride (0.4 mole) was added with ice-bath cooling and vigorous stirring during 2–4 minutes. After stirring 30 minutes the ice-bath was removed. The reaction mixture was allowed to stand 4 hours and then worked up as described in the rapid saturation procedure. Ethyl acetate was removed in the manner described for ethylene chloride.

Alkaline Cleavage of 2-Acyl Cyclic Ketones.—The β-diketone (0.1–0.2 mole) was dissolved in excess of 5% sodium hydroxide solution (containing a molecular equivalent plus 10% of the base) and the resulting solution refluxed two hours. After washing with ether, the cooled alkaline solution was acidified with hydrochloric acid, and the liberated keto acid isolated by distillation.

2-*n*-Butyrylcyclopentanone gave a 78–90% yield of δ-*n*-butyryl-*n*-valeric acid, b.p. 140–142 at 1 mm., m.p. 38–39°, neut. equiv. calcd. 172.2, found 171.1.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.78; H, 9.37. Found: C, 62.96; H, 9.45.

2-*n*-Butyrylcyclohexanone gave a 65% yield of ϵ-*n*-butyryl-*n*-caproic acid, b.p. 157–158° at 2.5 mm., m.p. 42–43°, neut. equiv. calcd. 186.2, found 185.1.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.50; H, 9.74. Found: C, 64.61; H, 9.79.

---

[15] Ligroin is usually advantageous, especially in acetylations, because it removes very little acetic acid from the aqueous phase, whereas ether removes a considerable amount of the acid, the subsequent removal of which requires numerous washings with sodium bicarbonate solution.

[16] For acylations with anhydrides higher than acetic anhydride, the corresponding higher carboxylic acid may be used in a similar manner.

[17] Ethylene chloride (75–100 ml.) may be used to keep the solid complex from caking, which occurred when the stirring was not sufficiently rapid.

[18] The solid appears to consist of a mixture of mono- and diacetic acid–boron fluoride complexes. The mono-acetic acid complex may be prepared conveniently on a relatively large scale and used as required, 0.6 mole being employed with 0.2 mole of ketone and 0.4 mole of anhydride. Since the diacid complex, which is a liquid (Meerwein and Pannwitz, *J. prakt. Chem.*, **141**, 123 (1934)), is soluble in ethylene chloride, the solid monoacetic acid complex is obtained by saturating an ethylene chloride solution of acetic acid with boron fluoride, filtering and washing the precipitate with the solvent. It is hygroscopic and should be protected from moisture.

DURHAM, N. C.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Friedel–Crafts Reactions of Methanesulfonyl Chloride with Benzene and Certain Substituted Benzenes[1]

BY WILLIAM E. TRUCE AND CALVIN W. VRIESEN[2]

RECEIVED MAY 20, 1953

The Friedel–Crafts reaction of methanesulfonyl chloride with benzene has been examined with respect to the type of catalyst, time of reaction, amount of catalyst, and the effect of solvent. The reaction with toluene in the presence of aluminum chloride resulted in a mixture of isomers, the para/meta ratio indicating that the reagent exhibits comparatively low selectivity. A good yield of the *p*-isomer was obtained when chlorobenzene was treated with this reagent. Mesityl methyl sulfone was produced in a low conversion in the presence of stannic chloride. Phenyl methanesulfonate was formed in the reaction with anisole. The difference in behavior of methanesulfonyl chloride and aromatic sulfonyl chlorides in the Friedel–Crafts reaction is discussed.

Good conversions have frequently been obtained with aromatic sulfonyl chlorides in the preparation of diaryl sulfones by the Friedel–Crafts method.[3]

An early attempt[4] to apply this reaction to aliphatic sulfonyl chlorides, consisting of treating toluene with phenylmethanesulfonyl chloride in the presence of aluminum chloride, resulted in tar formation only. Methanesulfonyl chloride is reported[5] to react with benzene in the presence of excess aluminum chloride to give methyl phenyl sulfone in a conversion which is "not large." This observation was made in connection with a study of the complex of methanesulfonyl chloride with aluminum chloride; this complex decomposed to sulfur dioxide and methyl chloride when it was heated gently. Burton and Hoggarth[6] studied the reaction of methanesulfonyl chloride with hydroquinone dimethyl ether in the presence of zinc chloride and obtained *p*-anisyl methanesulfonate. Sulfonates also were obtained in similar reactions with 3-methylbutanesulfonyl chloride. Recently[7] the internal Friedel–Crafts reaction of ω-phenylalkanesulfonyl chlorides leading to cyclic sulfones was studied.

In view of the scarcity of information on the preparation of alkyl aryl sulfones by the Friedel–

---

[1] An abstract of a thesis submitted by Calvin W. Vriesen to the Faculty of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, August, 1952.

[2] Purdue Research Foundation Fellow.

[3] C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 673–675.

[4] R. Otto, *Ber.*, **13**, 1287 (1880).

[5] J. Böeseken and H. W. van Ockenburg, *Rec. trav. chim.*, **33**, 320 (1914).

[6] H. Burton and E. Hoggarth, *J. Chem. Soc.*, 14 (1945).

[7] W. E. Truce and J. P. Milionis, THIS JOURNAL, **74**, 974 (1952).