Reagents for Organic Synthesis

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Introduction

Arrangement. Suppliers mentioned in the text are listed in a section placed before the indexes and easily located by an indenture.

For enhanced usefulness the book is provided not only with a subject and an author index but also with an index of types, that is, types of reactions or types of compounds, for example: acetylation, bromination, characterization (of a, b, c, etc.), decarboxylation, or: π-acids, benzyne precursors, carbene precursors, diimide precursors. Listed alphabetically under each such entry are all the reagents which figure in the operation or group cited, whether as prime reactant, catalyst, solvent, scavenger, etc. A given reagent may fit appropriately in two or more categories. When a reagent does not fit easily into a reasonable category, we leave it unclassified rather than make a forced assignment. With no less than 92 reagents available as oxidants and 101 for use as reducing reagents, it seemed out of the question to attempt to indicate in the index of types further details about these general reactions. In a few instances a procedure cited for the preparation of one reagent provides a good example of the use of another one. For example, a preferred route to allene is by reaction of 2,3-dichloropropene with zinc dust and ethanol; in the index of types the entries under "Dechlorination" include "Zinc dust–ethanol, *see* Allene, preparation."

Names and spelling. One guideline we have followed is the rule recently adopted by *Organic Syntheses* that when an ester, ether, or peroxide contains two or more alkyl, aryl, or acyl groups the name must indicate the number of such groups:

Formula	*Correct*	*Incorrect*
$(CH_3)_2O$	Dimethyl ether	Methyl ether
$(C_2H_5O)_2SO_2$	Diethyl sulfate	Ethyl sulfate
$(C_6H_5)_2O$	Diphenyl ether	Phenyl ether
$(CO_2CH_3)_2$	Dimethyl oxalate	Methyl oxalate
$CH_2(CO_2C_2H_5)_2$	Diethyl malonate	Ethyl malonate
$(C_6H_5COO)_2$	Dibenzoyl peroxide	Benzoyl peroxide
$HC(OC_2H_5)_3$	Triethyl orthoformate	Ethyl orthoformate
$(C_2H_5O)_4C$	Tetraethyl orthocarbonate	Ethyl orthocarbonate

That the situation previously was highly confused is evident from the following entries in the index of *Org. Syn., Coll. Vol.*, **4**: "Diethyl oxalate" and "Diethyl malonate" (both correct), but "Ethyl orthoformate" and "Ethyl orthocarbonate" (both incorrect). The following entry is describable as a double error: "Triethyl orthoformate, *see* Ethyl orthoformate." To locate all references to a given ester, it is thus necessary to search under two names. We urge suppliers to revise their catalogs in accordance with the rule cited. In this book we do not even list, with cross references, names which we consider to be incorrect.

Similar reform in the nomenclature of polyhalogen compounds may come some day, but for the present we consider it imprudent to do more than make a start. Thus the correct names for BF_3 and for $ClCH_2CH_2Cl$ surely are boron trifluoride and ethylene dichloride, and we feel no restraint from using them. However, although the names methylene chloride for CH_2Cl_2 and aluminum chloride for $AlCl_3$ seem

incorrect, we cannot bring ourselves to break with tradition and employ other names.

As explained in our *Style Guide for Chemists* (p. 77), we disapprove of the weak-sounding dioxăn, furăn, tryptophăn, and urethăn and add the letter *e* to these words to produce the strong pronunciations dioxāne, furāne, tryptophāne, and urethāne. For the same reason we favor desoxo- and desoxy- over deoxo- and deoxy-.

Abbreviations. Short forms of abbreviations of journal titles are as follows:

Journal of the American Chemical Society
Angewandte Chemie
Annalen der Chemie
Annales de chimie (Paris)
Chemische Berichte (formerly Berichte der deutschen chemischen Gesellschaft)
Bulletin de la société chimique de France
Chemical Communications
Acta Chemica Scandinavica
Collection of Czechoslovak Chemical Communications
Comptes rendus hebdomadaires des séances de l'académie des sciences
Gazzetta chimica italiana
Helvetica Chimica Acta
Journal of the Chemical Society (London)
Journal of Organic Chemistry
Monatshefte für Chemie
Organic Syntheses
Organic Syntheses, Collective Volume
Recueil des travaux chimique des Pays-Bas (The Netherlands)

The book by one of us, *Organic Experiments*, D. C. Heath and Co., Boston (1964), is referred to as *Org. Expts.*

Abbreviations

Ac	Acetyl	MeOH	Methanol
AcOH	Acetic acid	Ms	Mesyl, CH_3SO_2
BuOH	Butanol	NBS	N-Bromosuccinimide
Bz	Benzoyl	Ph	Phenyl
Cathyl	Carboethoxy	Phth	Phthaloyl
Cb	Carbobenzoxy	PrOH	Propanol
Diglyme	Diethylene glycol dimethyl ether	Py	Pyridine
DMF	Dimethylformamide	THF	Tetrahydrofurane
DMSO	Dimethyl sulfoxide	Triglyme	Triethylene glycol dimethyl ether
DNF	2,4-Dinitrofluoro-benzene	Trityl	$(C_6H_5)_3C-$
DNP	2,4-Dinitrophenyl-hydrazone	Ts	Tosyl, p-$CH_3C_6H_4SO_2-$
EtOH	Ethanol	TsCl	Tosyl chloride
Glyme	1,2-Dimethoxyethane	TsOH	Tosic acid, p-$CH_3C_6H_4SO_3H$

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A

Acetaldehyde, CH_3CHO. Mol. wt. 44.05, b.p. 20.8°, sp. gr. 0.78. Suppliers: B, E, F, MCB.

Preparation. (a) Measure 20 ml. (20 g.) of paraldehyde into a 50-ml. round-bottomed flask, add a cooled mixture of 0.5 ml. each of concd. sulfuric acid and water, attach a fractionating column, condenser, and ice-cooled receiver, and heat gently with a microburner at such a rate that acetaldehyde distils at a temperature not higher than 35°. To avoid charring of the mixture, continue only until about half of the material has been depolymerized.

(b) *p*-Toluenesulfonic acid has been recommended as catalyst for depolymerization of paraldehyde without specification of details.[1]

[1]N. L. Drake and G. B. Cooke, *Org. Syn., Coll. Vol.*, 2, 407 (1943)

Acetaldoxime, $CH_3CH{=}NOH$. Mol. wt. 59.07, m. p. 47°. Suppliers: A, B, KK.

The reagent reacts with a diazonium salt to form an oxime which on acid hydrolysis affords an aryl methyl ketone.[1]

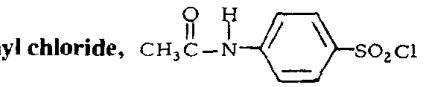
$$ArN_2Cl + CH_3CH{=}NOH \longrightarrow Ar\overset{\displaystyle CH_3}{\underset{|}{C}}{=}NOH \xrightarrow{H^+} Ar\overset{\displaystyle CH_3}{\underset{|}{C}}{=}O$$

[1]W. F. Beech, *J. Chem. Soc.*, 1297 (1954)

Acetamide, CH_3CONH_2. Mol. wt. 59.07, m.p. 82°. Suppliers: A, B, E, F, KK, MCB.

Acetamide is useful in the bromination of acid-sensitive compounds since it forms a stable complex with hydrogen bromide, $CH_3CONH_2 \cdot HBr$, which is insoluble in common bromination solvents.[1]

[1]K. Zeile and H. Meyer, *Ber.*, **82**, 275 (1949)

***p*-Acetamidobenzenesulfonyl chloride**, 

Mol. wt. 233.68, m.p. 149°. Suppliers: E, F, MCB.

Preparation from acetanilide and chlorosulfonic acid.[1] Use as catalyst for the Beckmann rearrangement of oximes in pyridine.[2]

[1]S. Smiles and J. Stewart, *Org. Syn., Coll. Vol.*, **1**, 8 (1941)

[2]St. Kaufmann, *Am. Soc.*, **73**, 1779 (1951); H. Heusser *et al.*, *Helv.*, **38**, 1399 (1955); G. Rosenkranz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org.*, **21**, 520 (1956)

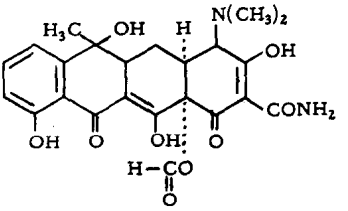
Acetic anhydride, $(CH_3CO)_2O$. Mol. wt. 102.09, b.p. 139.6°, sp. gr. 1.08.

Reagent that has stood for a time after a bottle has been opened should be tested either in a preliminary run or by shaking a sample with ice water and rapidly titrating the free acetic acid. Fractionation affords pure anhydride; material of practical grade should first be distilled from anhydrous sodium acetate to eliminate halogen compounds and metals.

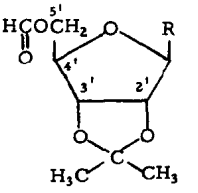
Procedures for acetylation described in *Organic Experiments*: DL-alanine (Chapt. 28); of amines in aqueous solution (Chapts. 34.3, 53.4); reductive acetylation (Chapt. 42.4); salicylic acid, order catalytic activity: $H_2SO_4 > BF_3 > Py > NaOAc$ (Chapt. 48).

Acetic–formic anhydride, $CH_3C(=O)-O-CH=O$. The reagent is prepared by cooling 2 volumes of acetic anhydride to 0°, slowly adding 1 volume of 100% formic acid, heating at 50° for 15 min., and cooling immediately to 0°.[1] It formylates alcohols, including tertiary alcohols that are dehydrated on attempted acetylation, and so is useful for the analysis of oils containing such alcohols.[1]

It has been used for the preparation in high yield of O^{12a}-formyltetracycline (1)[2] and of 5′-O-formyl derivatives of nucleoside 2′,3′-acetonides (2),[3] in each case in piperidine at −20 to 0°. The O-formyl group is suggested for the protection of the



(1)



(2)

5′-hydroxyl group since it is cleaved more readily than an acetyl group; for example, it is removed by boiling methanol.

Japanese chemists[4] prepare the reagent either by the reaction of acetyl chloride with sodium formate or of formic acid with ketene. The reagent formylates amino acids in formic acid as solvent. The N-formyl group is useful as a blocking group in peptide synthesis. It is surprisingly resistant to basic hydrolysis but readily solvolyzed in dilute acid.[5]

[1]V. C. Mehlenbacher, *Org. Analysis*, **1**, 37 (1953); W. Stevens and A. Van Es, *Rec. trav.*, **83**, 1287, 1294 (1964)

[2]R. K. Blackwood, H. H. Rennhard, and C. R. Stephens, *Am. Soc.*, **82**, 5194 (1960)

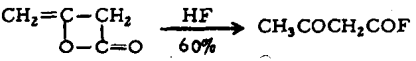
[3]J. Žemlička, J. Beránek, and J. Smrt, *Coll. Czech.*, **27**, 2784 (1962)

[4]L. Muramatsu, M. Murakami, T. Yoneda, and A. Hagitani, *Bull. Chem. Soc. Japan*, **38**, 244 (1965)

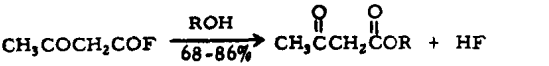
[5]J. C. Sheehan and D.-D. H. Yang, *Am. Soc.*, **80**, 1154 (1958)

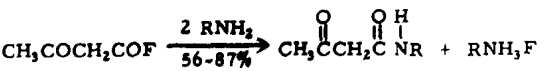
Acetoacetyl fluoride, CH_3COCH_2COF. Mol. wt. 104.08, b.p. 132–134°.

Prepared[1] by reaction of diketene with anhydrous hydrogen fluoride, the reagent can be stored for weeks at 0°, but at room temperature it slowly decomposes to form



dehydroacetic acid. It is unsatisfactory for Friedel-Crafts acylation, but serves as an acetoacetylating agent for alcohols and amines:



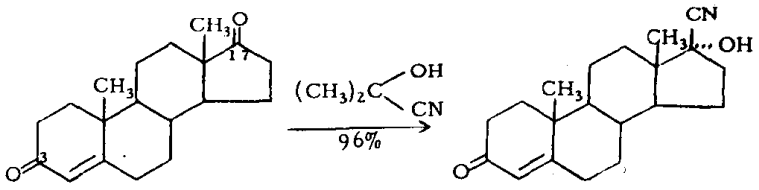


[1]G. A. Olah and S. J. Kuhn, *J. Org.*, **26**, 225 (1961)

Acetone cyanohydrin, $(CH_3)_2C(OH)CN$. Mol. wt. 85.10, b.p. 80°/15 mm. Suppliers: Rohm and Haas, Union Carbide, A, B, MCB.

Preparation. (a) By addition of 40% sulfuric acid to an aqueous solution of acetone and sodium cyanide at 10–20°.[1] (b) Reaction of potassium cyanide with the sodium bisulfite addition compound of acetone gives material which is less pure but satisfactory for immediate use.[2]

Use for ***transcyanohydrination***: preparation in high yield of the 17-monocyanohydrin of a 3,17-diketo-Δ^4-steroid by hydrogen cyanide exchange with the reagent.[3]

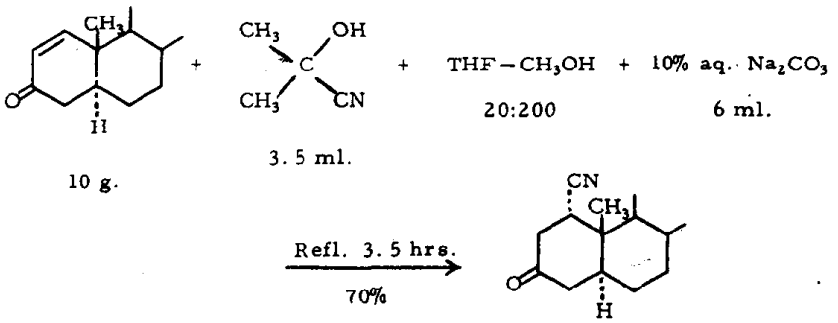


Δ^4-Androstene-3,17-dione

Use for the ***addition of hydrogen cyanide*** to benzalacetophenone and other α,β-unsaturated ketones; 5–10% aqueous sodium carbonate is the most satisfactory

$$C_6H_5CH{=}CHCOC_6H_5 \xrightarrow[95\%]{(CH_3)_2C(OH)CN} C_6H_5CHCH_2COC_6H_5 \quad (CN)$$

catalyst.[4] The addition of hydrogen cyanide to conjugated steroid ketones usually gives mixtures and poor yields, but Julia *et al.*[5] achieved smooth addition to Δ^1-5α-cholestene-3-one as follows. A solution of the ketone and acetone cyanohydrin in tetrahydrofurane–methanol was treated with a little aqueous sodium carbonate

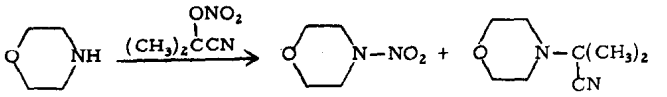


and refluxed for 3.5 hrs. After evaporation in vacuum, chromatography separated 1.2 g. of starting material and afforded 1α-cyano-5α-cholestane-3-one in good yield.

[1]R. F. B. Cox and R. T. Stormont, *Org. Syn., Coll. Vol.*, **2**, 7 (1943)
[2]E. C. Wagner and M. Baizer, *ibid.*, **3**, 324 (1955)
[3]A. Ercoli and P. de Ruggieri, *Am. Soc.*, **75**, 650 (1953)
[4]B. E. Betts and W. Davey, *J. Chem. Soc.*, 4193 (1958)
[5]S. Julia, H. Linarès, and P. Simon, *Bull. soc.*, 2471 (1963)

Acetone cyanohydrin nitrate, $(CH_3)_2C(ONO_2)CN$. Mol. wt. 130.11, b.p. 65–66°/10 mm. Supplier: Aldrich. Preparation by nitration of acetone cyanohydrin with fuming nitric acid and acetic anhydride.[1] *Caution*: moderately explosive.

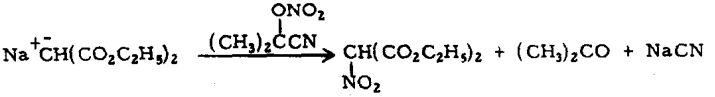
Acetone cyanohydrin nitrate is useful for conversion of primary and secondary amines into nitramines.[2] The reaction is unique in that nitration is carried out under



(1) (2)

neutral or alkaline conditions. Thus N-nitromorpholine (1, m.p. 54°) is obtained in 57–64% yield by reaction of morpholine with 2 equivalents of the reagent;[1] hydrochloric acid is added to the reaction mixture to dissolve excess morpholine and the by-product (2), and (1) is extracted with methylene chloride. In nitrating other amines, particularly on a large scale, acetonitrile can be used as solvent for better control of temperature.

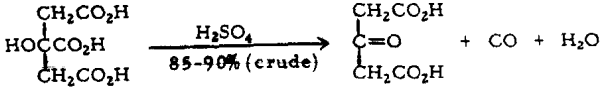
The reagent is useful also for the nitration of active-methylene compounds in the form of the sodio derivatives; this is the basis for a general synthesis of α-nitro esters.[3]



[1]J. P. Freeman and I. G. Shepard, *Org. Syn.*, **43**, 83 (1963)
[2]W. D. Emmons and J. P. Freeman, *Am. Soc.*, **77**, 4387 (1955)
[3]*Idem, ibid.*, **77**, 4391 (1955)

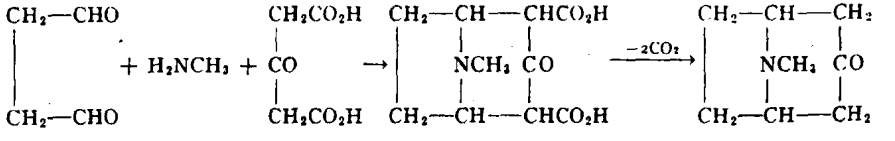
Acetonedicarboxylic acid, $HO_2CCH_2COCH_2CO_2H$. Mol. wt. 146.10, m.p. 138° dec. Suppliers: Baker, Eastern, Pfizer.

The diacid can be obtained in high yield by the action of fuming sulfuric acid on citric acid at 0–30°,[1] but material so prepared is not stable and should be crystallized



from ethyl acetate or converted into the diethyl ester by Fischer esterification.[2] Diethyl acetonedicarboxylate (b.p. 145–148°/17 mm.) is supplied by Aldrich.

Robinson's classical synthesis of tropinone was achieved by condensation of succindialdehyde and methylamine with acetonedicarboxylic acid.[3] Schöpf[4] later carried out the reaction in a solution buffered to pH 5 and at room temperature and



Tropinone

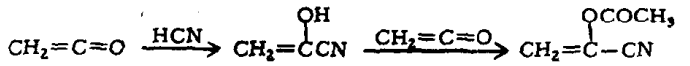
under these simulated physiological conditions the intermediate diacid loses carbon dioxide spontaneously and tropinone was obtained in yield as high as 90%. *See also* Glutaraldehyde.

[1]R. Adams, H. M. Chiles, and C. F. Rassweiler, *Org. Syn., Coll. Vol.*, **1**, 10 (1941)
[2]R. Adams and H. M. Chiles, *ibid.*, **1**, 237 (1941)

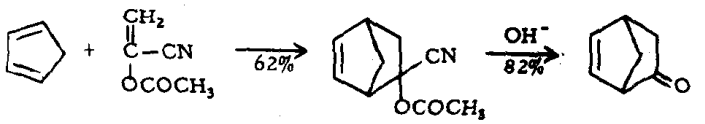
[3]R. Robinson, *J. Chem. Soc.*, 111, 762 (1917)
[4]C. Schöpf and G. Lehmann, *Ann.*, 518, 1 (1935)

Acetone dimethyl ketal, *see* 2,2-Dimethoxypropane.

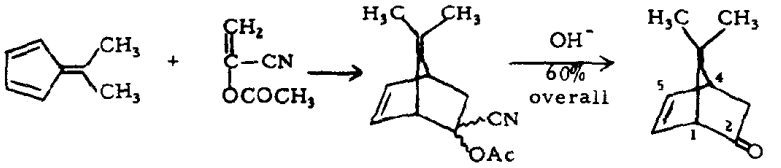
α-Acetoxyacrylonitrile, $CH_2{=}C(OCOCH_3)-CN$. Mol. wt. 111.10., b.p. 173°/772 mm. Preparation by addition of hydrogen cyanide to ketene; best yields are obtained with a mildly basic catalyst such as potassium acetate.[1]



The reagent is useful as a dienophile because the product on hydrolysis affords a ketone, as in the synthesis of dehydronorcamphor:[2]



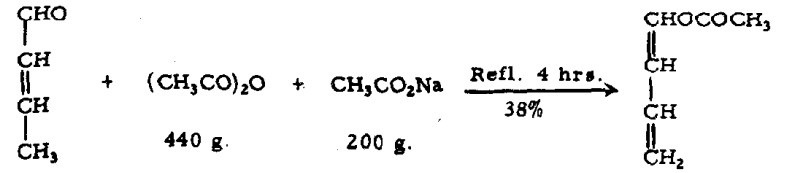
A further example is in the synthesis of 7-isopropylidenebicyclo[2.2.1]-5-heptene-2-one:[3]



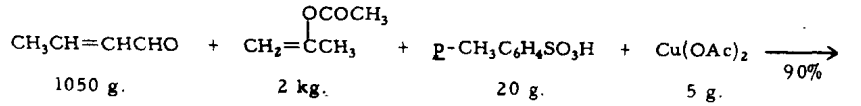
[1]S. Deakin and N. T. M. Wilsmore, *J. Chem. Soc.*, 97, 1971 (1910); F. Johnston and L. W. Newton, U. S. patent 2,395,930 (1946) [*C.A.*, 40, 4078 (1946)]; H. J. Hagemeyer, Jr., *Ind. Eng. Chem.*, 41, 765 (1949)
[2]P. D. Bartlett and B. E. Tate, *Am. Soc.*, 78, 2473 (1956)
[3]C. H. De Puy and P. R. Story, *Am. Soc.*, 82, 627 (1960)

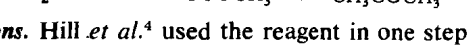
1-Acetoxybutadiene, Mol. wt. 112.16, b.p. 42–43°/16 mm., 51–52°/30 mm.

Preparation. This diene, the enol acetate of crotonaldehyde, can be prepared

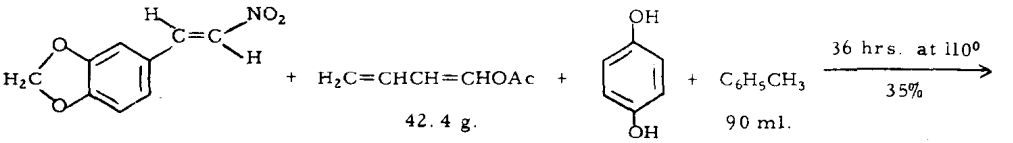


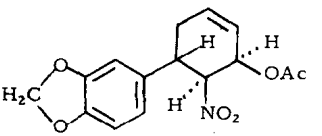
by refluxing the aldehyde with acetic anhydride and sodium acetate.[1] Workup includes removal of considerable crotonaldehyde (powerful lachrymator) with bisulfite; this fact together with the low yield[2] suggests that the reaction reaches equilibrium. A much better method described by Hagemeyer and Hull[3] consists in reaction of crotonaldehyde with isopropenyl acetate, a catalytic amount of *p*-toluenesulfonic acid, and a little copper acetate (function not stated). The aldehyde is added to the other components in 2–3 hrs. with provision for continuous removal of acetone to displace the equilibrium. The yield of twice-distilled 1-acetoxybutadiene is 90%.



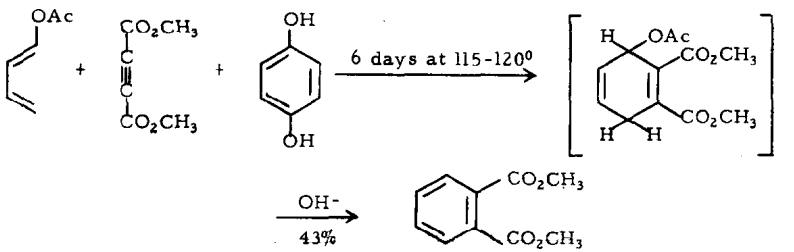


Diels-Alder reactions. Hill *et al.*[4] used the reagent in one step of a synthesis of the parent structure of lycorine.

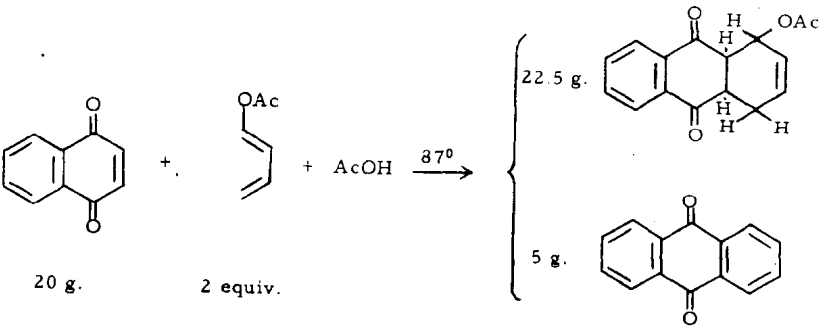




Hill and Carlson[5] demonstrated use of the reagent in combination with an acetylene for the direct production of an aromatic ring. The reagent adds normally to quinones,



but in acetic acid at steam bath temperature the adduct is partially aromatized.[6]



[1]O. Wichterle and M. Hudlicky, *Coll. Czech.*, **12**, 564 (1947)
[2]P. Y. Blanc, *Helv.*, **44**, 1 (1961), used essentially the same procedure and reports a yield of 35%.
[3]H. J. Hagemeyer, Jr., and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949)
[4]R. K. Hill, J. A. Joule, and L. J. Loeffler, *Am. Soc.*, **84**, 4951 (1962)
[5]R. K. Hill and R. M. Carlson, *J. Org.*, **30**, 2414 (1965)
[6]W. Flaig, *Ann.*, **568**, 1 (1950)

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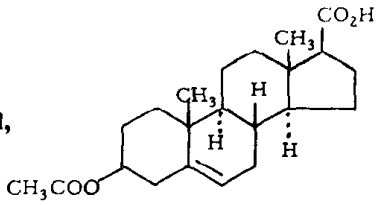
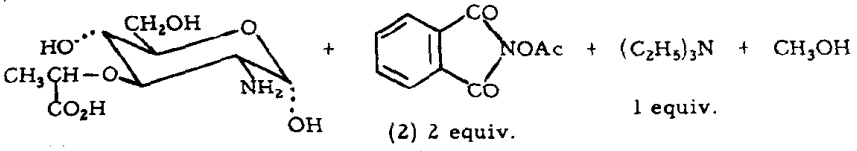
3β-Acetoxy-Δ⁵-etienic acid,



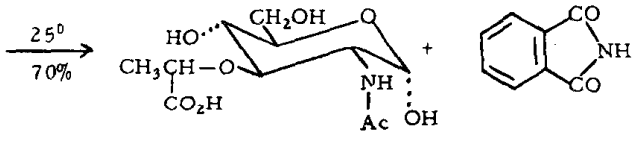
Mol. wt. 360.48, m.p. 238°. Preparation by hypobromite oxidation of pregnenolone acetate (available from Syntex S. A.).[1] The corresponding acid chloride has been used for the resolution of 1α-hydroxydicyclopentadiene,[2] of *cis,cis*-l-decalol,[3] and of *trans*-3-*t*-butylcyclohexanol[4] (in this case conventional resolution of acid phthalate salts with alkaloids failed).

[1]J. Staunton and E. J. Eisenbraun, *Org. Syn.*, **42**, 4 (1962)
[2]R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959)
[3]C. Djerassi and J. Staunton, *Am. Soc.*, **83**, 736 (1961)
[4]C. Djerassi, E. J. Warawa, R. E. Wolff, and E. J. Eisenbraun, *J. Org.*, **25**, 917 (1960)

N-Acetoxyphthalimide (2). The reagent is prepared by reaction of sodium N-hydroxyphthalimide (*which see*) with acetyl chloride.[1] It is recommended specifically[1,2] for N-acetylation of muramic acid (1), since acetylation with acetic anhydride and pyridine gives products of intramolecular cyclization (lactams). Osawa and Jeanloz[2] treated a solution of (1) in methanol at 0° with 2 equivalents of the reagent and 1 equivalent of triethylamine and let the mixture stand at room temperature for 20 hrs.



(1) 358 mg. (1 equiv.) (2) 2 equiv. 1 equiv.



(3)

After evaporation, the residue was extracted with water and the filtered solution adjusted to pH 3.5 with Amberlite IR 120 and extracted with ethyl acetate. The residual sirup crystallized spontaneously, and recrystallization from ethyl acetate–methanol afforded pure (3) in 70% yield. When the reaction was carried out with only 1 equivalent of N-acetoxyphthalimide,[1] the product was a mixture of (1) and (3).

[1]P. M. Carroll, *Nature*, **197**, 694 (1963)
[2]T. Osawa and R. W. Jeanloz, *J. Org.*, **30**, 448 (1965)

2- and 3-Acetoxypyridine, $C_5H_4NOCOCH_3$.[1] Mol. wt. 137.14.

Preparation. The 2-isomer (b.p. 110–112°/10 mm.) by the action of acetyl chloride on the sodium salt of 2-hydroxypyridine; the 3-isomer (b.p. 92°/9 mm.) from 3-hydroxypyridine and acetic anhydride.

Acetylation. The reagents can be used for the acetylation of alcohols, phenols, and amines and for Friedel-Crafts acetylation of reactive aromatics. In general 2-acetoxypyridine is more reactive than the 3-isomer.

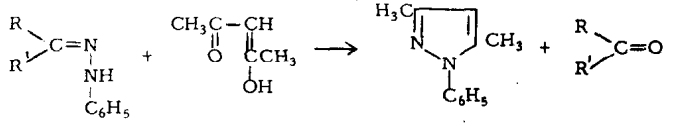
[1]Y. Ueno, T. Takaya, and E. Imoto, *Bull. Chem. Soc. Japan*, **37**, 864 (1964)

Acetylacetone (2,4-Pentanedione), $CH_3COCH_2COCH_3$. Mol. wt. 100.11, b.p. 134–136°; sp. gr. 0.975. Suppliers: B, E, F, MCB.

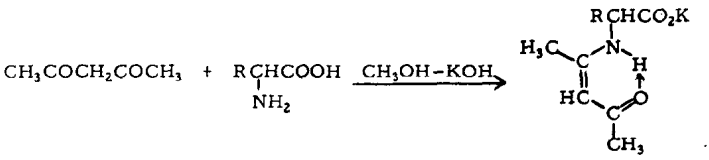
Preparation.[1]

$$(CH_3CO)_2O + CH_3COCH_3 \xrightarrow[80\text{-}85\%]{BF_3} CH_3COCH_2COCH_3$$

Cleavage of—N= derivatives. This reagent is more effective than pyruvic acid for the cleavage of phenylhydrazones and semicarbazones.[2] Reaction with a phenylhydrazone produces 3,5-dimethyl-N-phenylpyrazole and liberates the free carbonyl compound.

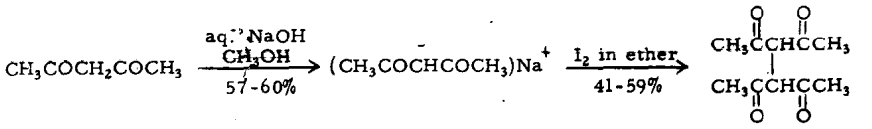


Peptide synthesis.[3] This β-diketone reacts with an amino acid in the presence of methanolic potassium hydroxide to give the potassium salt of an azomethine, formulated as an enamine stabilized by hydrogen bonding. These derivatives can be

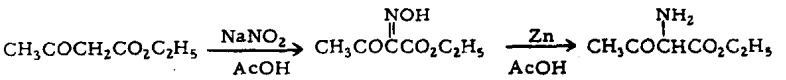


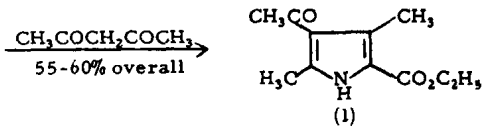
used for peptide synthesis by the DCC or the cyanomethyl ester method. The protective group is split by 2 *N* hydrochloric acid or by acetic acid.

Preparation of tetraacetylethane.[4]

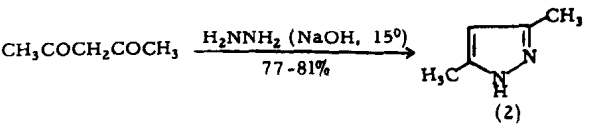


Heterocycles. Syntheses are formulated for the preparation of 2,4-dimethyl-3-acetyl-5-carboethoxypyrrole (1)[5] and 3,5-dimethylpyrazole (2).[6]





(1)



(2)

[1]C. E. Denoon, Jr., *Org. Syn., Coll. Vol.*, **3**, 16 (1955)
[2]W. Ried and G. Mühle, *Ann.*, **656**, 119 (1962)
[3]E. Dane, F. Drees, P. Konrad, and T. Dockner, *Angew. Chem., Internat. Ed.*, 1, 658 (1962)
[4]R. G. Charles, *Org. Syn., Coll. Vol.*, **4**, 869 (1963)
[5]H. Fischer, *ibid.*, **3**, 513 (1955)
[6]R. H. Wiley and P. E. Hexner, *ibid.*, **4**, 351 (1963)

Acetyl chloride, CH_3COCl. Mol. wt. 78.50, b.p. 52°, sp. gr. 1.10. Preparation from acetic anhydride and calcium chloride.[1] Suppliers: B, E, F, MCB.

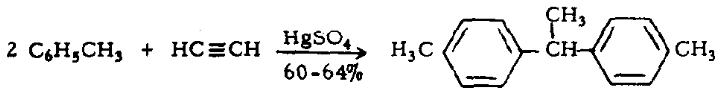
An approximately 3% solution of hydrogen chloride in methanol (Fischer esterification) can be prepared by addition of 1 ml. of acetyl chloride to 20 ml. of methanol.

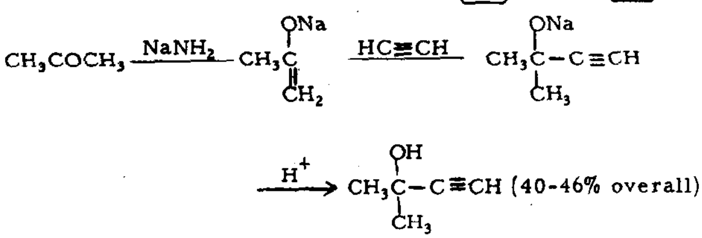
[1]J. Gmünder, *Helv.*, **36**, 2021 (1953)

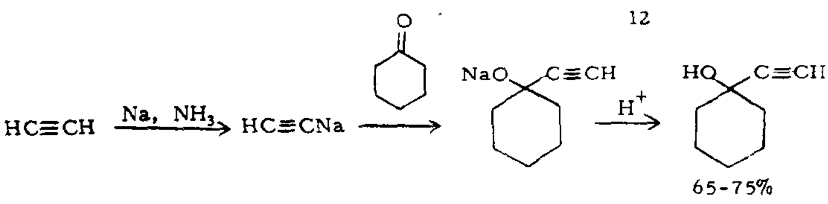
Acetylene, HC≡CH. Mol. wt. 26.04, b.p. −83°. Supplier: MCB.

An early technique[1] for purifying acetylene from a cylinder containing acetone consisted in passing the gas through water to absorb acetone and then through concd. sulfuric acid. Later workers for the most part pass the gas through a trap at −80°, a mercury safety valve, an empty bottle, concd. sulfuric acid, and finally a soda-lime tower.[2,3] Another scheme is to pass the gas through a tower of 10-mesh alumina and then into sulfuric acid.[3]

Typical syntheses utilizing acetylene are as follows:

1.[1] 

2.[4] 

3.[5] 

4.[2] $ClCH_2CO_2H + HC{\equiv}CH \xrightarrow[42-49\%]{Ag_2O} ClCH_2CO_2CH{=}CH_2$

5.[6] $HC{\equiv}CH \xrightarrow[-1/2\ H_2]{Na(NH_3)} HC{\equiv}CNa \xrightarrow[70-77\%]{n\text{-}C_4H_9Br} n\text{-}C_4H_9C{\equiv}CH$

6.[7] $(CH_3)_2CHCH_2CH_2COCl + HC{\equiv}CH \xrightarrow[54-64\%]{AlCl_3} (CH_3)_2CHCH_2CH_2COCH{=}CHCl$

β-Chlorovinyl isoamyl ketone

7.[3] $HC{\equiv}CH \xrightarrow{C_2H_5MgBr} HC{\equiv}CMgBr \xrightarrow{C_6H_5CH=CHCHO} C_6H_5CH{=}CHCH(OH)C{\equiv}CH$

[1]J. S. Reichert and J. A. Nieuwland, *Org. Syn., Coll. Vol.*, **1**, 229 (1941)
[2]R. H. Wiley, *ibid.*, **3**, 853 (1955)
[3]L. Skattebøl, E. R. H. Jones, and M. C. Whiting, *ibid.*, **4**, 793 (1963)
[4]D. D. Coffman, *ibid.*, **3**, 320 (1955)
[5]J. H. Saunders, *ibid.*, **3**, 416 (1955)
[6]K. N. Campbell and B. K. Campbell, *ibid.*, **4**, 117 (1963)
[7]C. C. Price and J. A. Pappalardo, *ibid.*, **4**, 136 (1963)

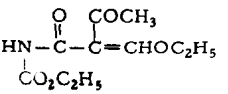
Acetylenedicarbonitrile, *see* Dicyanoacetylene.

Acetylenedicarboxylic acid, $HO_2CC{\equiv}CCO_2H$, m.p. 176°. Suppliers: Farchan, A, B, F. Preparation by reaction of α,β-dibromosuccinic acid with methanolic potassium hydroxide, isolation of the potassium acid salt, acidification, and extraction with ether.[1] The potassium acid salt is available from National Aniline and from Eastman.

The diacid is a useful dienophile (*see also* Dimethyl acetylenedicarboxylate).

[1]T. W. Abbott, R. T. Arnold, and R. B. Thompson, *Org. Syn., Coll. Vol.*, **2**, 10 (1943)

α-Acetyl-β-ethoxy-N-carboethoxyacrylamide. Mol. wt. 229.23, m.p. 90°.

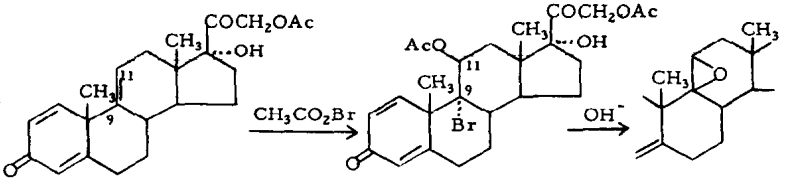


The reagent is used for determination of the N-terminal residue of a protein or peptide.[1]

[1]J. H. Dewar and G. Shaw, *J. Chem. Soc.*, 3254 (1961)

Acetyl hypobromite, CH_3COOBr. Mol. wt. 138.96.

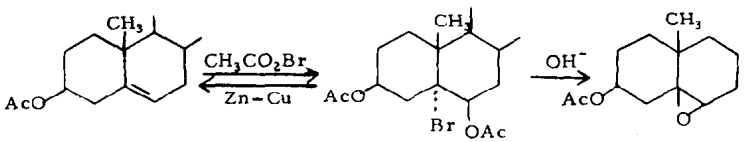
The reagent (or its equivalent) can be generated by addition of N-bromoacetamide to an acetic acid solution of lithium acetate and an olefinic substrate such as (1); *trans*-diaxial addition gives the bromohydrin acetate (2) in 74% yield.[1] Reaction conditions are essentially neutral, acid-sensitive groups are not attacked, and the



(1) (2) (3)

acetoxy group introduced is resistant to oxidation. Treatment of (2) with base gives the β-epoxide (3), and treatment with zinc–copper in ethanol regenerates the olefin (1).

In a second method [2] a solution of bromine in carbon tetrachloride is added to a stirred suspension of silver acetate in the same solvent, and the clear supernatant



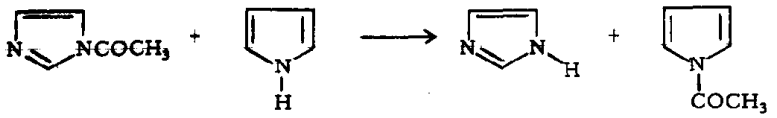
(4) (5) (6)

solution of acetyl hypobromite is added at 0° to a carbon tetrachloride solution of an olefinic substrate such as cholesteryl acetate (4). The reaction is less stereospecific than that above, but the major product is the *trans*-diaxial bromohydrin acetate (5), convertible into the β-oxide (6). In contrast to the reaction of the $\Delta^{9(11)}$-compound (1) with acetyl hypobromite generated by the first method, methyl 3α-acetoxy-$\Delta^{9(11)}$-cholenate failed to react with a solution of reagent prepared by the second method.

[1]C. H. Robinson, L. Finkenor, M. Kirtley, D. Gould, and E. P. Oliveto, *Am. Soc.*, **81**, 2195 (1959)
[2]S. G. Levine and M. E. Wall, *ibid.*, **81**, 2826 (1959)

N-Acetylimidazole (1). Mol. wt. 110.12, m.p. 101.5–102.5°.

The reagent is prepared by dissolving imidazole in a slight excess of acetic anhydride and removing the generated acetic acid and remaining anhydride under vacuum (yield quant.).[1] When the reagent (1) is refluxed for 90 min. with an equimolar amount of pyrrole (2), the acetyl group is transferred to pyrrole to give N-acetylpyrrole (4) is about 90% yield.[2] N-Acetylpyrrole is difficult to prepare by usual



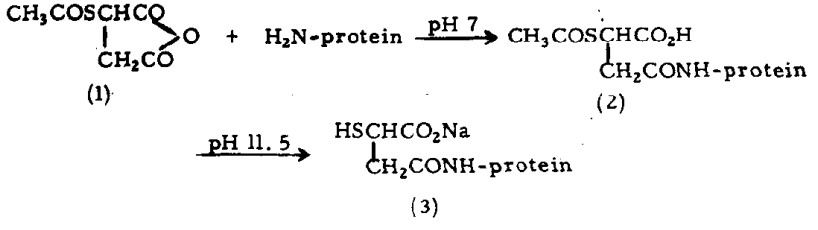
(1) (2) (3) (4)

methods since direct acetylation of pyrrole gives 2- and 3-acetylpyrrole in about equal amounts.

[1]J. S. Reddy, L. Mandell, and J. H. Goldstein, *J. Chem. Soc.*, 1414 (1963)
[2]J. S. Reddy, *Chem. Ind.*, 1426 (1965)

S-Acetylmercaptosuccinic anhydride (1). Mol. wt. 174.18, m.p. 77°. Supplier: Columbia. Preparation in 83% yield by addition of thiolacetic acid to maleic anhydride.[1]

A method for the introduction of thiol groups into proteins (and polyhydroxylic molecules such as dextran or polyvinyl alcohol) involves adding solid anhydride to a protein solution at pH 7 under nitrogen.[2] Hydrolyzed anhydride is removed with an anion exchanger, salts with a mixed-bed exchanger or by dialysis, and the



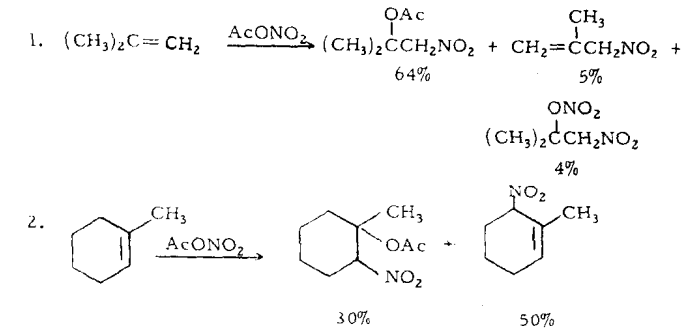
(1) (2) (3)

mercaptosuccinoylated protein (2) is isolated by lyophilization. The acetyl-S linkage is split rapidly in dilute sodium hydroxide at pH 11.5 (3).

[1]R. Brown, W. E. Jones, and A. R. Pinder, *J. Chem. Soc.*, 2123 (1951)
[2]I. M. Klotz and R. E. Heiney, *Am. Soc.*, **81**, 3802 (1959)

Acetyl nitrate, CH_3COONO_2. Mol. wt. 105.05. Potentially explosive.

Reagent prepared by adding 4.5 g. of 70% nitric acid to 35 ml. of acetic anhydride at 25–30° reacts with simple alkenes to give mixtures of β-nitro acetates, nitroolefins,



and β-nitronitrates,[1] as illustrated in examples (1) and (2). Styrene, stilbenes, and 1,1-diarylalkenes give 40–70% yields of β-nitro acetates.

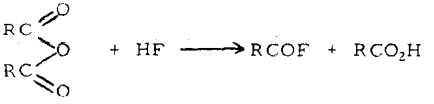
[1]F. G. Bordwell and E. W. Garbisch, Jr., *Am. Soc.*, **82**, 3588 (1960); *J. Org.*, **27**, 2322, 3049 (1962); *ibid.*, **28**, 1765 (1963)

Acrylonitrile, $CH_2{=}CHCN$. Mol. wt. 53.06, b.p. 78.5°, sp. gr. 0.81. Suppliers (pract.): B, E, F, MCB. Purification:[1] wash successively with 10% H_2SO_4, 10% Na_2CO_3, and a saturated solution of Na_2SO_4; dry over $CaCl_2$, fractionate in air, and then distil in vacuum.

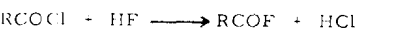
Used for the cyanoethylation of alcohols, mercaptans, aldehydes, ketones, malonic ester, nitromethane, bromoform, etc.[2]

[1]J. C. Bevington and D. E. Eaves, *Trans. Farad. Soc.*, **55**, 1777 (1957)
[2]H. A. Bruson, *Org. Reactions*, **5**, 79 (1949)

Acyl fluorides.[1] An acyl fluoride can be prepared by stirring 2 moles of the corresponding acid anhydride at −10° with a Teflon-covered magnetic stirring bar and adding 45 g. (2.25 moles) of liquid anhydrous hydrogen fluoride.[2] After 1 hr. at −10° the mixture is let stand for 2 hrs. without cooling, treated with 15 g. of anhydrous

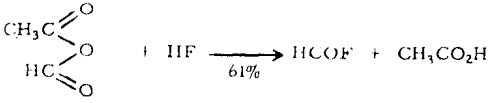


sodium fluoride to remove excess hydrogen fluoride, filtered, and distilled. Operations involving anhydrous hydrogen fluoride are performed in equipment of fused silica or of plastic (polyethylene, polypropylene, Teflon, Kel-F). An acid chloride can be converted into the corresponding fluoride either by the same procedure or by



stirring 2 moles of the acid chloride at −5 to 0° and passing in anhydrous gaseous hydrogen fluoride at a rate of about 1 g./min. for 1 hr. Twenty-one acyl fluorides were obtained by these procedures in yields of 78–93%.

Formyl fluoride is prepared by reaction of acetic-formic anhydride with hydrogen fluoride at atmospheric pressure with continuous removal of formyl fluoride (b.p.



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