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NEWER
METHODS
OF
PREPARATIVE
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Volume
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Volume IV

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Wilhelm Foerst



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Newer Methods of
Preparative
Organic Chemistry

Volume IV

Foreword

Generally speaking, the articles in the volumes of this series have been expanded considerably since their appearance in "Angewandte Chemie". In particular, the number of experimental procedures has increased greatly.

In their present form the articles cover 335 pages as against 210 columns when they appeared in the Journal (one page of this book corresponds to about nine-tenth of a column in the Journal) — an increase of more than 40 p. c.

The article by E. Schenker "The Use of Complex Borohydrides and of Diborane in Organic Chemistry" has been revised completely and, with 1900 references, probably represents the most complete review of this subject that is available at the present time.

Heidelberg, January 1968

W. Foerst

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α -Additions to Isonitriles

Triple Additions and Four-Component Condensations*

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Isonitriles can undergo triple additions and four-component condensations. Suitable reaction partners for triple additions include carboxylic acids and carbonyl compounds; hydrazoic acid and carbonyl compounds; tropylium salts and water; and two moles of thiocyanic acid. Amines (ammonia, primary and secondary aliphatic and aromatic amines, hydrazines), aldehydes or ketones, and acids (H_2O , $H_2S_2O_3$, H_2Se , HN_3 , $HNCO$, $HNCS$, RCO_2H , $ROCO_2H$) take part in four-component condensations with isonitriles. The amine and carbonyl components in four-component condensations may be replaced by Schiff bases or enamines. Four-component condensations can be used to prepare, e.g., amides, thioamides, and selenoamides of α -amino carboxylic acids, 1,5-disubstituted tetrazoles, hydantoin and thiohydantoin imides, amides of α -acylamino carboxylic acids, oligopeptide derivatives, β -lactams, penicillanic acid derivatives, urethanes, diacyl imides, and hydrazine derivatives. The reactions are simple to carry out and proceed under mild conditions. Yields above 90% are not uncommon.

1. Introduction

2. Triple Additions

3. Four-Component Condensations

3.1 Reaction Mechanism

3.2. Scope of the Reaction

3.3. Procedures

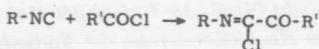
1. Introduction

Isonitriles are the only stable organic compounds containing formally bivalent carbon [1], and this is the reason for the exceptional position of these compounds in organic chemistry.

The ability of isonitriles to undergo α -additions was the most important evidence for the formal bivalence of the isonitrile carbon atom. Before the turn

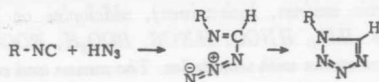
* The terms "four-component condensation", " α -aminoalkylation of isocyanides and acids", and "Ugi-Reaction" [7c, d, f] are equivalent. Since Schiff bases and enamines are derived from carbonyl components and amines, the triple additions of Schiff bases or enamines and acids to isocyanides are regarded here as four-component reactions, since they correspond to four-component reactions with regard to mechanism and final products.

of the century, only a few simple additions of this type were known, *e. g.* the formation of isonitrile dichlorides and *N*-substituted 2-oxoimidoyl chlorides [2].

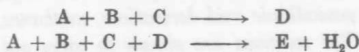


It is now known that many other reactions of isonitriles not leading to α -adducts as final products are initially α -additions; the stable end products are formed by extremely fast, spontaneous secondary reactions of the labile α -adducts.

The tetrazole synthesis described by OLIVERI-MANDALA and ALAGNA [3], for example, may be interpreted as an α -addition of a proton and an azide ion to isonitriles, followed by ring closure (*cf.* Section 2.2.).



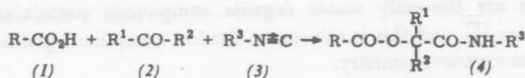
Because of their ability to undergo α -additions, isonitriles can enter into triple additions and four-component condensations in accordance with the schemes:



2. Triple Additions

2.1. Passerini Reaction

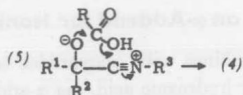
The first triple additions of isonitriles were observed by PASSERINI [4], who found that the reaction of carboxylic acids and carbonyl compounds with isonitriles provides an elegant and general synthesis of α -acyloxy carboxamides (4).



Had PASSERINI been familiar, some forty years ago, with present-day views on organic reaction mechanisms, he would probably have added a fourth reactant, namely ammonia or a primary amine, and would thus have discovered the α -aminoalkylation of isonitriles and acids.

PASSERINI believed that (4) was formed *via* a hemiacetal-like compound of (1) and (2).

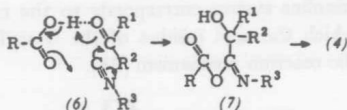
Some twenty years later, DEWAR [5] suggested that the reaction proceeds *via* a polar adduct of (2) and (3), which reacts with the carboxylic acid in a multicenter reaction (5) to give (4).



This view was elaborated by BAKER and STANONIS [6]; from the observation that the reaction is of the third order, they concluded that the addition of (2) and (3) is an equilibrium process, and that the rate of the reaction is determined by step (5).

However, the experimental results are only partly compatible with this mechanism. The Passerini reaction is faster and gives better yields in aprotic non-polar solvents than in strongly polar solvents which can take part in hydrogen bonding; this observation can hardly be explained on the basis of a mechanism in which an extremely polar intermediate plays a decisive part. Moreover, the reaction of the carboxylic acid and the nitrilium-alkoxide zwitterion is more likely to lead to the instantaneous formation of (7) than to be a rate-determining slow combination in accordance with (5).

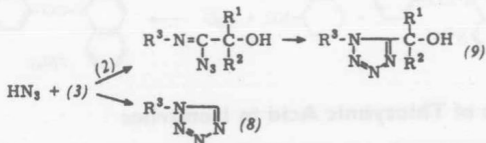
An obvious interpretation, which fits all the facts, including the well-known ability of isonitriles to participate in α -additions [7], involves the α -addition of a hydrogen-bonded adduct of the carboxylic acid and the carbonyl compound to the isonitrile (6), followed by intramolecular transacylation in the resulting α -adduct (7) [cf. (14g)] [8].



2.2. Formation of 1,6-Disubstituted Tetrazoles from Isonitriles, Carbonyl Compounds, and Hydrazoic Acid

If the Passerini reaction is regarded as an α -addition accompanied by rearrangement, one may expect other acids besides carboxylic acids to react in this way with carbonyl compounds and isonitriles. However, only those acids can be used as substitutes in the Passerini reaction which react more rapidly with carbonyl compounds and isonitriles than with isonitriles alone.

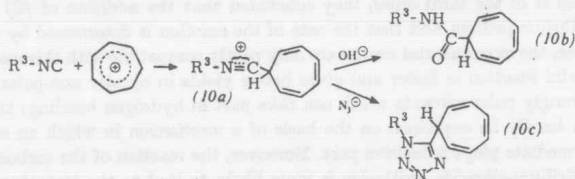
This condition is satisfied by hydrazoic acid, which combines with reactive aldehydes or ketones and isonitriles to give 1,5-disubstituted tetrazoles (9) [e. g. (9a) and (9b)] [8] from isobutyraldehyde or chloral; when carbonyl compounds with low reactivities are used, formation of 1-substituted tetrazoles [3] (8) occurs. This side reaction is avoided if aluminum azide is used instead of hydrazoic acid [8].



(9),	R ¹	R ²	R ³	Yield (%)
a	H	iso-C ₃ H ₇	cyclo-C ₆ H ₁₁	85 %
b	H	CCl ₃	p-(C ₂ H ₅) ₂ N-C ₆ H ₄	95 %

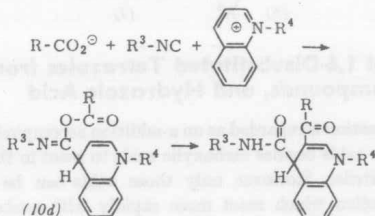
2.3. Tropylium Ion as an α -Addend for Isonitriles

The tropylium ion combines with isocyanides to give nitrilium ions (10a), which react with water or hydrazoic acid, *via* α -adducts, to form *N*-substituted cycloheptatrienecarboxamides (10b) or 1,5-disubstituted tetrazoles (10c), respectively [9].

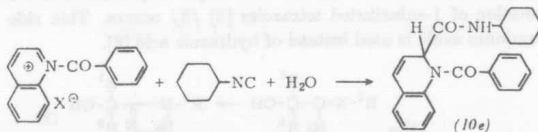


2.4. *N*-Alkylquinolinium Ions and Carboxylate Anions as α -Addends for Isonitriles

The labile α -adducts (10d) of *N*-alkylquinolinium ions, carboxylate anions, and isocyanides undergo an O,C acyl shift. In the α -adduct (10d), the 3-position of the 1,4-dihydroquinoline system corresponds to the nucleophilic β -position of an enamine, to which the acyl residue of the *O*-acylimido acid system is transferred by a cyclic reaction mechanism [9a].

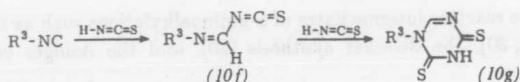


The *N*-benzoylquinolinium ion [10] reacts with cyclohexyl isocyanide and water to form *N*-benzoyl-1,2-dihydroquinoline-2-(*N'*-cyclohexyl)carboxamide (10e) [11, 12].



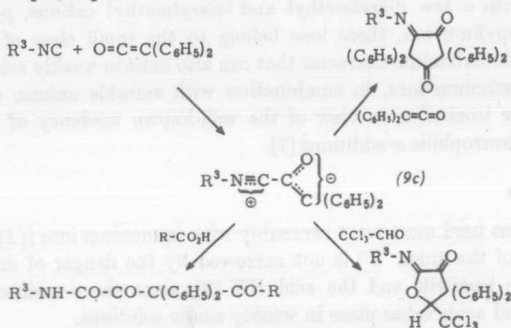
2.5. Addition of Thiocyanic Acid to Isonitriles

Isonitriles react with two molar equivalents of thiocyanic acid to form 1-alkyl- or 1-aryl-1,2,3,4-tetrahydrotriazine-2,4-dithiones (10g) [13–15]. The 1:1 α -adducts (10f) are stabilized by addition of a second molecule of thiocyanic acid [16].



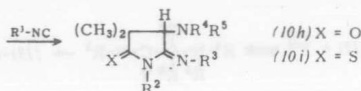
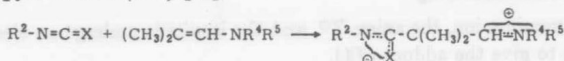
2.6. Reactions of Isonitriles with Ketenes

Diphenylketene (as well as other ketenes) adds to isocyanides to form a polar adduct (9c), which can combine with chloral, carboxylic acids, or additional diphenylketene [15, 17].



2.7. Enamines and Isocyanates as Addends for Isonitriles

Isocyanates, as well as isothiocyanates, undergo triple additions with enamines and isocyanides, the products being iminopyrrolidones (10h) or iminothiopyrrolidones (10i) [18].



3. Four-Component Condensations

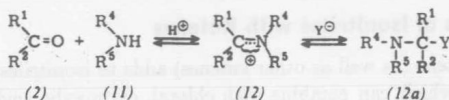
3.1. Reaction Mechanism

3.1.1. Immonium Ions

Immonium ions (12)*, which are formed from amines and carbonyl compounds or their condensation products in solutions of suitable acidity, are

* The chemistry of immonium ions justifies the use of the alternative term α-amino-alkyl ions. For example, the immonium ion formed by proton addition to *N*-(1-benzylethylidene)benzylamine may be called the 1-benzyl-1-benzylaminoethyl cation as well as the *N*-(1-benzylethylidene)benzylammonium ion.

known as the reactive intermediates of α -aminoalkylations such as the Mannich reaction [19, 20], the Strecker synthesis [20], and the Asinger condensation [20, 21].



Along with a few diarylmethyl and triarylmethyl cations, pyrylium ions, and the tropylium ion, these ions belong to the small class of electrophilic particles with carbonium character that can also exist in weakly acidic solutions.

Thus immonium ions, in combination with suitable anions, are ideal co-reactants for isonitriles, in view of the well-known tendency of the latter to enter into electrophilic α -additions [7].

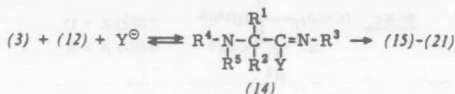
3.1.2. Anions

The anions used must react reversibly with immonium ions [(12) \rightleftharpoons (12a)]. The choice of the anion Y^- is not narrowed by the danger of direct reaction between the isonitrile and the acid HY [8], since the α -aminoalkylation of isonitriles and acids takes place in weakly acidic solutions.

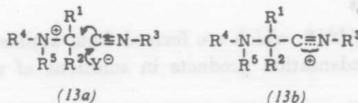
The anions OH^- , SeH^- , $\text{S}_2\text{O}_3^{2-}$, N_3^- , NCO^- , NCS^- , $\text{R}-\text{CO}_2^-$, and $\text{CH}_3\text{O}-\text{CO}^-$ have been found to be suitable. These anions can be divided into two groups on the basis of the secondary reaction of their α -adducts (cf. Sections 3.1.4.1. and 3.1.4.2.).

3.1.3. The α -Addition Step

The immonium ion, the anion Y^- , and the isonitrile undergo an electrophilic α -addition to give the adduct (14).



The three reactants can combine either by a one-step three-center mechanism, or in two steps involving a nitrilium intermediate (13b).



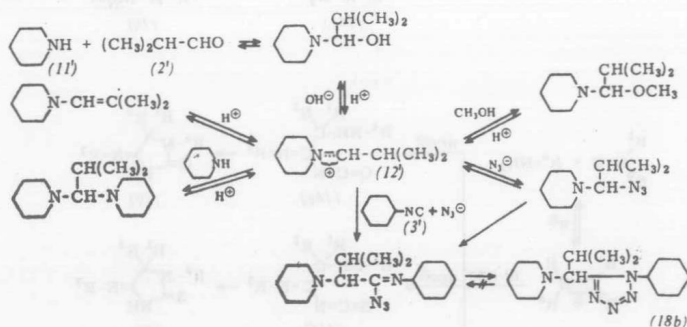
On the basis of the results available one cannot decide whether the one-step α -addition proceeds as an insertion into (12a), or whether an oriented contact ion pair [(12) + Y^-] adds to the isonitrile (cf. Section 3.2.4.3.).

3.1.4. The Secondary Reaction

The behavior of the α -adduct (14) depends primarily on the anion component Y^\ominus . If the constitution of the anion satisfies certain conditions (cf. Sections 3.1.4.1. and 3.1.4.2.), the α -adduct is converted into stable derivatives of α -amino carboxylic acids, the practically irreversible formation of the final product providing the driving force for the entire reaction.

The carbonyl compound (2), the amine (11), the isonitrile (3), and HY condense to form a uniform product if this secondary reaction is the only or by far the fastest irreversible reaction of the system. Often this is true only at high concentrations, whereas in dilute solution the difference between the rates of the principal reaction and the irreversible side reactions is not so pronounced.

The condensation of cyclohexyl isocyanide (3') with isobutyraldehyde (2'), piperidine (11'), and hydrazoic acid in benzene/methanol to give (18b) (see also Section 3.2.2.) should also be mentioned at this point to show how during the α -amino-alkylation of isocyanides and acids, the irreversible α -addition and secondary reaction affects the formation of the final product from a multi-component system of coupled equilibria [19, 20]*.



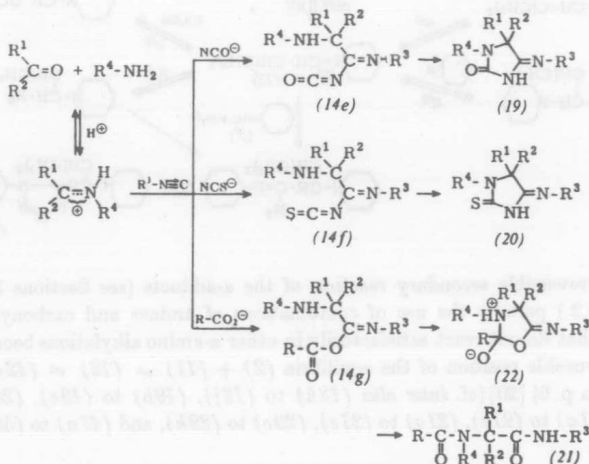
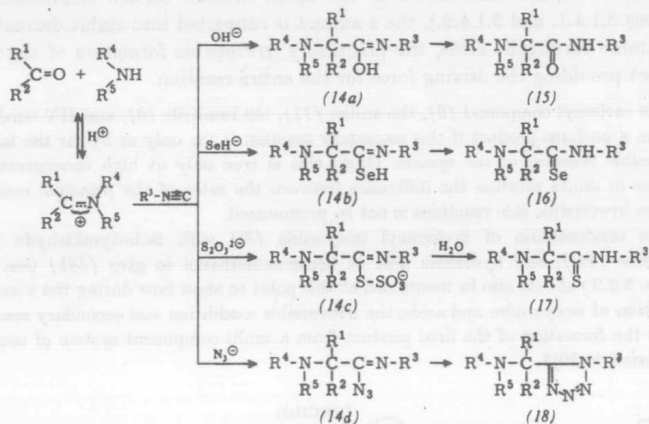
The irreversible secondary reaction of the α -adducts (see Sections 3.1.4.1. and 3.1.4.2.) permits the use of combinations of amines and carbonyl components that do not react satisfactorily in other α -amino alkylations because of the unfavorable position of the equilibria $(2) + (11) \rightleftharpoons (12) \rightleftharpoons (12a)$ (see scheme on p. 6) [20] [cf. *inter alia* (18h) to (18j), (19b) to (19e), (20a) to (20e), (21a) to (21e), (21o) to (21s), (29c) to (29k), and (47a) to (50k)].

3.1.4.1. Formation of Non-acylated Derivatives of α -Amino Acids

The α -adducts formed from immonium ions, isocyanides, and hydroxide, hydrogen selenide, thiosulfate, or azide ions undergo secondary reactions not

* According to OPITZ et al. [22], α -amino azides react smoothly with isocyanides to form 1,5-disubstituted tetrazoles.

involving the amine nitrogen. Consequently, primary and secondary amines in combination with these anions react in fundamentally the same manner.



The α -adducts (14a) and (14b) of the hydroxide and hydroselenide ions form the final products (15) and (16) by a simple proton shift. Thiosulfate forms α -adducts (14c) that are stabilized by hydrolysis in aqueous solution.

The azide ion gives intermediates (14d) that cyclize to 1,5-disubstituted tetrazoles