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α-METALATED ISOCYANIDES IN ORGANIC SYNTHESIS

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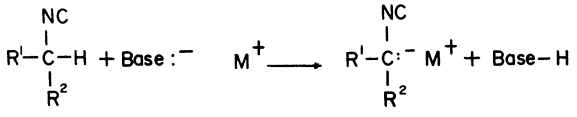
Abstract - α-Alkali-metalated isocyanides, which can be obtained from isocyanides and bases, are both nucleophilic and electrophilic. They can add to polar double bonds, forming heterocycles. They are also synthons for α-metalated primary amines. This paper describes their use in organic synthesis: 1) In heterocyclic synthesis to gives 2-oxazolines, 2-thiazolines, 2-imidazolines, pyrroles, oxazoles, thiazoles, 2-imidazolin-5-ones, 1,3-oxazines and -thiazines. 2) In the field of formylaminomethylenation, transformation of ketones and aldehydes with alkyl isocyanoacetate to formylamino acrylic esters and chain lengthening of ketones to carboxylic acids or carbonitriles with tosyl methylisocyanide. 3) In connection with their use as synthons for primary amines it is demonstrated how they may be used for preparation of 1,2- and 1,3-amino alcohols, 2,3-diaminoalkanoic acids and for synthesis of amino acids.

INTRODUCTION

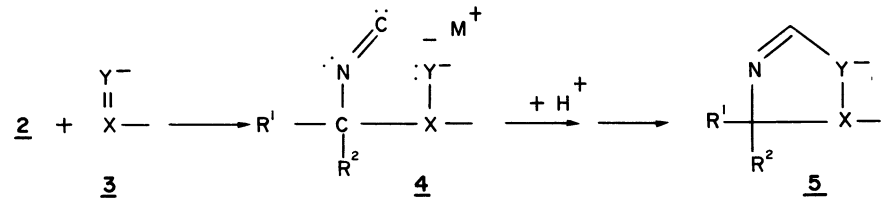
The activating effect of the cyano group on C–H bonds has been known for nearly a century. However, it was only in 1968 that Schöllkopf and Gerhart (Ref. 1)discovered that alkyl isocyanides 1 can be anionized (metalated) in α-position.



1 2

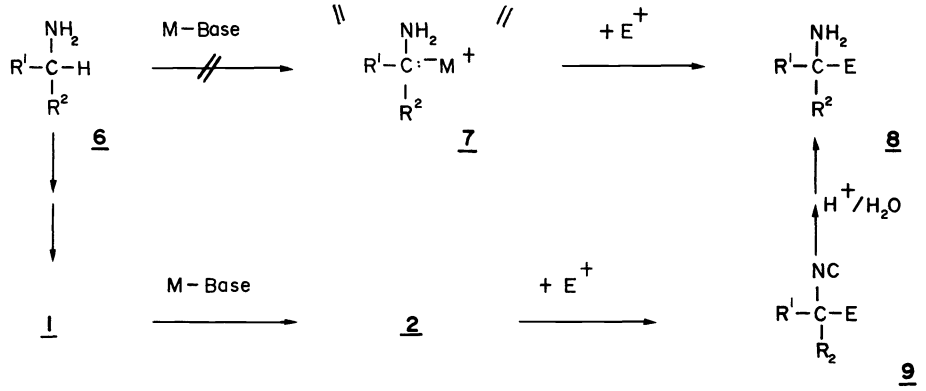
Metalation (anionization) is accomplished with the usual bases employed in carbanion chemistry such as butyllithium, potassium tert-butoxide, sodium hydride, DBU or triethylamine; the precise choice depends upon the substituents R^1 and R^2. The α-metalated isocyanides 2 are not isolated but subjected to reaction in the same vessel. Any alkyl isocyanide 1 can be metalated provided that its parent hydrocarbon is as acidic or more acidic than methane. sec-Alkyl isocyanides without activating substituents cannot be metalated; cyclopropyl isocyanide is an exception to this rule.

The synthetic significance of α-metalated isocyanides 2 is due, on the one hand, to their ambivalent nature. They contain a nucleophilic center, the metalated carbon atom, which can add to polar multiple bonds 3, and an electrophilic center, the isocyanide carbon atom, which permits cyclization of the adducts 4 to heterocycles of type 5.



3 4 5

On the other hand, the α-metalated isocyanides 2 are synthons for the (hypothetical) α-metalated primary amines "7" and permit chain extension of primary amines by electrophiles E^+ [6 → 8] according to the following scheme.

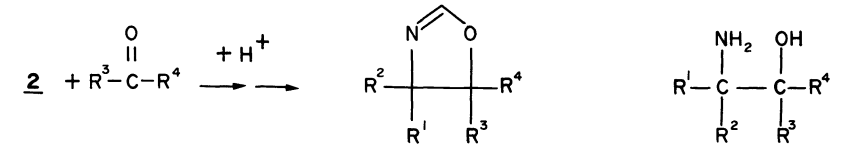


Amines 6 can be readily transformed into isocyanides 1, either via the N-formyl derivatives (Ref. 2) or directly by the Makosza variant of the carbylamine reaction (Ref. 3). According to a toxicological study performed at Bayer AG (Ref. 4), isocyanides appear to be practically non-toxic towards warm-blooded animals, with few exceptions. Nevertheless, operations should be performed in a hood and all equipment washed with acids immediately after use. Both these measures are recommended if only because of the unpleasant odor of the lower alkyl isocyanides. Higher alkyl isocyanides, diisocyanides, or isocyanides containing a further functional group are largely or completely odorless.

SYNTHESES OF HETEROCYCLES

2-Oxazolines

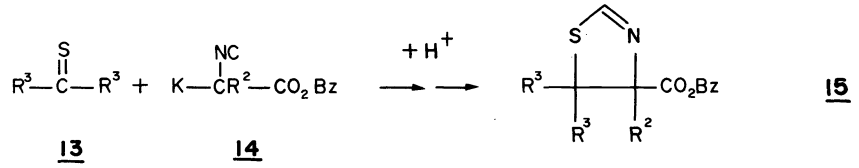
On reaction with aldehydes and ketones 10, α-metalated isocyanides 2 afford 2-oxazolines 11 (Ref. 5).



The advantage of this oxazoline synthesis consists in the linkage of the C-4—C-5 bond during the reaction. Starting with α-isocyano esters (R^1 = CO_2Et in 1) 2-oxazoline-4-carboxylic esters (R^2 = CO_2Et in 11) are obtained, precursors for serines 12, R^1 = CO_2H (Ref. 6).

2-Thiazoline-4-carboxylic esters

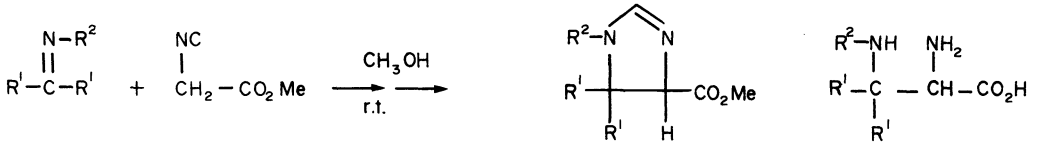
Thioketones 13 react with α-metalated isocyano esters of type 14 to form 2-thiazolinecarboxylic esters of type 15 (Ref. 7). The main difficulty lies in the preparation and manipulation of the thioketones 13.



2-Thiazolines of type 15 command interest as starting compounds for the synthesis of structural variants of penicillin. For instance, starting with benzyl 5,5-dimethyl-4-methyl-2-thiazolinecarboxylate (±) -2,2-dimethyl-3-methyl-6ß-phenoxyacetamino-penam-3-carboxylic acid was prepared, a C-3 methyl derivative of penicillin V (Ref. 8).

2-Imidazolines

α-Metalated isocyanides 2 can also add to the carbonylanalogous azomethine group. Thus methyl isocyanoacetate 17 reacts with Schiff bases 16 in methanol at room temperature to form methyl 2-imidazoline-4-carboxylates 18 (Ref. 9). The amine present in trace amounts in azomethine presumably acting as anionizing base.

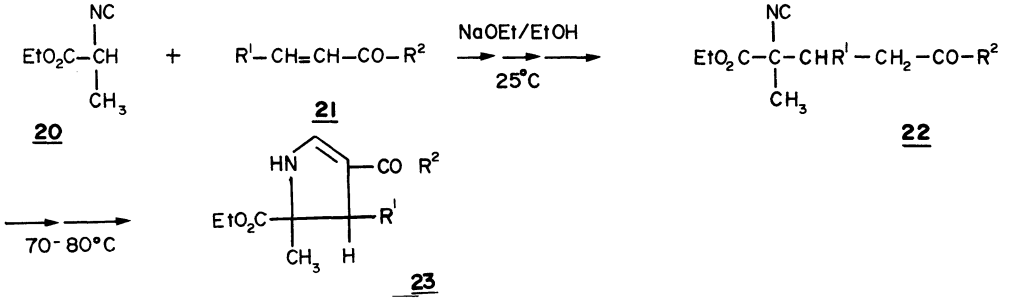


16 17 18 19

2-Imidazolines of type 18 warrant interest on account of their proven or potential pharmacological activity. Since imidazolines, being cyclic amidines, are readily susceptible to acid hydrolysis this synthesis is also suitable for preparation of 2,3-diaminoalkanoic acids (α,ß-diamino acids) 19 (Ref. 9).

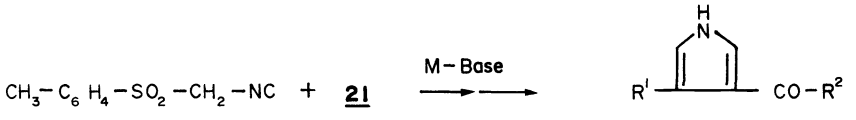
2-Pyrrolines and Pyrroles

Reaction of, for example, ethyl isocyanopropionate 20 with α,ß-unsaturated carbonyl compounds 21 under the conditions of the Michael addition affords ethyl 2-isocyano-2-methyl-5-oxoalkanoates of type 22, which cyclize to the pyrrolines 23 on heating to 70-80°C (Ref. 10).



20 21 22 23

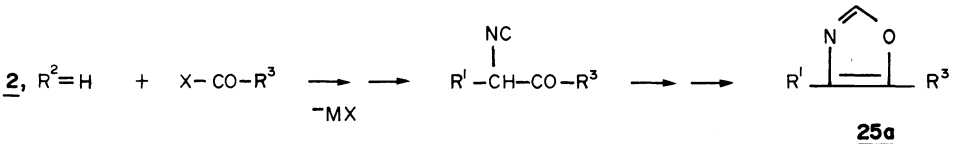
Particular preparative interest attaches to a synthesis developed by van Leusen et al. (Ref. 11) for 3-acyl-substituted pyrroles of type 25 by reaction of p-toluenesulfonylmethyl isocyanide 24 with activated olefins 21 in glycol dimethyl ether/dimethyl sulfoxide with sodium hydride as base. Michael addition and cyclzation are followed by elemination of toluenesulfinate and tautomerization. 2-Unsubstituted 3-acyl-pyrroles are not readily accessible by conventional methods.



24 25

Oxazoles

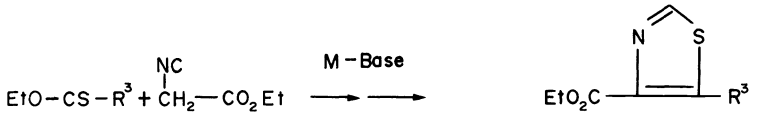
Oxazoles 25a are formed on treatment of α-metalated isocyanides 2, R^2= H, with acylating agents such as acyl chlorides, esters or imidazolides (Ref.12). The intermediate α-isocyanoketones are not isolable; they cyclize to give oxazoles 25a on workup.



25a

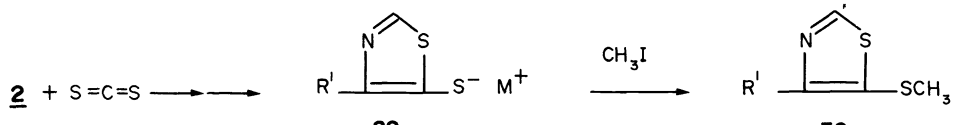
In same cases - especially with acyl chlorides - two equivalents of the metalated isocyanide 2 are required. However, on optimum choice of acylating agent, solvent and reaction conditions also leads to good yields of oxazoles 25 when 2 and 23 are used in a ratio of 1:1.
Oxazoles are valuable synthetic intermediates. Their acid hydrolysis affords α-amino ketones (or α-amino enols). 3-Amino-4-hydroxycoumarin derivatives, key components for the preparation of bactericidal compounds, have been synthesized by Matsumoto et al. (Ref. 13). Their approach was to treat 2-chloroformylphenyl acetate with methylisocyanoacetate (in tetrahydrofuran with triethylamine as base) to obtain the oxazole derivatives which yield the coumarin on acid hydrolysis.
Not only monocyclic heterocycles can be synthesized with α-metalated isocyanides, but also sequences of heterocycles. Thus methyl isocyanoacetate and oxalyl diimidazolide - prepared in situ from oxalyl dichloride and imidazole - react smoothly (in tetrahydrofuran with triethylamine as base) to give dimethyl 5,5'-bioxazole-4,4'-dicarboxylate (Ref. 12).

Thiazoles
α-Metalated isocyanides 2 also react with hetero-analogous acylating agents. Hartmann et al. (Ref. 14) obtained ethyl-4-thiazolecarboxylates 28 from thionic esters 26 and ethyl isocyanoacetate 27 (in methanol with potassium cyanide as catalyst).



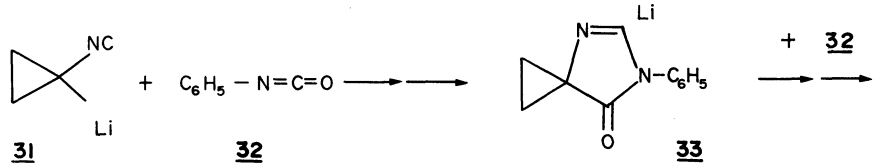
26 27 28

α-Metalated isocyanides 2, R^2= H, react with carbon disulfide to give thiazolethiolates 29, which afford 5-(methylthio)thiazoles 30 with methyl iodide (Ref. 15). Other 5-(alkylthio)thiazoles should be accessible in analogous manner.

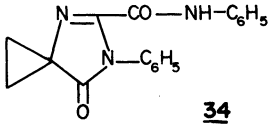


29 30

2-Imidazolin-5-ones
Reaction of 1-lithiocyclopropyl isocyanide 31 (in tetrahydrofuran at -65°C) with phenyl isocyante 32 give mainly the bisadduct 34 (Ref. 16) because the intermediate 33 quickly reacts with remaining isocyanate.

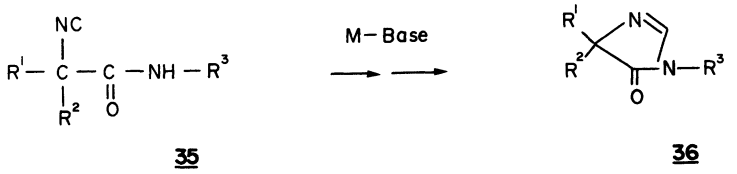


31 32 33



34

2-Unsubstituted 5-imidazolines of type 36 are formed, however, when 2-isocyanoalkanamides 35 - prepared from methyl 2-isocyanoalkanoates and amines with p-toluenesulfonic acid as catalyst (Ref. 17) - are subjected to base-induced cyclization (Ref.17).

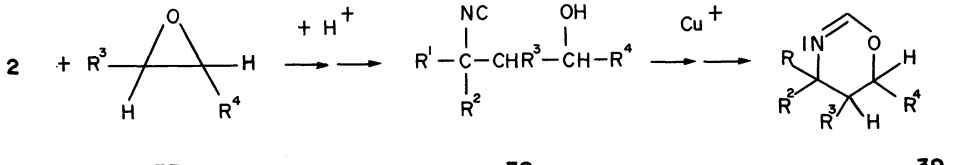


35 36

With 36, R^3= phenylethyl, R^1= H, base-induced benzylation at C-4 occurs with almost complete asymmetric induction. Hydrolysis of the benzylation product gives optically pure α-methylphenylalanine (Ref. 18).

5,6-Dihydro-4H-1,3-oxazines and -thiazines

α-Metalated isocyanides 2 add to epoxides 37 giving 3-hydroxy-alkyl isocyanides 38 which can be cyclized to 5,6-dihydro-4H-1,3-oxazines 39 (Ref. 19). The addition take place in accord with the pattern valid for nucleophilic epoxide cleavage.

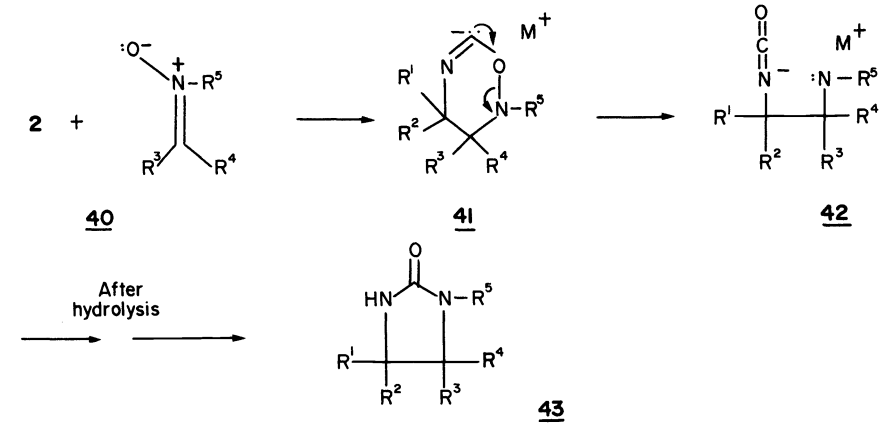


37 38 39

Dihydrothiazines (S in place of O in 39)are accessible analogously (Ref. 2o), although some episulfides are attacked by α-metalated isocyanides 2 at sulfur.

2-Imidazolinones

α-Metalated isocyanides 2 are ambivalent reagents. Consequently, they should react with the likewise ambivalent 1,3-dipoles (Ref. 21) to form six-membered heterocycles. As tried so far, nitrones 4o give 1-substituted 2-imidazolinones 43, presumably via the intermediates 41 and 42 (Ref. 22).

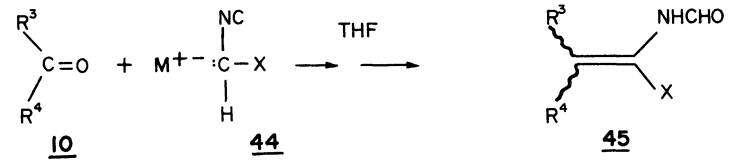


40 41 42 43

Formylaminomethylenation of carbonyl compounds

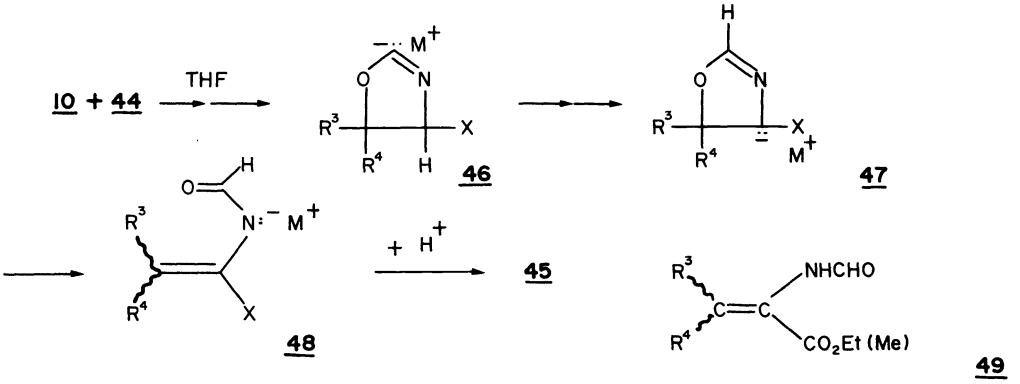
General

Reaction of α-metalated isocyanides of type 44 bearing a relatively strongly acidifying group X on the isocyano-substituted carbon atom with carbonyl compounds 1o in an aprotic medium gives N-(1-alkenyl)formamides of type 45. An oxo oxygen atom is formally replaced by the formylaminomethylene group in this reaction (Ref.23).



10 44 45

Formylaminomethylenation begins with formation of the 2-metalated oxazoline 46. This isomerizes by proton shift from C-4 to C-2 to 47 in which the substituent X stabilizes the negative charge. Electrocyclic ring opening transforms 47 into 48 which can be isolated as the N-alkenylformamide 45.



α-Formylaminoacrylic esters

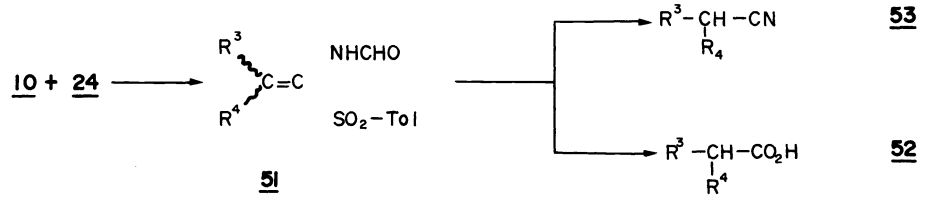
α-Formylaminoacrylic esters 49 are obtained by formylaminomethylenation of aldehydes and ketones 1o with isocyanoacetate esters (X = CO_2R in 44). Two procedures are recommended. In the first one, the ester 17 or 27 is metalated with potassium tert-butoxide in THF at -70°C; the carbonyl compound 1o is added and workup is as usual after warming to room temperature (Ref.23). However, the sterically hindered carbonyl group in 3-methoxyestrone needed refluxing in THF (Ref. 24). In the second procedure, sodioisocyanoacetic ester is generated in situ (in THF) with sodium hydride as base (Ref.23).

Formylaminomethylenation has several advantages over the classical azlactone procedure of Erlenmeyer. It occurs under milder conditions and has a wider scope. Moreover, reaction gives not the acids but the esters which are more valuable for further reactions, and the formyl group can be removed easily and selectively. There are many applications of formylaminoacrylic esters 49.

Dehydratation gives α-isocyanacrylic esters 5o, NC in 49 instead of NHCHO, which add nucleophiles with great avidity to their double bond. The addition products can be cyclized to heterocycles with ester groups. Thus, reaction with ammonia gives 2-imidazoline-4-carboxylic esters 18, R^2= H (Ref.9), addition of hydrogen sulfide 2-thiazoline-4-carboxylic esters 15, R^2= H (Refs. 25 & 26).

N-(1-Toluenesulfonyl-1-alkenyl)formamides; Chain Elongation of Ketones

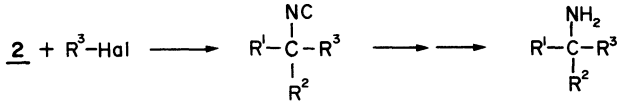
Formylaminomethylenation of ketones 1o with p-toluenesulfonylmethyl isocyanide 24 affords N-(1-toluenesulfonyl-1-alkenyl)formamides 51 (Ref. 27). These compounds can be transformed into the carboxylic acids 52 with aqueous acids (Ref. 27) and into the nitriles 53 with alkoxide (Ref. 28). This means that formylaminomethylenation with 24 solves an important problem of preparative organic chemistry, i.e. the straightforward and productive transformation of a ketone 1o into the next-higher carboxylic acid or the next-higher nitrile. Mention should be made of a particularly convenient single-pot process developed by van Leusen et al. (Ref. 28) for the transformation 1o ⟶ 53.



α-METALATED ISOCYANIDES AS SYNTHONS FOR α-METALATED PRIMARY AMINES

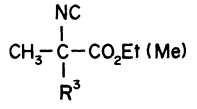
Chain Elongation with Alkylating Agents; Amino Acid Synthesis

Chain elongation of common primary amines 6 with alkyl halides 54 to gives higher amines 56 proceeds according to the above mentioned Scheme via the metalated isocyanides 2 (Ref. 29). In this way amines can also be prepared which cannot obtained otherwise, or only with difficulty.



54 55 56

Reaction of α-metalated 2-isocyanopropionic ester, prepared from the ester 2o and potassium tert-butoxide or sodium hydride in THF or THF/DMSO (Ref. 3o) with alkyl halides furnishes the higher 2-isocyano-2-methylalkanoic esters 57 and thence, by hydrolysis, amino acids (Refs. 3o & 31). Examples are the synthesis of α-methylphenylalanine 58a (Ref. 3o) or α-methylhistidine 58b (Ref. 31). To synthesize optically active α-methyldopa 58c, alkylation of optically active menthyl and bornyl α-isocyanopropionate with 3,4-dimethoxybenzyl bromide was investigated. The yields were 8o-85%, the enantiomeric purity was only 10% (Ref. 31).



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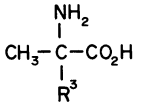
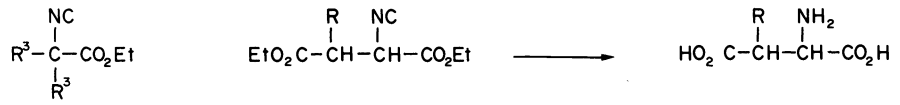


58	R^3
a	$CH_2C_6H_5$
b	4-imidazolyl
c	$CH_2-C_6H_3$ (m, pOH)$_2$

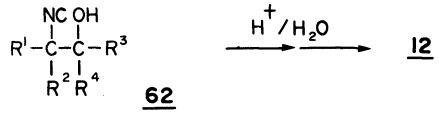
Benzyl 6-isocyanopenicillanate was alkylated in 6-position via the 6-potassium derivative (readily obtained with potassium carbonate in DMF). The isocyano group of the 6ß-alkylated products was converted into the amino group by p-toluenesulfonyl hydrate (Ref. 32).
On alkylation of ethyl isocyanoacetate 27 with "small" and/or particularly reactive alkyl halides 54, bisalkylation to give 59 predominates (Ref. 3o); nevertheless, α-halo carboxylic esters give satisfactory yields of isocyanosuccinic esters of type 6o, which furnish aspartic acids 61 on hydrolysis (Ref. 33). The tendency to undergo double alkylation can be exploited in cycloalkylation, e.g. with 1,2-dibromomethane to prepare ethyl 1-isocyano-1-cyclopropanecarboxylate, the precursor of 1-amino-1-cyclopropanecarboxylic acid (Ref. 3o) - Amino acid synthesis by alkylation of 2-isocyanoalkanoic esters is comparable with the (acylamino)malonic ester method, and sometimes superior to it (Ref. 33). The isocyano ester procedure also permits synthesis of α-substituted amino acids.



59 60 61

α-Hydroxyalkylation of Primary Amines, Ring Expansion of Cyclic Ketones by the Isocyanomethyllithium Method

One variant of α-hydroxyalkylation of primary amines 6 with carbonyl compounds 1o to form 2-amino alcohols 12 has already been mentioned in connection with 2-oxazoline syntheses (Ref. 5). Another variant consists in trapping of the initial adducts obtained from 2 and 1o as α-isocyano alcohols 62 by addition of glacial acetic acid and conversion of 62 into amino alcohols 12, e.g. with hydrochloric acid in methanol.



62

In the isocyanomethyllithium process for ring expansion of cyclic ketones, the cyclic ketone is treated with isocyanomethyllithium, $LiCH_2NC$, to give 1-(isocyanomethyl)-1-cycloalkanol, which is hydrolyzed to the aminomethyl compound before being subjected to a Tiffeneau-Demyanov rearrangement to yield the ring-enlarged ketone (Ref. 34 & 35).

Chain Elongation by Michael Addition or Cyanoethylation

The Michael addition of 2-isocyanopropionic ester 2o to 21, giving the adducts 22, has already been mentioned. Hydrolysis of 22 should afford the corresponding amino acids. Ethyl isocyanoacetate 17 reacts with sterically unhindered Michael acceptors to give bisadducts [with ethyl acrylate (Ref. 1o), with ethyl methacrylate (Ref. 1o), with acrylonitrile or methacrylonitrile (Ref. 36)].

Acknowledgement - Thanks are due to F. Gerhart, D. Hoppe, R. Schröder, I. Hoppe, R. Harms, R. Meyer, D. Stafforst, R. Jentsch, K.Madawinata,H.-H. Hausberg, K.-W. Henneke, K.-H. Scheunemann, E. Eilers, K. Hantke, E. Blume, P.-H. Porsch and P. Böhme for their dedicated assistance. Support of this work by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, BASF AG, Ludwigshafen, and Dynamit Nobel AG, Troisdorf, is gratefully acknowledged.

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2. a) With phosgene: I. Ugi et al., Angew. Chem. 77, 492 (1965); Angew.Chem. Int. Ed. Engl. 4, 472 (1965); b) with "diphosgene": G. Skorna and I. Ugi, Angew. Chem. 89, 267 (1977); Angew. Chem.Int. Ed. Engl. 16, 259 (1977); c) with phosphorus oxide chloride: H. Böhme, G. Fuchs, Chem. Ber. 1o3, 2775 (197o); d) with toluenesulfonyl chloride: R.E. Schuster, J.E. Scott and J. Casanova, Org. Synth. 46, 75 (1966); e) with thionyl chloride/dimethylformamide: H. M. Walborsky and G. E. Niznik, J. Org. Chem. 37, 187 (1972); f) with triphenylphosphane/Tetrachloromethane: R. Appel, R. Kleinstück and K.-D. Ziehn, Angew. Chem. 83, 143 (1971); Angew. Chem. Int. Ed. Engl. 1o, 132 (1971); N-alkylformamides are obtained either by formylation of amines or from the halides by treatment with N-sodioformamide in acetonitrile. Numerous applications are listed in Ref. 5.
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