1-Isocyano-2-dimethylamino-alkenes: Versatile Reagents in Diversity-Oriented Organic Synthesis

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Abstract: 1-Isocyano-2-dimethylamino-alkenes are versatile and multifunctional reagents in organic synthesis. Two useful protocols are given for multicomponent reactions (MCRs) for the assembly of a 6-oxo-1,4,5,6-tetrahydropyrazine-2-carboxylic acid methyl ester derivative and a highly substituted thiazole. The procedures, in a modified set-up, are useful for array synthesis.

Key words: isocyanide, multicomponent reaction, heterocycle synthesis, thiazole

Introduction

Ivar Ugi in 1961 foresaw the usefulness of isocyanide-based multicomponent reactions (MCRs), for the synthesis of very many compounds, nowadays called chemical libraries: ‘Since in this condensation reaction four components react with each other, the number of possible products is quite high. Already the use of ten of each component leads to $10^4$ combinations’ (translated from German).1 Today, isocyanide-based MCRs form an integral part of combinatorial synthesis in modern pharmaceutical and agrochemical research.2 Generally appreciated are their versatility in terms of scaffolds, number of accessible compounds (‘chemical space’), their easy automatization, their convergent character and their one-pot way of performing the reaction with all its advantages.3,4 MCR have been especially fruitful for the versatile synthesis of heterocycles by a sequence of an initial MCR followed by ring closure reaction.5 Herein, the multifunctional 3-N,N-dimethylamino-2-isocyano-acrylate and its multiple transformations toward heterocycles are summarised and two new MCR procedures are given (Scheme 1).

Multifunctional 3-Dimethylamino-2-isocyanoacrylic Acid Esters

1-Isocyano-2-dimethylamino alkenes are remarkable multifunctional starting materials. Three different functional groups contribute to their interesting pathways of reactivity. The isocyano function undergoes multicomponent $\alpha$-additions and subsequent rearrangements to stable...
compounds. The double bond undergoes Michael additions and the dimethylamino-leaving group in 2-position undergoes substitution reactions (Scheme 2). The ester functionality might serve to attach the reagents onto solid support.

\[ \text{Scheme 2} \]

Densely functionalized 3-\(N,N\)-dimethylamino-2-isocyano-acrylic acid methyl ester 1. Four different functional groups are arranged in this compound. With a molecular formula of \( \text{C}_7\text{H}_10\text{N}_2\text{O}_2 \) there is a functional group per 2.75 heavy atoms (functional group density, FGD).

\( \alpha,\beta \)-Unsaturated isocyanides with a dimethylamino-leaving group in the 2-position have been introduced 30 years ago. They are versatile multifunctional reagents in organic synthesis, especially useful in heterocyclic synthesis. Meerwein et al. introduced the first example of this class of reagents, namely 3-dimethylamino-2-isocyano-acrylic acid methyl ester (1).\(^6\) According to Schöllkopf it can be conveniently synthesised on a 100 g scale by reacting commercially available isocyanic acid methyl ester (2) with dimethyl formamide dimethyl acetel (3) (Scheme 3).\(^7\) Advantageously, the liquid and strongly smelling isocyanic acid methyl ester (2) is transformed during this reaction into a solid, non-smelling and stable product. Similarly, \(\alpha\)-acidic isocyanides undergo the transformation towards 2-dimethylamino-1-isocyano derivatives. Today, several isocyanide derivatives of this class have been described (1, 4–8, Scheme 3).\(^8\) Alternatively, bromine at the 2-position can be used as a leaving group, e.g. 3-bromo-2-isocyanoaclates (BICA). Due to the long synthetic route involving reactive and unstable \(\alpha,\beta\)-unsaturated isocyanides, these reagents are more complicated to synthesise and less popular. Moreover, they exist as distinct \(E\)- and \(Z\)-isomers, which leads to different reaction products depending on the stereochemistry.\(^9\) In contrast, the stereochemistry of the derivatives of 1 has been shown to be exclusively in \(Z\)-configuration, proven by several X-ray structure analyses and NMR investigations (Scheme 3).

Many applications of 3-dimethylamino-2-isocyano-acrylic acid esters in heterocyclic chemistry have been described in the past (9–18, Scheme 4). Schöllkopf et al. first described the versatility of this reagent in organic synthesis. He reacted ester 1 with \(\text{H}_2\text{S}\) in \(\text{THF}\) in the presence of \(\text{Et}_3\text{N}\) to form thiazole-4-carboxylic acid esters 9 in 78% yield.\(^10\) This is an alternative to access this otherwise not easily amenable heterocyclic building block, even on a multigram scale.\(^13\),\(^15\)–\(^18\) Ester 1 can be transformed with acid chlorides to give substituted 2-oxo-1-methyl-1\(H\)-imidazole-4-carboxylic acid esters 10 in generally good yields, whereas it reacts with alkyl bromides to give 2-alkyl-1-methyl-1\(H\)-imidazole-4-carboxylic acid esters 11.\(^19\) Moreover a useful way for the regioselective synthesis of 1-\(N\)-substituted imidazole-4-carboxylic acid esters 12 has been introduced, by simply reacting 1 with an appropriate primary amine.\(^20\) This versatile reaction has recently described for the purpose synthesising pharmacological active compounds.\(^21\) To our knowledge this constitutes the most practical and versatile approach towards this important substituted heterocycle. The volatility and leaving group ability of the 2-dimethylamino group has been used advantageously to prepare libraries of isocyanides with different 2-amino functionality 13.\(^22\)

Bienaymé synthesised combinatorial arrays of bicyclic tetrazoles 14 by reacting 1, hydrogen azide, primary amines and aldehydes or ketones in a one-pot MCR.\(^23\) This constitutes a sequence of a Ugi four-component reaction (U-4CR) forming an \(\alpha\)-amino tetrazole containing a secondary amine, followed by a ring closing reaction with the dimethyl amine from the former isocyanide acting as a leaving group. Marcaccini et al. described the formation of bis-heterocyclic systems by reacting 1 with aromatic sulphenyl chlorides.\(^24\)
Recently we introduced four new MCRs based upon the multiple reactivity of 3-dimethylamino-2-isocyano-acrylic acid esters (Scheme 4, G–J). Studying the so far unknown reactivity of thiocarboxylic acids in the Ugi four component reaction, we noticed a completely regioselective formation of the $\alpha$-aminoacylthioamides. The concomitant formation of $\alpha$-aminothioacylamides was not observed. We figured out a way to use this unexpected finding for the synthesis of thiazoles by using $\text{I}$ as isocyanide components. This reaction turned out to be of quite generality, being compatible with quite a range of differently substituted starting materials. Thus we could synthesise thousands of differently substituted thiazoles by this novel methodology. Knowing about the versatility of isocyanide-based MCRs, we wondered if $\beta$-amino thiocarboxylic acids would react to give the corresponding $\beta$-lactams. The increase in molecular complexity here is dramatic as two heterocyclic moieties, a thiazole and a $\beta$-lactam ring, and 2 C-N, 2 C-S and 1 C-C bonds are formed simultaneously and under mild conditions.

In the course of our studies on the reactivity of $\text{I}$, we also performed solid phase variations on that theme. The 4-component thiazole synthesis has been performed on Rink amide resin $\text{19}$. Acidic cleavage yields the products $\text{22}$ in reasonable to good yields and purities (Scheme 5). Moreover we synthesised a solid phase bound variation of $\text{I}$. Thus we developed a new synthesis of the corresponding solid phase bond isocyanoacetic acid $\text{24}$, by simply reacting a brominated resin, e.g. 4-(bromomethyl)phenoxymethyl polystyrene or 4-(bromomethyl)benzolic acid coupled onto aminomethyl polystyrene, with the potassium salt of isocyanoacetic acid, leading to acid-labile Wang-resin-bound and to the base-labile resin-bound isocyanoacrylic acids. As compared to other described methods by multi-step chemistries on the resin, the isocyanide is assembled separately in solution and is finally at-

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**Scheme 4**  Reactions of 3-dimethylamino-2-isocyano-acrylic acid esters $\text{1}$: A: $\text{I}$, H$_2$S, Et$_3$N, EtOH; B: COR, 80 °C, 12 h; C: $\text{I}$, R$^1$Br, 100 °C, THF; D: $\text{I}$, HNR$^2$, 80 °C, neat, 3 h; E: $\text{I}$, HNR$^1$R$^2$, 20 °C; F: 1) $\text{I}$, R$^2$NH, R$^1$CHO, 20 °C, 24 h; 2) aq HCl; G: $\text{I}$, R$^1$CO, R$^2$NH, RCO$_2$H, 20 °C, 24 h; H: $\text{I}$, R$^2$CO, R$^1$CO$_2$H, BF$_3$OEt, 20 °C, 24 h; I: $\text{I}$, R$^1$CHO, H$_2$NCH$_2$CHR$^2$CO$_2$H, 20 °C, 24 h; J: $\text{I}$, R$^1$CHO, R$^2$NH$_2$, 20 °C, 24 h.

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**Scheme 5**  ‘Ugi-type’ four-component thiazole synthesis of $\text{I}$, aldehyde $\text{20}$ and thiocarboxylic acid $\text{21}$ with Rink amide $\text{19}$ as amine component.
tached to the resin. These isocynoacetate acid resins can than be converted to 1a and 1b and are useful for the solid phase synthesis of substituted thiazoles 28 and other heterocycles (Scheme 6).29

![Scheme 6](image)

Scheme 6 Synthesis of resin-bound variations of 1.

Synthesis of resin bound 1a and 1b was carried out as follows. Bromo Merryfield resins 23 react smoothly with the potassium salts of α-aminoacid derived isocyanides 25.27 Glycine derived isocyno resin is converted with dimethylformamide dimethyl acetal (3) to yield acid or base cleavable 1a or 1b, for use in solid phase synthesis (SPS).

Although the 4-component reaction of 1, thiocarboxylic acids, primary amines and oxo components runs easily and mostly in good to excellent yields, it took us a while to find conditions for the corresponding 3-component ‘Passerini-like’ thiazole synthesis towards 16.30 Under typical Passerini conditions no product formation is observed. Only the addition of a stoichiometric amount of a strong Lewis acid such as BF3·OEt2 yields the expected 2-served. Only the addition of a stoichiometric amount of a typical Passerini conditions no product formation is observed.

In a variation of this theme unprotected α-amino acids react to give iminodicarboxylic acid methyl ester intermediates bearing a secondary amine, which cyclize analogously to give 29. This reaction has been studied under array conditions. It is noteworthy that optimal yields can be obtained by the addition of one equivalent of Yb(OTf)3 or BF3·OEt2 (Scheme 8). A general feature of MCRs is often their compatibility with unprotected functional groups, e.g. the medicinally and chemically important amidine functionality, which otherwise is introduced at the end of a multi-step synthesis (Pinner reaction), can be used here directly in its unprotected form to yield the expected product 30 without interfering with the reaction mechanism.

The reactivity of 1 in different reactions leading to a multitude of heterocycles is based upon a highly dense functionalisation. The variety of possible molecular scaffolds renders 1 interesting for diversity-oriented synthesis. The herein-described reactions leading to diverse thiazoles and other heterocycles are useful for array synthesis and for the synthesis of fragments of highly bioactive natural products, e.g. tubulysin, helicoptin or dolabellin. Moreover it can be anticipated that more useful transformations of 1 will be discovered in the future.

1H and 13C NMR spectra were obtained in CDCl3 or DMSO-d6 and determined with a Mercury 400 spectrometer. Chemical shifts are expressed in ppm (δ) with respect to TMS as an internal standard. Electrospray ionisation mass spectra (ESI) were obtained using a MSD (Hewlett-Packard HPLC 1100 driven electrospray MS instrument). The purity was determined utilizing a Hewlett-Packard LC 1100 system [YMC column, 2 mm × 50 mm, 2 μm ODSA, 220 nm and 254 nm; 0.6 mL/min, 6 min gradient from 90% H2O to 10% H2O (0.5% CH3COOH) vs. CH3CN]

All starting materials used are commercially available. Isocyanide 1a, its derivatives and resin-bound variations are available at www.priaton.de.

4-(3-Carbamimidophenyl)-6-oxo-5-(3,4,5-trimethoxyphenyl)-1,4,5,6-tetrahydropyrazine-2-carboxylic Acid Methyl Ester (30) 3,4,5-Trimethoxybenzaldehyde (294 mg, 1.5 mmol) and 3-amino-benzenemide dihydrochloride (312 mg, 1.5 mmol) were dissolved in MeOH (6 mL). The mixture was stirred for 10 min at r.t. BF3·OEt2 (2 equiv) and 1 (231 mg, 1.5 mmol) were added. The reaction mixture was stirred at 20 °C for 12 h. The solvent was evaporated. The resulting residue was purified by preparative HPLC yielding 30 as a yellow powder in 38% yield. The preparative HPLC was performed at 254 nm using a flow rate of 50 mL/min on the following column: GROM-SIL 120 ODS-4 HE, 10 μm, 100 × 30 mm; gradient: MeOH +0.5% CH3COOH–H2O + 0.5% CH3COOH. Rt = 2.656 min (column: YMC, 50 × 2.1 mm; gradient: CH3CN + 0.5% CH3COOH–H2O + 0.5% CH3COOH).

1H NMR (400 MHz, DMSO-d6): δ = 3.62 (s, 3 H, CH3), 3.68 (s, 6 H, 2 × CH3), 3.74 (s, 3 H, CH3), 5.69 (s, 1 H, CH), 6.64 (s, 2 H, 2 × CH), 7.42 (m, 2 H, 2 × CH), 7.52 (m, 2 H, 2 × CH), 7.82 (s, 1 H, CH), 9.32 (br m, 4 H, amidine, NH).

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13C NMR (100 MHz, DMSO-d6): δ = 51.7, 55.9, 59.9, 62.3, 103.3, 109.2, 116.2, 121.5, 122.0, 129.2, 130.1, 131.5, 137.6, 143.0, 153.1, 161.6, 161.9, 165.0.

MS (ESI): m/z = 441.2 [M + H]+.

2-{1-[Acetyl-(3-methoxyphenyl)-amino]-3-methylbutyl}-thiazole-4-carboxylic Acid Methyl Ester

3-Methyl butanal (87 mg, 1 mmol) and 3-methoxy aniline (124 mg, 1 mmol) were stirred in anhyd MeOH (1 mL) at 20 °C for 0.5 h. Freshly distilled thioacetic acid (77 mg, 1 mmol) (Attention: thioacetic acid has a unpleasant odor; use a well ventilated fume hood!) was added to this solution followed by 1 (155 mg, 1 mmol) at 0 °C. This solution was then allowed to come to 20 °C and was stirred for 24 h. The solvent was evaporated under vacuum and the residue was purified by silica gel chromatography (EtOAc–hexane, 1:1); yield: 256 mg (68%); yellow oil; Rt = 3.761 min (column: YMC, 50 × 2.1 mm; gradient: CH3CN + 0.5% CH3COOH–H2O + 0.5% CH3COOH).

1H NMR (400 MHz, CDCl3): δ = 0.87–0.89 (dd, 6 H, 2 × CH3), 1.58–1.67 [m, 1 H, CH(CH3)], 1.79 (s, 3 H, OCH3), 1.84–1.88 (m, 2 H, CH2), 3.67 (s, 3 H, OCH3), 3.85 (s, 3 H, OCH3), 6.00–6.04 (m, 1 H), 6.48 (s, 2 H), 6.80 (d, 1 H), 7.14–7.20 (m, 2 H), 8.09 (s, 1 H).

13C NMR (100 MHz, CDCl3): δ = 22.4, 22.7, 23.3, 25.0, 40.4, 52.3, 55.7, 114.1, 114.9, 121.5, 127.3, 128.7, 130.0, 140.9, 145.7, 153.4, 160.2, 161.8, 170.8, 171.1 (some peaks appear double due to distinct rotamers about the tertiary amide bond.)


Acknowledgment

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References

(b) Original text: ‘Da solche Kondensations-Reaktionen zwischen insgesamt vier Komponenten stattfinden, ist die Zahl der Variationsmöglichkeiten sehr hoch. Bereits bei Verwendung von je zehn der vier Kondensations-Komponenten ergeben sich 104 Kombinationen.’

