Synthetic Methods

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Modulating the Reactivity of α-Isocyanoacetates: Multicomponent Synthesis of 5-Methoxyoxazoles and Furopyrrolones**

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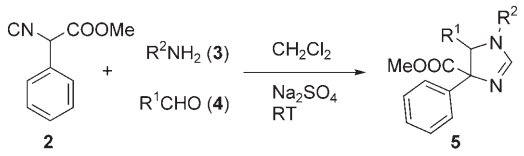
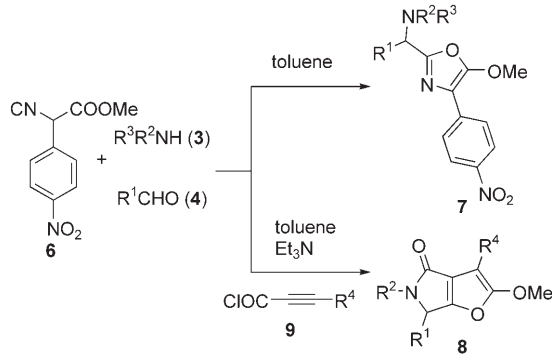
The chemistry of methyl α-isocyanoacetate (**1**) was investigated thoroughly in the 1970s, mainly by the research groups of Schöllkopf and Matsumoto.[1,4] One particularly powerful transformation is the reaction of metalated **1** with polar multiple bonds to afford heterocycles.[2] By taking advantage of the higher acidity of the α-phenyl-α-isocyanoacetate **2**, Orru and co-workers recently developed an elegant three-component synthesis of imidazolines **5** without the need for premetalation (Scheme 1).[3] The reaction was initiated by the nucleophilic addition of the α carbanion derived from **2** to an iminium ion generated in situ from **3** and **4**, which was followed by cyclization and protonation. The presence of the phenyl group is essential for this one-pot process: The reaction with α-isocyanoacetate **1** under otherwise identical conditions provided the corresponding imidazoline in low yield.[4] The phenyl group was thought to render the α CH position acidic enough to be deprotonated by a weak base. In general, the exploitation of the nucleophilicity of the α carbon atom and the electrophilicity of the divalent carbon atom of the isocyanide for the effective construction of C–C and C–N bonds characterized the known chemistry of α-isocyanoacetates.[1–4] In all these transformations, the ester functionality served only as an activator without participating in the bond-forming process, and the nucleophilicity of the divalent carbon atom of the isocyanide was exploited only for trapping a proton.



Scheme 1. Three-component synthesis of imidazolines described by Orru and co-workers.

In connection with our ongoing project aimed at the development of novel multicomponent reactions[5,6] with functionalized isocyanides as a key component,[7–9] we became interested in the reactivity profile of hitherto unknown methyl α-(*p*-nitrophenyl)-α-isocyanoacetate (**6**). The nitro group is strategically incorporated into the phenyl ring to render the α C–H bond even more acidic, so that it can be deprotonated by weaker bases. Whereas the ready formation of the carbanion is the key consideration in the development of the three-component reaction described by Orru and co-workers, we expected that the carbanion derived from **6** would display decreased nucleophilicity, as it is highly stabilized. Consequently, its reaction with a polar double bond, such as that of an imine, would be initiated by the nucleophilicity of the divalent carbon atom of the isocyanide and lead to different heterocycles.[10,11] We report herein the development of a three-component synthesis of 5-methoxyoxazoles **7** and a four-component synthesis of furopyrrolones **8** on the basis of the unique reactivity of methyl α-(*p*-nitrophenyl)-α-isocyanoacetate (**6**; Scheme 2).

Compound **6** was synthesized readily by a nucleophilic substitution reaction (S_NAr) between the commercially available α-isocyanoacetate **1** and 4-fluoronitrobenzene (**10**) under basic conditions that we developed previously for the monoalkylation of **1** (Scheme 3).[12] Detailed NMR spectroscopic studies indicated that **6** exists as the ester and not in the enol form in common organic solvents. To evaluate the chemical reactivity of **6**, we next examined its three-component reaction with morpholine (**3a**) and cyclohexanal (**4a**). Gratifyingly, when a solution of **3a**, **4a**, and **6** in toluene was simply stirred at room temperature for 4 h, the corresponding 5-methoxyoxazole **7a** was obtained in 92% yield.[13] The same



Scheme 2. Multicomponent synthesis of 5-methoxyoxazoles **7** and furopyrrolones **8**.

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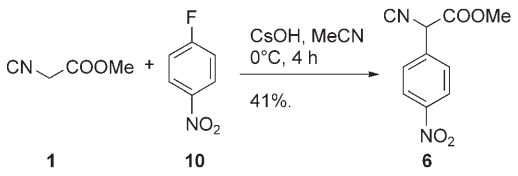
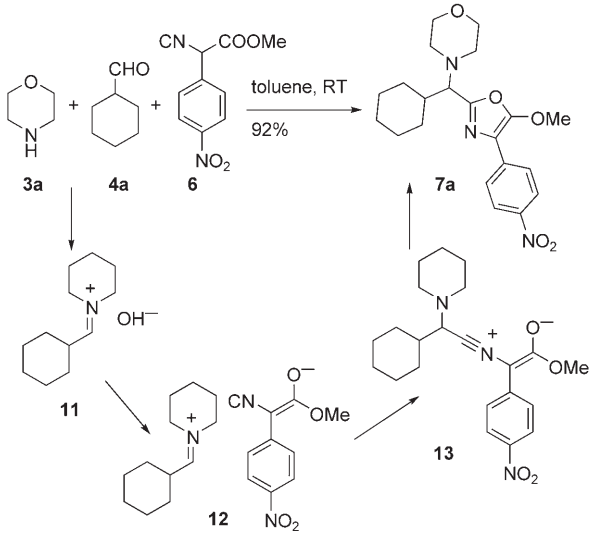
Supporting information for this article, including experimental procedures, product characterization, and ^{1}H NMR spectra of **6**, **7**, and **8**, is available on the WWW under http://www.angewandte.org or from the author.



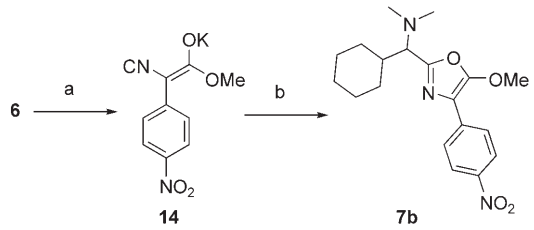
Scheme 3. Synthesis of methyl α-(*p*-nitrophenyl)-α-isocyanoacetate (**6**).

reaction proceeded smoothly in MeOH to afford **7a** in 90% yield. That this reaction occurred in toluene in the absence of any additive is intriguing, as nonpolar aprotic solvents are known to favor the alternative Passerini-type reaction.[14] The colorless solution of the aldehyde and the amine turned deep red instantaneously upon the addition of the yellowish solution of **6**. A possible reaction scenario is shown in Scheme 4: Condensation of the aldehyde with the amine affords the iminium ion **11**. The hydroxide counterion then serves as a base to abstract the α hydrogen atom of **6** to furnish the enolate **12**. The addition of the isocyanide to the iminium ion provides the nitrilium intermediate **13**, which undergoes cyclization to afford the 5-methoxyoxazole.[15] In this reaction, the carbene-like reactivity of the divalent carbon atom is exploited fully for the formation of one C–C bond and one C–O bond, whereas the ester functionality serves as an internal nucleophile to trap the incipient nitrilium intermediate. Thus, the reactivity profile of **6** is completely different from that of **2**, and more like that of α-isocyanoacetamide.[7]

The high acidity of the α C–H bond of the isocyanide **6** was clear from the following control experiment: The treatment of **6** with aqueous potassium hydroxide led to exclusive formation of the enolate **14** instead of the potassium salt of the carboxylic acid. It is noteworthy that the enolate is formed and stable under aqueous conditions. The treatment of **14** with the hydrochloride salt of dimethylamine and cyclohexanal afforded the corresponding oxazole **7b** in 55% yield over two steps (Scheme 5). These experimental results provided indirect evidence that the reaction of **6** with **3a** and **4a** might indeed proceed via the enolate intermediate **12**.



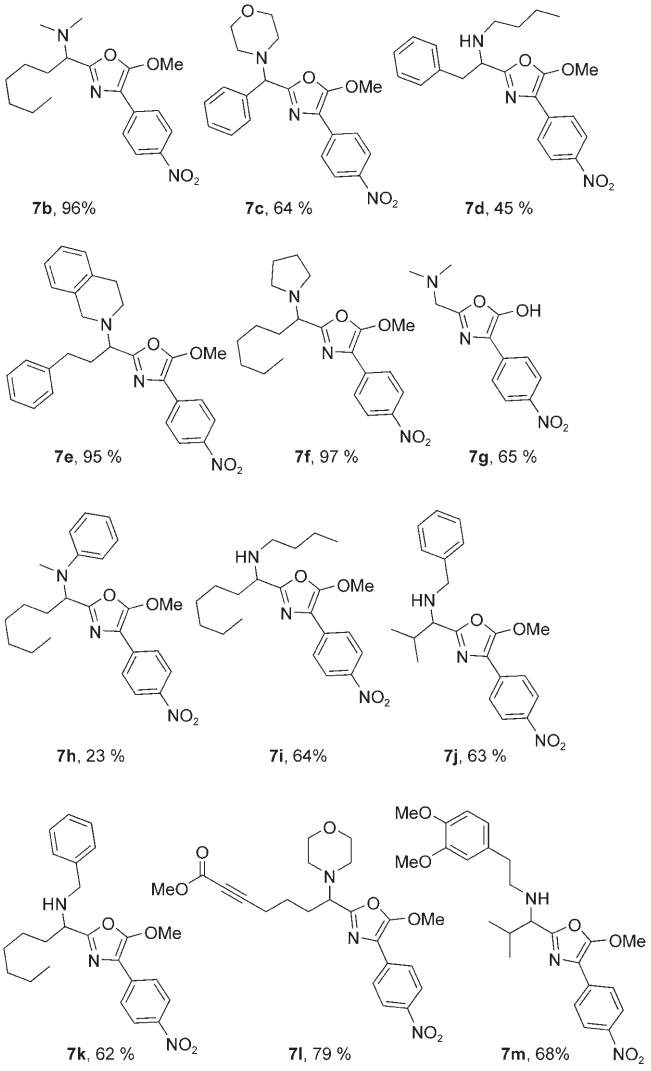
Scheme 4. Three-component synthesis of the 5-methoxyoxazole **7a**.



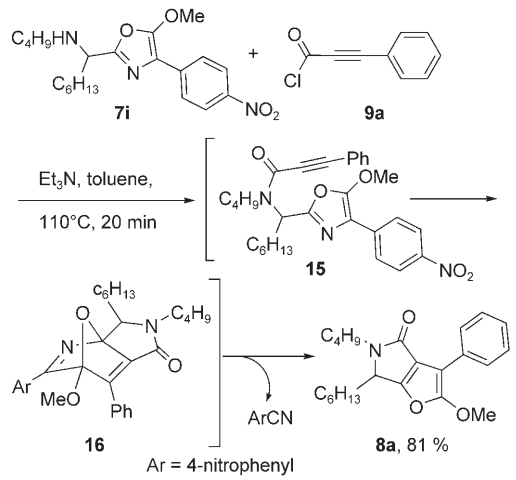
Scheme 5. Synthesis and three-component reaction of the potassium enolate **14**: a) KOH, THF/H_2O; b) $Me_2NH{\cdot}HCl$, *c*-$C_6H_{11}CHO$, toluene.

The scope of this reaction was examined by using eight amines and seven aldehydes as starting materials (see the Supporting Information). Some representative 5-methoxyoxazoles synthesized are listed in Scheme 6. In most cases, the reaction was performed with an approximately equimolar amount of the three components and was complete within 4 h in toluene at room temperature. Aliphatic aldehydes, including formaldehyde, linear aldehydes, and α-branched aldehydes, were found to be good substrates, as were aromatic aldehydes. Both aliphatic and aromatic amines participated in the reaction; cyclic secondary amines generally afforded the oxazole product in higher yield than primary amines. Although the corresponding oxazole was formed in excellent yield with dimethylamine, more hindered acyclic secondary amines, such as dibenzylamine, failed to provide the three-component adduct. When dibenzylamine was used, the addition of the isocyanide to the aldehyde occurred to afford 2-(1-hydroxyalkyl) 5-methoxyoxazoles in excellent yield.[16] Most probably, dibenzylamine serves only as a base to deprotonate **6**, and the ammonium enolate thus formed undergoes a Passerini type of reaction. This observation is also in line with the mechanistic proposal shown in Scheme 4 and might highlight the importance of the ion-pair intermediate **12** in the multicomponent process. When **3a** and **6** were treated with ketones, such as 4-phenylcyclohexanone, the corresponding 2-(hydroxyalkyl) 5-methoxyoxazoles were obtained.

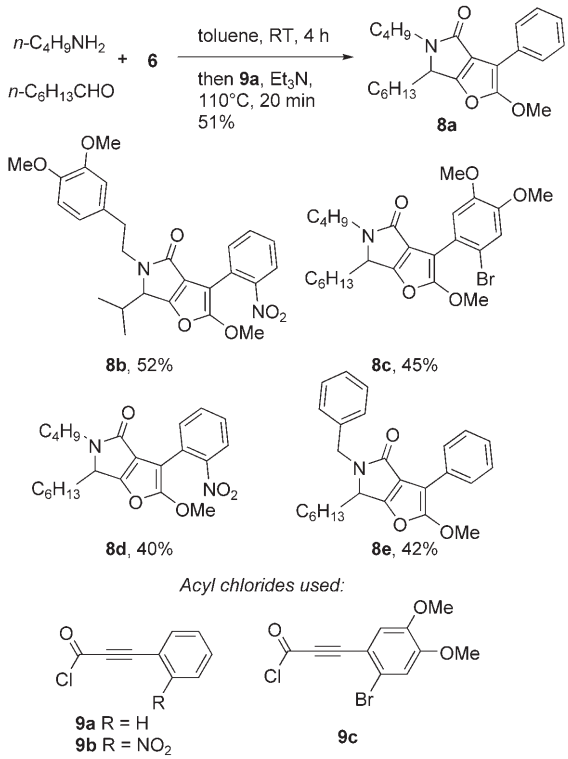
One shortcoming of this three-component reaction is that it provides only two points of diversity. To further illustrate the utility of methyl α-(*p*-nitrophenyl)-α-isocyanoacetate (**6**) in the development of novel multicomponent reactions for heterocycle synthesis, the chemical transformation of the products **7** was next investigated by taking advantage of the functionalities of the 5-methoxyoxazoles. As 5-methoxyoxazole is known to be an active diene that readily undergoes Diels–Alder reactions with a range of dienophiles,[17] our initial experiments focused on the intermolecular cycloaddition between **7a** and dimethyl acetylenedicarboxylate (DMAD). However, no cycloadduct was produced under thermal conditions, and decomposition occurred instead under forcing conditions. On the other hand, when a solution in toluene of the oxazole **7i** and 3-phenylprop-2-ynoyl chloride (**9a**) was heated at reflux, the furopyrrolone **8a** was obtained in 81% yield. The formation of **8a** can be explained by a three-step domino sequence (Scheme 7): Acylation of the secondary amine **7i** with the acyl chloride **9a** affords the tertiary amide **15**, which undergoes an intramolecular Diels–Alder cycloaddition to furnish the oxa-



Scheme 6. Structures of 5-methoxyoxazoles synthesized.



Scheme 7. Synthesis of the furopyrrolone **8a** by a domino process.



Scheme 8. One-pot four-component synthesis of furopyrrolone.

bridged polyheterocycle **16**. A retro-Diels–Alder reaction of **16** then affords the observed product **8a** together with 4-nitrophenylcyanide, which was also isolated from the reaction mixture.

Both the three-component synthesis of the oxazole and the subsequent domino process are performed in toluene and are therefore potentially compatible. We therefore attempted a four-component synthesis of the furopyrrolone. Thus, when a solution in toluene of *n*-butylamine, *n*-hexanal, and **6** was stirred for 4 h, after which time the acyl chloride **9a** and triethylamine (Et_3N) were added, and the resulting mixture was heated at reflux for 10 min, the corresponding furopyrrolone **8a** was obtained in 51 % overall yield. This four-component reaction turned out to be quite general. Some representative furopyrrolones synthesized are shown in Scheme 8. Both electron-withdrawing groups and electron-donating groups are tolerated in the aromatic ring of 3-aryl prop-2-ynoyl chlorides **9**. The presence of a substituent *ortho* to the triple bond did not interrupt the reaction sequence. In the case of **8c** and **8d**, the ^{1}H NMR spectra indicated the presence of two diastereomers, which exist because of hindered rotation about the biaryl axis. Although the yield is moderate, we emphasize that two C–N bonds, one C–O bond, one C–C bond, and two C=C double bonds are created in this experimentally simple process. Furthermore, the reaction allowed the introduction of three points of diversity and should therefore be highly useful for the synthesis of libraries of medicinally important heterocycles of this type. Since the 4-nitrophenyl substituent of the isocyanide **6** is not incorporated in the structure of the final product, the invariability of this substrate is not a major concern in this novel four-component reaction.[18]

In conclusion, by carefully considering the acidity of the α C–H bond(s) versus the nucleophilicity of the conjugate base, we have uncovered a new reactivity pattern of the well-

known α-isocyanoacetates. These studies highlighted the concept of a substrate-design approach to the development of novel multicomponent reactions.[5e] Indeed, by simply incorporating a nitro group into the phenyl ring of **2**, we obtained an isocyanoacetate, **6**, which displayed a completely different reactivity profile to that of **2** as a result of the increased acidity of the α C–H bond and hence the decreased nucleophilicity of the resulting carbanion. We have demonstrated previously that the exchange of the ester group of an isocyanoacetate for an amide group also modulates the reactivity of these compounds, in this case by decreasing the acidity of the α C–H bond(s). The multicomponent reactions reported herein should find applications in a number of fields in view of the synthetic and medicinal importance of 5-methoxyoxazoles[19] and furopyrrolones.[20]

Experimental Section

Typical procedure: Heptanal (25 μL, 0.18 mmol, 1.2 equiv) was added to a solution of *n*-butylamine (20 μL, 0.20 mmol, 1.3 equiv) in toluene (1 mL), and the mixture was stirred for 10 min at room temperature. The isocyanide **6** (33 mg, 0.15 mmol, 1.0 equiv) was then added, and stirring was continued for 4 h at room temperature. The reaction mixture was then cooled to 0 °C, and triethylamine (100 μL, 0.75 mmol, 5.0 equiv) was added, followed by a solution of 3-phenylpropioloyl chloride (49 mg, 0.30 mmol, 2.0 equiv) in toluene (0.7 mL). The reaction mixture was warmed to room temperature and was then heated at reflux for 10 min. The solvent was removed in vacuo, and the crude product was purified by preparative TLC (SiO_2, 30 % ethyl acetate in heptane) to afford **8a** (28.5 mg, 51 %) as a colorless oil.

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