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Simultaneous assembly of the β-lactam and thiazole moiety by a new multicomponent reaction

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Abstract—A novel multicomponent reaction of β-aminothiocarboxylic acids, aldehydes, and 3-dimethylamino-2-isocyanoacylate is described. During the course of this reaction two heterocyclic moieties, a thiazole and a β-lactam ring, are formed simultaneously and under mild conditions. The increase in molecular complexity here is dramatic as 2 C–N, 2 C–S and 1 C–C bonds are formed in a new 'one-pot' multicomponent reaction. © 2002 Published by Elsevier Science Ltd.

A major challenge of modern drug discovery is the design of highly efficient chemical reaction sequences which provide a maximum of structural complexity and diversity with just a minimum number of synthetic steps to assemble compounds with interesting properties.[1] According to *Corey* molecular size, element and functional group content, cyclic connectivity, stereocenter content, chemical reactivity, and structural instability all contribute to molecular complexity.[2]

Recently multicomponent reactions (MCRs) have emerged as a highly valuable synthetic tool in the context of modern drug discovery. The atom economical and convergent character, the simplicity of a one-pot procedure, the possible structural variations, the accessible complexity of the molecules, as well as the very large number of accessible compounds are among the described advantages of MCRs.[3] Thus, they are perfectly amenable to automation for combinatorial synthesis.[4] Amongst the known multicomponent reactions, isocyanide based MCRs are especially valuable.[5] Many different scaffolds are accessible, each with very many examples.[6] Thus they are prototypic complexity and diversity generating reactions.

But is it possible to discover new MCRs that may also lead to novel scaffolds?

In the classical chemistry of two component reactions, few reactions are discovered anymore.[7] However in the area of MCRs new reactions leading to novel scaffolds are described frequently. The immense possibilities of synthetic variations make it likely to find starting materials and conditions suitable for the discovery of new MCRs.[8]

Continuing our interest in the discovery of new MCRs,[9] we herein disclose the hitherto unknown three component reaction, which, starting from acyclic precursors and under mild conditions, affords a product constituted of a highly strained β-lactam ring with an appended heteroaromatic thiazole moiety. Recently, we discovered that thiocarboxylic acids, aldehydes, primary amines, and isocyanides react in a Ugi-type reaction highly regioselectively to afford the corresponding α-aminoacyl thioacylamides rather than a mixture of the α-aminoacyl thioacylamides and the α-aminothioacyl acylamides.[10] Using a special class of isocyanides, the 3-dimethylamino-2-isocyanoacrylates, we then found that the intermediate α-aminoacyl thioacylamides cyclize to the heteroaromatic thiazoles.[11] Thus, highly substituted thiazoles are synthetically accessible employing this four component reaction. Significantly, when the same isocyanide or a derivative thereof, is reacted with aldehydes in the presence of bifunctional β-aminothiocarboxylic acids, 1-thiazole-2-yl-methyl-azetidin-2-ones are smoothly formed (Scheme 1).[12] A plausible mechanism based on existing knowledge regarding MCRs can be proposed: during the course of the reaction the β-aminothiocarboxylic acid, the 3-dimethylamino-2-isocyanoacrylates, and the aldehyde react to form a seven-membered intermediate **I**. The secondary amine is then intramolecularly acylated, resulting in a ring contraction. The

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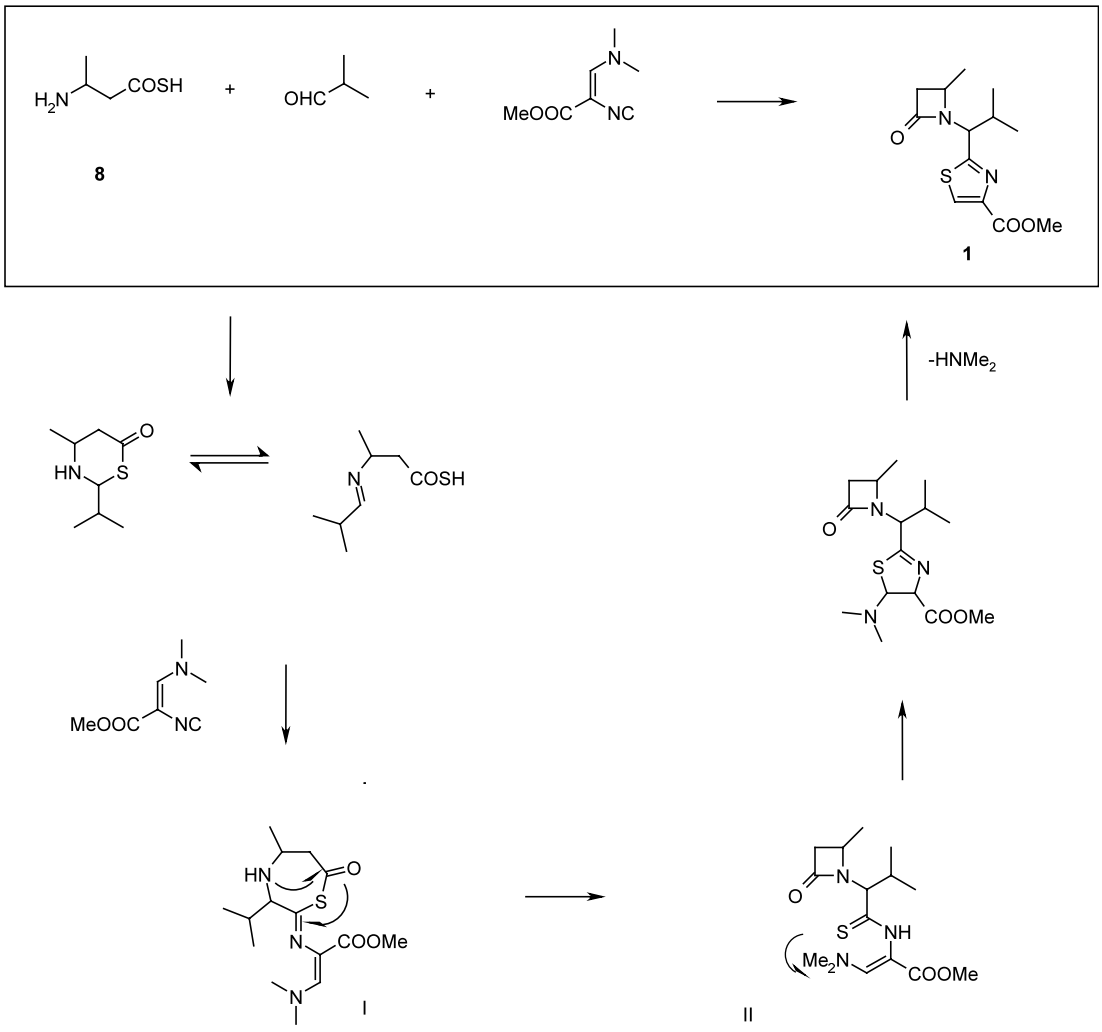


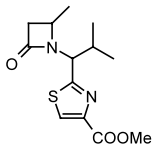
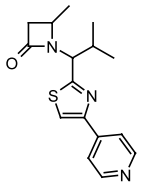
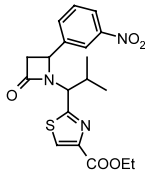
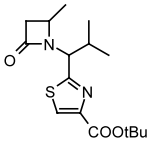
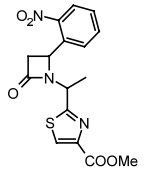
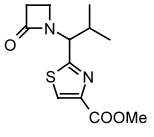
Scheme 1. Proposed reaction mechanism.

sulfur atom of the intermediate **II** adds to the acrylic acid moiety in a Michael-type manner. Finally the thiazole ring is formed by elimination of dimethylamine. The special reactivity of this isocyanide, first described by Schöllkopf et al.[13] is based upon three inherent properties: the isocyano reactivity, paired with the Michael acceptor character, and the built-in leaving group ability of dimethylamine. On employing unsymmetrical oxocomponents and another chiral component (e.g. isocyanide or β-aminothiocarboxylic acid), rather then symmetrical ketones or formaldehyde, diastereomers are formed. Not unexpectedly, the diasteromeric excess is poor, as it generally is true for MCRs of isocyanides. The reaction demonstrably works well with a number of starting materials in acceptable to good yields. Typical examples are shown in Table 1.

The thus-far relatively unknown β-aminothiocarboxylic acids are synthetically accessible via a two-step sequence.[14] After much experimentation, we have developed a new and expedient synthetic route for their preparation. We treated *Z*-protected β-amino acids with PBr_3 yielding the homo-Leuchs' anhydrides.[15] These sensitive compounds are then converted to the β-aminothiocarboxylic acids with gaseous H_2S (Scheme 2, Table 2). The third starting material, the β-dimethylaminoisocyano acrylic acid derivatives, are accessible in some variety from monosubstituted methylisocyanides analogously to the described procedure (Scheme 3).[16]

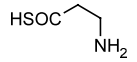
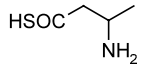
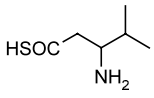
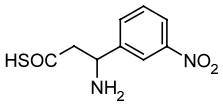
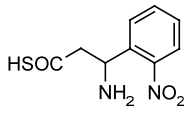
In conclusion a new three component reaction of β-aminothiocarboxylic acids, β-dimethylamino-2-isocyanoacrylates, and aldehydes yielding substituted 1-thiazole-2-ylmethyl-azetidin-2-ones has been developed. This new MCR is particularly noteworthy because under mild conditions, and starting from acyclic precursors, products containing two heterocycles are formed in good yields. In contrast, classical thiazole syntheses require much harsher conditions and typically the strained β-lactam ring system is also not easily formed.[17] In addition, the products emanating from this MCR are variable at three positions. Moreover, the corresponding starting materials are easily accessible from their available precursors. Compounds of this class, namely substituted 1-thiazole-2-ylmethyl-azetidin-2-ones, are potentially useful as protease inhibitors, as antibiotics, or as cholesterol absorption modifiers.[18] Further efforts in our laboratory are

Table 1. Structures and yields of some prepared thiazole-β-lactams according to the new one-pot procedure

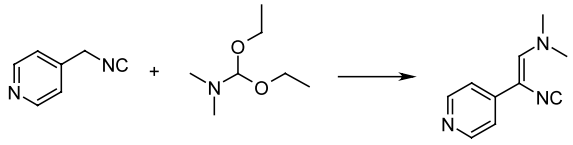
No.	Structure	Yield (%)
1		69
2		38
3		52
4		45
5		36
6		58

directed towards solid-phase variations of this reaction, the synthetic utility of such reactive compounds and an in-depth biological evaluation of this interesting class of compounds. This reaction is yet another example of how highly convergent MCRs can function as a superior tool for diversity-oriented and complexity-generating synthesis.[19]

Table 2. Synthesized β-aminothiocarboxylic acids according to Scheme 2

No.	Structure	yield (%)[a]
7		55 59
8		68 78
9		78 49
10		71 45
11		50 72

[a] 1st and 2nd steps' yield given.



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Scheme 3. Synthesis of 2-dimethylamino-1-(4-pyridyl)-1-ethenylisocyanide.

Acknowledgements

Dedicated to the 72nd birthday of Professor Ivar Ugi. We thank Robert Eckl for measurement of the NMR spectra and Sepp Achatz for his support in isocyanide chemistry.

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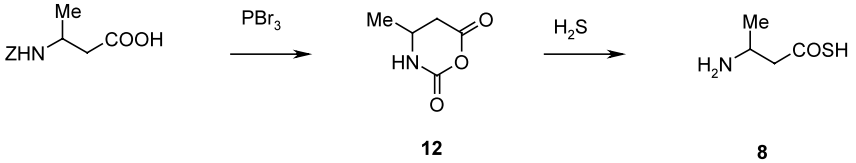

12 8

Scheme 2. Synthesis scheme for β-aminothiocarboxylic acid.

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12. Procedure for 2-[2-methyl-1-(2-methyl-4-oxo-azetidin-1-yl)-propyl]-thiazole-4-carbonic-acid methylester **1** as a diastereomeric mixture: under a dry nitrogen atmosphere, a solution of 5 mmol (0.596 g) β-aminothiopropionic acid and 0.5 g $MgSO_4$ in dry methanol (10 mL) was stirred and cooled to −15°C. Isobutyric aldehyde (5 mmol, 0.361 g) in methanol (5 mL) was slowly added to the solution and was stirred for a further hour. 3-Dimethylamino-2-isocyanoacrylicacid methylester (5 mmol, 0.77 g) was added. The mixture was allowed to reach 20°C and was stirred for an additional 24 h. After evaporation of the solvent, the residue was dissolved in 40 ml of DCM, extracted three times each with 10 ml of 1% phosphoric acid, 10 ml of saturated sodium hydrogencarbonate solution and 10 ml of distilled water. The organic phase was dried over Na_2SO_4, and the solvent was evaporated. The resulting oil was purified with chromatography on SiO_2 to give 0.98 g (69%) of a foam, as a mixture of diastereomers (de = 0.84). Characterization of compound **1**: MW ($C_{13}H_{18}N_2O_3S$) = 282.36; HPLC-MS spectra (Hewlett–Packard HP1100; YMC column, 2×50 mm, 2 μm ODSA, 220 and 254 nm; 0.6 mL/min, 4 min, gradient from 90% H_2O to 10% H_2O (0.5% CH_3COOH versus CH_3CN) coupled with a MSD mass spectrometer using electronspray ionization (ESI)): $t_{R,\ 254\ nm}$ = 3.348 min; m/z = 305 $[M+Na]^+$, 283 $[M+H]^+$, 241 $[M-CON]^+$. Determination of de: (Hewlett–Packard HP1100; YMC column, 2×50 mm, 2 μm ODSA, 220 and 254 nm; 0.6 mL/min, 32 min, gradient from 90% H_2O to 10% H_2O (0.5% CH_3COOH versus CH_3CN) t_R (minor) = 6.167 min t_R (major) = 6.515 min. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.81–0.83 (m, 6H, $CHCH(C\underline{H}_3)_2$); 1.13–1.15 (m, 6H, $CHCH(C\underline{H}_3)_2$); 1.27–1.28 (m, 3H, β-lactam CH_3); 1.34–1.36 (m, 6H, β-lactam CH_3); 2.48–2.55 (m, 2H, β-lactam CH_2); 2.64–2.70 (m, 1H, $CHC\underline{H}(CH_3)_2$); 2.78–2.87 (m, 1H, $CHC\underline{H}(CH_3)_2$); 2.96–3.06 (m, 1H, β-lactam CH_2); 3.64–3.71 (m, 2H, β-lactam CH); 3.95 (s, 6H, $-OCH_3$); 4.26 (d, 1H, $N\text{-}C\underline{H}CH(CH_3)_2$); 4.46 (d, 1H, $N\text{-}C\underline{H}CH(CH_3)_2$); 8.17 (s, 1H, thiazole-H); 8.20 (s, 1H, thiazole-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.68 (β-lactam CH_3); 18.67 ($CHCH(\underline{C}H_3)_2$); 18.76 (β-lactam CH_3); 18.79 ($CHCH(\underline{C}H_3)_2$); 19.21 ($CHCH(\underline{C}H_3)_2$); 19.49 ($CHCH(\underline{C}H_3)_2$); 30.27 ($CH\underline{C}H(CH_3)_2$); 31.29 ($CH\underline{C}H(CH_3)_2$); 42.47 (β-lactam CH_2); 42.75 (β-lactam CH_2); 46.18 (β-lactam CH); 48.37 (β-lactam CH); 51.34 ($-OCH_3$); 51.39 ($-OCH_3$); 61.47 ($-\underline{C}HCH(CH_3)_2$); 61.96 ($-\underline{C}HCH(CH_3)_2$); 127.40 (thiazole-C-5); 127.98 (thiazole-C-5); 144.59 (thiazole-C-4); 145.08 (thiazole-C-4); 159.57 (thiazole-C-2); 160.60 (thiazole-C-2); 165.17 ($-CH_2\underline{C}O$); 165.43 ($-CH_2\underline{C}O$); 168.45 ($-\underline{C}OOCH_3$); 169.59 ($-\underline{C}OOCH_3$).
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15. General procedure for the preparation of *N*-carboxy-β-aminobutyric acid anhydride **12**: 50 mmol of the *N*-benzyloxycarbonyl protected β-amino acid (2-aminopropanic acid) was suspended in 400 mL DCM. Under a N_2 atmosphere 30 mmol phosphortribromid (8.121 g or 2.85 mL) was added via a septum. After 24 h the slurry was filtered under a N_2 atmosphere. The solvent was distilled of until it again starts to precipitates. Dry hexane was added. The precipitate was filtered under dry conditions to yield 4.38 g (68%) of the product. MW ($C_5H_7NO_3$) = 129.11; ^1H NMR: ($CDCl_3$, 400 MHz): δ = 1.36 (d, 3H, ^3J = 6.4 Hz, $-C\underline{H}_3$); 2.53 (dd, 1H, ^2J = 16.2 Hz, ^3J = 9.3 Hz, $-C\underline{H}_2$-); 2.87 (dd, 1H, ^2J = 16.2 Hz, ^3J = 4.3 Hz, $-C\underline{H}_2$-); 3.77 (m, 1H, $-C\underline{H}(CH_3)$); 6.74 (b, 1H, $-N\underline{H}$-). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.8 ($-C\underline{H}_3$); 36.2 ($-C\underline{H}_2$-); 42.9 ($-\underline{C}H(CH_3)$-); 150.2 ($-\underline{C}ONH$-); 164.4 ($-CH_2\underline{C}O$-).
16. Procedure for the preparation of 2-dimethylamino-1-(4-pyridyl)-1-ethenylisocyanide **13**: 5.9 g 4-isocyanomethylpyridin (Schöllkopf, U.; Eilers, E.; Hantke, K. *Liebigs Ann. Chem.* **1976**, 969) (50 mmol) and 7.35 g dimethylformamiddiethylacetal (50 mmol) were dissolved in 10 mL ethanol and stirred for 16 h at 20°C. The solvent was evaporated at reduced pressure and the residue was purified by chromatography on silica gel. Yield 2.4 g (28%) as a violet solid. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.49 (s, 6H, 2×N-CH3); 5.97 (s, 1H, =CH); 6.37 (d, 2H, Pyr); 7.66 (d, 2H, Pyr); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 42.47 ($N(\underline{C}H_3)_2$); 115.46 ($=\underline{C}HN(CH_3)_2$); 138.97 (Pyr-C-3); 142.70 (Pyr-C-4); 149.38 (Pyr-C-2); 167.41 ($-N\underline{C}$). These isocyanides are commercially available at: http://www.priaton.de/.

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