Pergamon

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Tetrahedron Letters 44 (2003) 3679–3682

TETRAHEDRON LETTERS

A new and efficient multicomponent solid-phase synthesis of 2-acylaminomethylthiazoles

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Received 7 February 2003; revised 10 March 2003; accepted 10 March 2003

Dedicated to Dr. Lutz Weber on the occasion of his 45th birthday.

Abstract—A new multicomponent reaction (MCR) for the preparation of 2-substituted thiazole libraries using Rink amide resin is described. Thiazoles are assembled in a one-pot MCR of a thiocarboxylic acid, aldehyde, 3-(*N*,*N*-dimethylamino)-2-isocyanoacrylate with a resin-bound primary amine. Aliphatic and aromatic thiocarboxylic acids as well as aliphatic and (hetero-) aromatic aldehydes work in the reaction. Cleavage of the product yields the substituted thiazoles in reasonable to good purity.

4-Carboxy-2-acylaminomethylthiazole is a common backbone in many peptide derived natural products. Examples are the tubulin poison Dolastatin 10 **1**,[1] the antibiotic Microccin P_1 **2**,[2] or the antifungal Leinamycin **3**[3] (Fig. 1). The biosynthesis of this class of secondary metabolites has been studied extensively and these derivatives are generally formed from their cystein-peptide precursor by the sequence cyclization/oxidation.[4]

Furthermore the substituted thiazole is an important heterocyclic nucleus in medicinal chemistry.[5,6] Several solid-phase routes for the synthesis of thiazole libraries have therefore been reported.[7]

Recently we described the use of 3-(*N*,*N*-dimethylamino)-2-isocyanoacrylate and thiocarboxylic acids in the Ugi four component reaction (U-4CR). To our surprise we found the neat formation of 2,4-disubstituted thiazoles.[8] When using aldehydes or ketones and primary amines 4-carboxy-2-acylaminomethylthiazole **1** is formed (Scheme 1). Interestingly the use of β-aminothiocarboxylic acids with 3-(*N*,*N*-dimethylamino)-2-isocyanoacrylate and an aldehyde react intramolecularly to give biheterocyclic 2-oxo-4-arylazetidin-1-ylmethylenthiazol-4-carboxylic acid esters **2** (Scheme 1).[9,10] Scope and limitations in solution-phase synthesis were evaluated in-depth with many combinations of several thiocarboxylic acids, aldehydes and ketones, primary amines, and 3-(*N*,*N*-dimethylamino)-2-isocyanoacrylates.[10] These four-component reactions comprise the first MCR towards thiazoles.

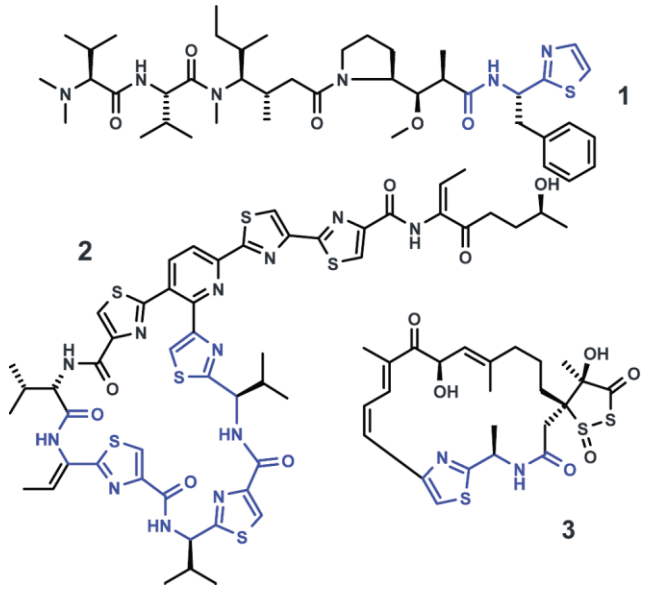

Figure 1. Natural products containing the motif 2-acylaminomethylthiazole (**1** = Dolastatin 10, **2** = Microccin P_1, **3** = Leinamycin).

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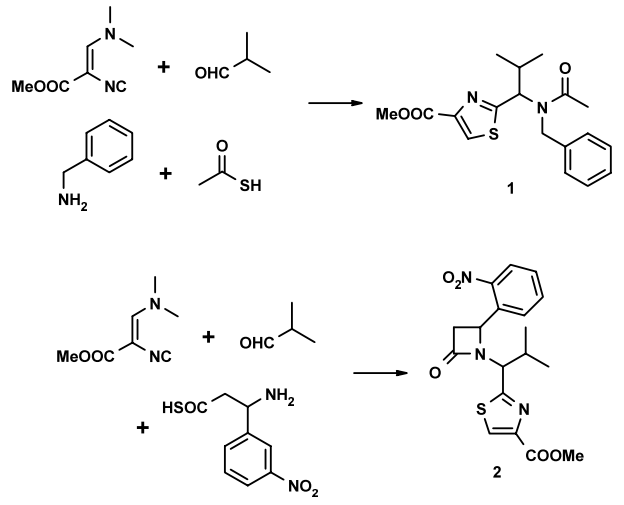
doi:10.1016/S0040-4039(03)00662-2



Scheme 1. Formation of 4-carboxy-2-acylaminomethylthiazole **1** and 2-oxo-4-arylazetidin-1-ylmethylenthiazol-4-carboxylic acid ester **2**.

In the present study, we wanted to synthesize 2-acylaminomethylthiazoles having a free amide nitrogen, which is in contrast to compounds published.[8] Therefore we investigated a new efficient MCR route for solid-phase synthesis of these thiazoles (Scheme 2). Two points of diversity were introduced.

As amine and resin component, we used the Rink amide resin that was purchased from PepChem in Tübingen, Germany. It was pre-condensed with a 10-fold excess of aldehyde for 16 h, then the excess aldehyde was filtered off. A sixfold excess of 3-(*N*,*N*-dimethylamino)-2-isocyanoacrylate and thiocarboxylic acid was added in DCM/MeOH 1/1 and reacted for 12 h at 20°C. The product was cleaved from the resin by reacting with TFA/DCM at 20°C for 2 h (Scheme 2).[11]

Table 1 shows a representative portion of a larger library of 4-carboxy-2-acylaminomethylthiazoles and the corresponding purity after TFA cleavage from the resin. We observed that the reaction works with a variety of aliphatic, (hetero-) aromatic, phenolic aldehydes and with thioacetic acid as well as with thiobenzoic acid. To our surprise aqueous formaldehyde reacted with both thioacids in good purities. Generally the observed purities were acceptable to good.

In summary, we have developed a new MCR solid-phase synthesis of 4-carboxy-2-acylaminomethylthiazoles. The Rink amide resin was used as the amine component. A variety of different aldehydes and two different thiocarboxylic acids were investigated and gave generally good purities after cleavage from resin. The technique described is useful in the context of combinatorial chemistry and could also have applications in natural product synthesis. Present studies in our laboratory are directed towards the attachment of other functional groups of the thiazole MCR on resin, e.g. the thiocarboxylic acid and 3-(*N*,*N*-dimethylamino)-2-isocyanoacrylate.

Acknowledgements

We thank Professor Dr. Wünsch for kindly supporting Michael Sax.

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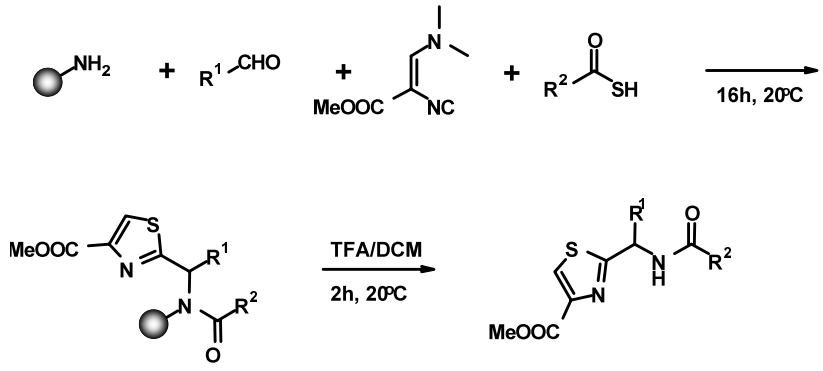
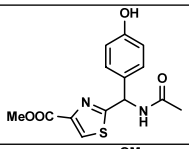
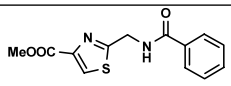
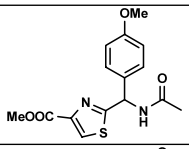
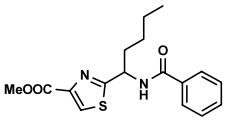
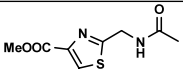
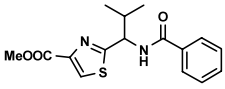
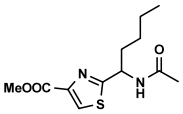
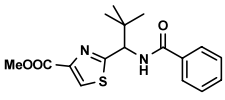
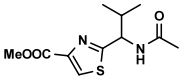
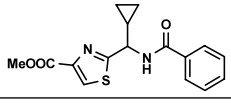
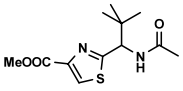
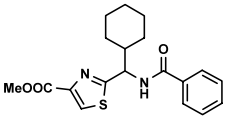
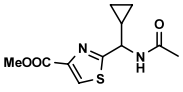
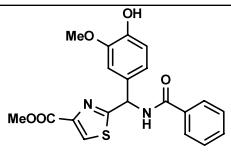
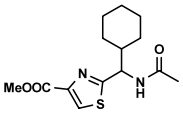
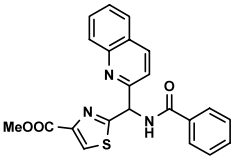
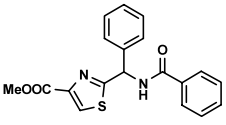
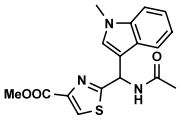
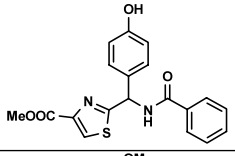
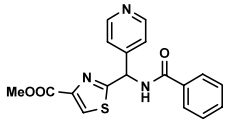
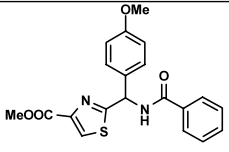
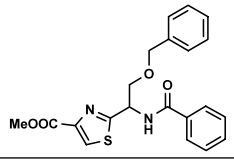
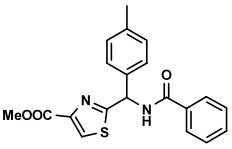
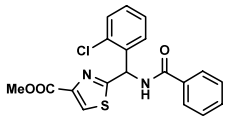


Scheme 2. Solid-phase synthesis of 4-carboxy-2-acylaminomethylthiazoles.

Table 1. 4-Carboxy-2-acylaminomethylthiazoles synthesized and their corresponding purities after cleavage from the resin

No	Thiazole[1]	HPLC puritiy %[2]	No	Thiazole[1]	HPLC puritiy %[2]
1		46	13		63
2		31	14		60
3		65	15		88
4		64	16		54
5		93	17		78
6		78	18		76
7		96	19		57
8		70	20		82
9		44	21		35
10		69	22		34
11		36	23		38
12		43	24		40

[1]All compounds have been characterized by NMR and HPLC-MS

[2]Purity are based on the peak area of HPLC spectra of crude products as detected at 254 nm.

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11. Representative example for the synthesis of 2-acylaminomethylthiazoles; synthesis of 2-(benzoylamino-2-methylpropyl)thiazole-4-carboxylic acid methylester **14**: 200 mg of deprotected Rink resin (purchased from Pepchem, Tübingen) (0.21 mmol) were washed with 3 ml of trimethylorthoformate. Isobutyraldehyde (0.192 ml, 2.1 mmol) were dissolved in 3 ml of trimethylorthoformate and given to the resin which was agitated for 16 h. The resin was filtered off and washed with trimethylorthoformate, with a 1:1 mixture of dichloromethane and methanol and finally with methanol three times each. Subsequently 194 mg 3-(*N*,*N*-dimethylamino)-2-isocyanoacrylate (1.26 mmol) and 0.147 ml thiobenzoic acid (1.26 mmol) dissolved in 3 ml of a mixture of dichloromethane and methanol (1:1) was given to the resin and reacted for 16 h. The resin was filtered off and washed twive with dichloromethane and methanol and again three times with dichloromethane. Then the resin was treated with 3 ml of 50% trifluoroacetic acid in dichloromethane for 2 h. The cleavage mixture was filtered off and the resin washed twice with dichloromethane. The combined solutions were evaporated to dryness. The crude product was purified via preparative HPLC using a methanol/water gradient. Yield: 47.5 mg (71.1%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.83 (d, $J=7.0$ Hz, 2H), 7.51 (t, $J=7.0$ Hz, 1H), 7.44 (t, $J_1=7.8$ Hz, $J_2=7.0$ Hz, 2H), 7.10 (d, $J=7.8$ Hz, 1NH), 5.39 (dd, $J=8.6$ Hz, 1H), 3.93 (s, 3H, methylester), 2.53 (sext., $J=7.0$ Hz, 1H), 1.05 (d, $J=7.0$ Hz, 3H), 0.98 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 167.5, 161.9, 147.1, 134.0, 132.1, 128.9, 127.6, 127.4, 57.0, 52.7, 33.8, 19.8, 18.6.