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Convergent multicomponent assembly of 2-acyloxymethyl thiazoles

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Dedicated to Professor Ivar Ugi on the occasion of his 73rd birthday

Abstract—Diverse substituted 2-acyloxymethyl thiazoles can be assembled by a new multicomponent reaction (MCR) of methyl 3-(*N*,*N*-dimethylamino)-2-isocyanoacrylate, aldehydes and thiocarboxylic acid under Lewis acid catalysis. The reaction is performed under mild conditions and is compatible with a wide range of functionalized starting materials. 13 examples are given.

Most thiazole-containing natural products are derived from cysteine peptide precursors, by sequential cyclization and oxidation, and thus contain the 2-aminoacylmethyl thiazole moiety.[1] They are known as non-ribosomal peptides and often comprise an outstanding structural diversity of microbial origin.[2] In contrast the biosynthetic pathway for 2-hydroxymethyl thiazoles has not yet been elucidated. Interestingly, it is an essential moiety of several cytoskeleton destroying, highly cytotoxic natural products, e.g. dolabellin **1**,[3] tubulysine D **2**,[4] and archazolide A **3** (Fig. 1).[5] As part of our ongoing interest in anticancer compounds this molecular scaffold attracted our attention and we have been investigating novel synthetic pathways.[6]

Several synthetic routes towards 2-hydroxymethyl thiazoles are already established. Thus, these compounds are accessible by lithiation of a thiazole precursor and subsequent reaction with an aldehyde or ketone.[7] Unfortunately, only a few suitable thiazoles are commercially available. Another prominent synthetic approach is a multi-step procedure using the Hantzsch thiazole reaction as a key transformation.[8] Furthermore, Dondoni et al. developed a straightforward and versatile synthesis of 2-hydroxymethyl thiazoles as a means to one-carbon aldehyde extensions.[9] In the course of our investigations of the structure–activity relationship of antimitotic natural products, we needed a general and fast access to substituted 2-hydroxymethyl thiazoles. We therefore communicate here our findings of a new one-pot multicomponent reaction towards this scaffold and discuss its scope and limitations (Fig. 1).

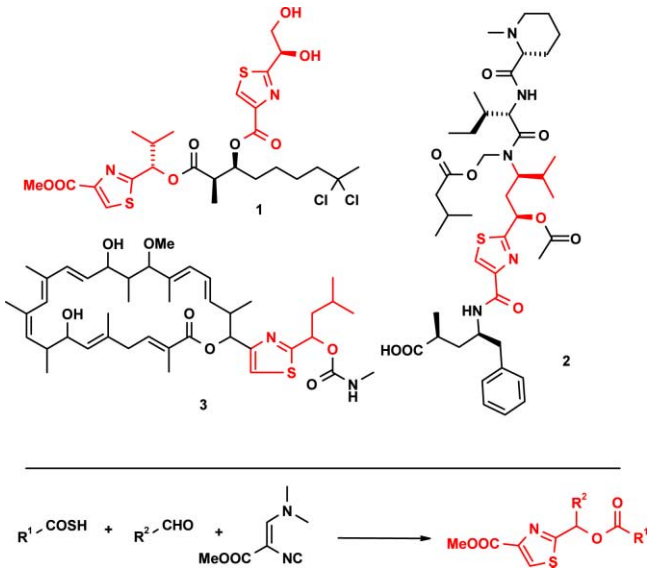

Figure 1. Bioactive natural products incorporating the 2-hydroxymethyl thiazole motif: actin cytoskeleton binding dolabellin **1** and archazolide A **3** and tubulin cytoskeleton binding tubulysin D **2**. A novel 3-CR opens access to functionalized thiazole moieties.

Keywords: isocyanide; multicomponent reaction; thiazole; Passerini reaction.

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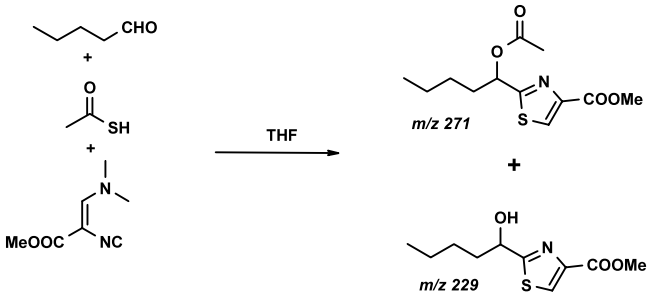
Recently, we discovered and investigated thoroughly a novel four-component condensation involving methyl 3-(*N*,*N*-dimethylamino)-2-isocyanoacrylate, thiocarboxylic acids, primary amines and oxo compounds yielding substituted 2-methylaminoacetyl-1,3-thiazoles.[10]

This new condensation is reminiscent of the classical Ugi-MCR except that a thiazole ring is formed concomitantly. Thus, we were wondering if we could develop a corresponding Passerini-type thiazole synthesis, omitting the primary amine. Unfortunately, initial experiments did not show the formation of any product. It is quite well established that Passerini-type reactions run best in apolar aprotic solvents, whereas Ugi-type reactions need polar protic solvents.[11] Screening of different solvents and temperatures including microwave irradiation did not result in success. The use of Brønstedt acids did not show any improvements. Finally we found that in the presence of the Lewis acid boron trifluoride etherate the expected product was formed. Performing the reaction at −78°C gave the optimal results. Higher temperatures, e.g. reflux, room temperature or microwave irradiation gave an excess of side products, as did prolonged (>2 h) reaction times. A nitrogen atmosphere was required. In addition we tried to optimize the required Lewis acid. Thus, we screened 14 different Lewis acids (Table 1) in a test reaction and compared the yields by HPLC-MS. Unfortunately, none of the Lewis acids tested showed any improvement. The amount of $BF_3{\cdot}OEt_2$ can be reduced from equimolar to 1/10 without any loss in yields. The resulting products were purified by silica gel chromatography.[12]

Table 1. Lewis acid screening: In this test reaction two major products were formed with *m*/*z* 229 and *m*/*z* 271. These correspond to the hydroxy and acetoxy derivatives. The extent of the formation of these products was judged by HPLC-MS. Formation of the products is very good (++), good (+), poor (–) or no product (––)

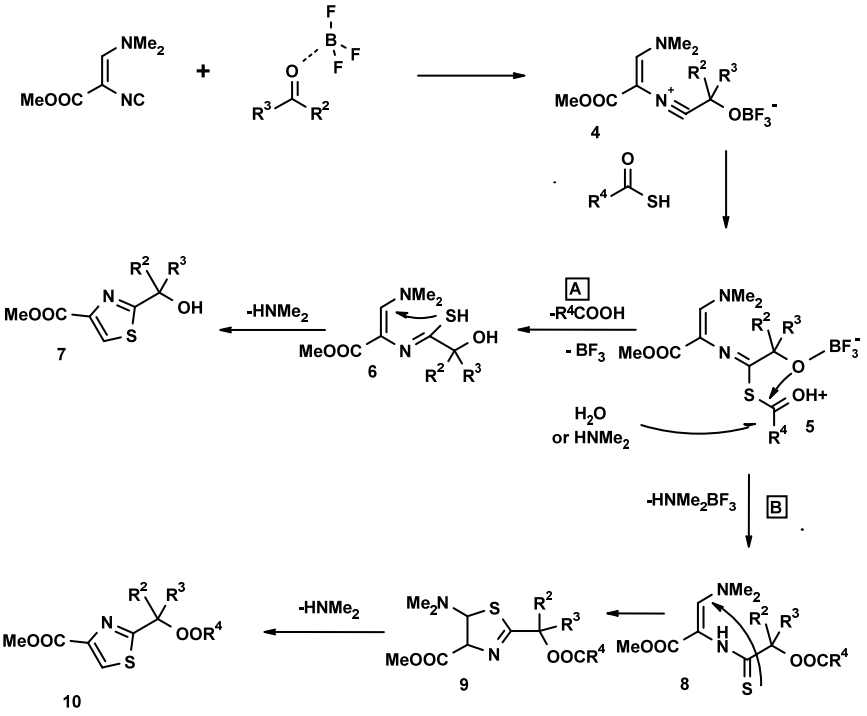


Entry	Lewis acid	Signal intensity	Signal intensity
		m/*z*: 229	*m*/*z*: 271
1	$MgBr_2{\cdot}OEt_2$	––	––
2	$ZnCl_2$	–	+
3	$Yb(OTf)_3$	+	+
4	$Zn(OTf)_2$	+	+
5	$Mg(OTf)_2$	––	––
6	$MgBr_2$	––	––
7	MgI_2	––	––
8	$ZrCl_4$	++	+
9	$Sc(OTf)_3$	++	+
10	$Mg(ClO_4)_2$	–	–
11	$Hf(OTf)_4$	++	+
12	$BF_3{\cdot}OEt_2$	++	++
13	$TiCl_4$	+	–
14	$AlCl_3$	+	+

A proposed mechanism explaining the observed products **7** and **10** is depicted in Scheme 1. Accordingly the aldehyde is activated by $BF_3{\cdot}OEt_2$ to render the carbon more nucleophilic allowing the addition to the isocyanide carbon forming the iminium ion **4**. Addition of the thiocarboxylic acid via the sulfur atom results in the α-adduct **5**. The strongly activated hetero anhydride **5** could be hydrolyzed by traces of water and/or by dimethylamine which is a side product of the reaction to give the tautomerized thioamide **6** which instantaneously cyclizes with elimination of dimethylamine giving the 2-hydroxy methyl thiazole **7**. The second reaction starting from the intermediate, α-adduct **5** follows the classical proposed Passerini mechanism by a transacylation towards **8** followed by an intramolecular Michael addition to the acrylic acid yielding **9** and elimination of dimethylamine resulting in **10**.

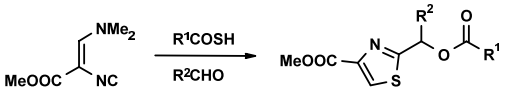
The 13 examples in Table 2 imply that this reaction works with a wide variety of aliphatic and aromatic aldehydes, even containing functional groups such as double bonds. The three different commercially available thiocarboxylic acids all worked well under the conditions used. Unfortunately, the yields of all the reactions were rather poor. Looking at the control reactions by HPLC-MS it was obvious that a number of side reactions take place. This can be rationalized in terms of the high reactivity of the trifunctional isocyanide and the thiocarboxylic acid. Nevertheless we think that this reaction is synthetically useful since none of the products are accessible in one step by other methodologies. For example the lithiation of a thiazole precursor followed by addition of an aldehyde is hardly compatible with the 4-methoxycarbonyl function.[7] Moreover, Schmidt et al. synthesized the ethyl ester of compound **19** via a 4-step synthesis starting from the commercially unavailable 1-(chlorocarbonyl)-3-methylbutyl trifluoroacetate (which is available in three more steps) in 64% yield.[8] This particular synthesis comprised conversion to the primary amide, followed by thionation with Lawesson's reagent, followed by a two-step Hantzsch ring-closure with ethyl bromopyruvate and dehydration with TFAA with partial racemization. Furthermore, this sequence relied on poorly available α-hydroxy acids.

In conclusion, a new three-component reaction of thiocarboxylic acids, methyl 3-(*N*,*N*-dimethylamino)-2-isocyanoacrylate, and aldehydes yielding substituted 2-acyloxymethyl thiazoles has been developed. This MCR is particularly noteworthy because it is highly convergent, is performed under mild conditions, and starts from acyclic precursors. Substituted 2-hydroxyacylmethyl thiazoles are important parts of many bioactive natural products. Continuing efforts in our



Scheme 1. Proposed reaction mechanism.

Table 2. Structures and yields of some 2-acyloxymethyl thiazoles prepared according to the one-pot procedure



Entry	R^1	R^2	Product	Yield (%)
1	Me	*p*-MeC_6H_4	**11**	12
2	Me	CH_2CH_2Ph	**12**	32
3	Me	CMe_3	**13**	29
4	Me	Cyclohexyl	**14**	31
5	Me	*n*-C_5H_{11}	**15**	28
6	Me	CH_2CHMe_2	**16**	31
7	Me	Cyclopropyl	**17**	35
8	Me	$C(Me_2)CH_2CH{=}CH_2$	**18**	15
9	CF_3	CH_2CHMe_2	**19**	11
10	Me	*p*-$MeOC_6H_4$	**20**	10
11	Me	*o*-BrC_6H_4	**21**	9
12	Ph	$CHMe_2$	**22**	19
13	Me	CH_2CH_2SMe	**23**	23

laboratory are directed towards improving yields and developing solid-phase variations of this reaction, exploring the synthetic utility of such reactive compounds and evaluating the biology of this class of compounds. Studies directed towards an asymmetric variation of the current MCR are in progress.[13]

Acknowledgements

We thank Robert Eckl for measurement of the NMR spectra.

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12. Representative procedure: Under a dry nitrogen atmosphere, a solution of 5 mmol of aldehyde in THF (1 M) was cooled to −78°C. 1 equiv. of $BF_3{\cdot}OEt_2$ was added by syringe and stirred for 5 min. Isocyanide and thiocarboxylic acid, 5 ml of a 1 M solution in THF, were added simultaneously over a period of 5 min. Upon the addition the solution turned deep red and was stirred for further 2 h at −78°C. The reaction was warmed to room temperature. The reaction was hydrolyzed with water (15 ml) then extracted with ethyl acetate (3×10 ml). The combined organics were washed with satd $NaHCO_3$ (3×10 ml), 5% citric acid (3×10 ml) and brine (1×10 ml), respectively. The organic phase was dried over $MgSO_4$, and the solvent was evaporated. The resulting oil was purified by chromatography on SiO_2 (ethyl acetate/petrol ether; 1/1) to give the product as an oil. Characterization of the compound 2-(1-acetoxy-2,2-dimethyl-pent-4-enyl)-thiazole-4-carboxylic acid methyl ester **18**: MW ($C_{14}H_{19}NO_4S$) = 297.37 g/mol; HPLC-MS spectra (Hewlett-Packard HP1100; YMC column, 2 mm×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 electron-spray ionization (ESI)): $t_{R,254\ nm} = 4.04$ min; $m/z = 320$ $[M+Na]^+$. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.98$ (s, 3H, $C(CH_3)_2$), 1.01 (s, 3H, $C(CH_3)_2$), 2.14–2.16 (m, 5H, CH_2 and $COCCH_3$), 3.92 (s, 3H, CH_3O), 5.01–5.08 (m, 2H, CH_2=CH), 5.75–5.86 (m, 1H, CH_2=CHC), 5.93 (s, 1H, CH), 8.14 (s, 1H, thiazole-H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 22.81$ and 22.94 ($(CH_3)_2$), 30.87 ($COCH_3$), 38.04 ($C_{quat.}$), 43.16 (CH_2), 52.38 (OCH_3), 78.69 (=CH), 118.34 (=CH_2), 127.49 (thiazole-CH), 133.67 ($C_{quat.}$), 146.53 ($C_{quat.}$), 161.75 ($C_{quat.}$), 169.15 (CO), 169.46 (CO).
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