ChemPubSoc Europe

DOI: 10.1002/chem.201403529

CHEMISTRY
A European Journal
Communication

Decarboxylative Acylation

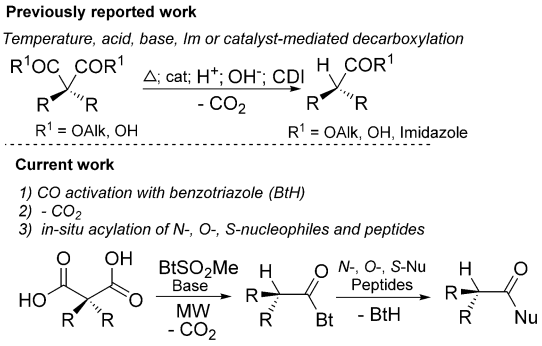
One-Pot Decarboxylative Acylation of N-, O-, S-Nucleophiles and Peptides with 2,2-Disubstituted Malonic Acids

Iryna O. Lebedyeva,*[a, b] Suvendu Biswas,[a] Kevin Goncalves,[a] Sean M. Sileno,[a] Ashton R. Jackson,[a] Kunal Patel,[a] Peter J. Steel,[c] and the late Prof. Dr. Alan R. Katritzky[a]

Abstract: Monocarbonyl activation of 2,2-disubstituted malonic acids with benzotriazole leads to decarboxylation of one of the carboxy groups and formation of a C–H bond. Intermediate carbonyl benzotriazoles then readily acylate nucleophilic reagents and peptides resulting in libraries of conjugates and peptidomimetics.

The process of decarboxylation has been widely used in Ag-,[1] Cu-,[2] and Pd-catalyzed[3] C–C bond formation,[4,5] Pd/Cu-catalyzed[6] cross couplings with aryl halides,[7,8] radical decarboxylative C–H arylation,[9] and protodecarboxylation.[10,11,5] Organocatalyzed decarboxylation of naturally occurring cinnamic acid leads to the flavor enhancement of decarboxylated products and is therefore of interest to the food chemistry community.[12] Decarboxylative C–C cross-couplings have found their uses in the synthesis of ketones,[13] biaryls,[7,14] (*E*)-1,2-diarylethenes,[3] heterocyclic 2,5-diarylsubstituted thiazoles and oxazoles,[15] 3*H*-pyrazolo[3,4-*c*]isoquinolines, thieno[3,2-*c*]isoquinolines,[16] and oxothiazolo- and oxazolo-C-C conjugates.[17] In such processes it is important to suppress parallel reactions and to minimize the formation of by-products during the metal-catalyzed decarboxylative C–C bond formations.[17] Decarboxylative C–H arylation provides a high yielding synthesis of C1–C4 substituted 9*H*-fluoren-9-ones,[9] whereas radical protodecarboxylation leads to the synthesis of substituted benzenes from benzoic acids.[10]

Decarboxylation of malonates[18] usually requires the presence of strong bases,[19,20] acids[18,21,22] or high temperatures (Scheme 1).[23,24] Enzymatic-[24,25–27] organometal-[28] or metal-catalyzed[21,20] carbon dioxide release also leads to protodecarboxylation or C–C bond formation in malonic acids. The use of carbonyldiimidazole (CDI) for the decarboxylative monocarbonylactivation of malonic acids has recently been reported.[29] The absence of literature on the effect of the leaving groups on decarboxylative acylation of malonic acids in the synthesis of chirally active peptidomimetics or *S*-nucleophilic conjugates led to the current study. In this work we have developed a feasible and straightforward three-step, one-pot synthesis of peptide conjugates and peptidomimetics based on monocarbonyl activation of malonic acids followed by loss of carbon dioxide and nucleophilic substitution with benzotriazole as a leaving group. This approach allows the synthesis of acylated chiral products under mild reaction conditions (Scheme 1, current work).



Scheme 1. Reported and novel reaction conditions that lead to decarboxylation of malonic acids.

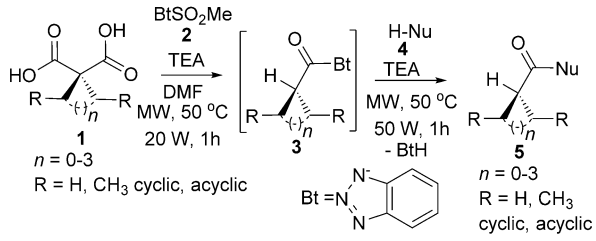
2,2-Disubstituted malonic acids **1** undergo mild decarboxylation as a result of monocarbonyl activation with benzotriazole to form intermediates **3** which then react with nucleophiles **4** to give conjugates **5**. In this work, the three-step reaction of malonic acids with nucleophilic reagents has been studied on amines **4** that provided products **5a–e** in 75–83% yields. As a result of the reaction of **1** with *O*- and *S*-nucleophiles, products **5f–k** have been isolated in 77–88% yields (Scheme 2 and Table 1). The three-step process proceeded without noticeable difficulties and gave the expected products **5a–k** in high yields within 2 h. After the microwave-mediated one-step CO-activation of **1** with 1-(methylsulfonyl)-1*H*-benzo[*d*][1,2,3]triazole **2** it also was possible to isolate decarboxylated intermediates **3a** (R=H, $n=0$, acyclic) and **3b** (R=H, $n=2$, cyclic) in yields of 89% and 92%, respectively. ^{1}H spectra for **3a,b** confirmed the formation of the intermediates **3** by the observation of two doublet and two triplet signals for the hydrogen atoms of the

[a] *Dr. I. O. Lebedyeva, Dr. S. Biswas, K. Goncalves, S. M. Sileno, A. R. Jackson, K. Patel, Prof. Dr. A. R. Katritzky*
Center for Heterocyclic Compounds, Department of Chemistry
University of Florida
Gainesville, FL 32611-7200 (USA)
Fax: (+1) 352-392-9199
E-mail: irynal@chem.ufl.edu

[b] *Dr. I. O. Lebedyeva*
Department of Chemistry and Physics, Georgia Regents University
1120 15th Street SCI W3005, Augusta, GA 30912 (USA)

[c] *Prof. Dr. P. J. Steel*
Department of Chemistry, University of Canterbury
Christchurch 8140 (New Zealand)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201403529.



Scheme 2. Decarboxylative acylation of *N*-, *O*-, *S*-nucleophiles with 2,2-disubstituted malonic acids.

Table 1. Products **5a–k**.

Cmpd	Nu **4**	R	*n*	Yield [%]
5a	NH-*n*Pr	CH_3	0 (acyclic)	75
5b	NH-C_6H_5	H	3 (cyclic)	84
5c	NH-Bn	H	0 (acyclic)	83
5d	NH-Bn	H	3 (cyclic)	78
5e	NH-2,5-$(CH_3)_2$-C_6H_3	H	0 (cyclic)	83
5f	O-C_6H_5	H	2 (cyclic)	86
5g	O-L-menthol	H	3 (cyclic)	81
5h	O-cholesterol	CH_3	0 (acyclic)	77
5i	S-C_6H_5	H	2 (cyclic)	88
5j	S-Boc-*N*-L-Cys	H	0 (cyclic)	83
5k	S-Cbz-*N*-L-Cys	H	2 (cyclic)	80

benzotriazole residue and a multiplet for the hydrogen of the newly formed C–H bond (see the Supporting Information). Two-step couplings were conducted following a general procedure using DMF as solvent at 50 °C for CO activation and 50 °C for the reaction with nucleophiles using a 1.5 excess of triethylamine (TEA) as base. Nucleophilic reagents were used in situ in 1.5 molar excess over the starting dicarboxylic acids **1** and microwave irradiation (50 W). The isolation of **5a–k** was achieved by extraction with ethyl acetate from saturated sodium carbonate solution and purification by column chromatography as required.

Introduction of benzotriazole as a monocarbonyl activating agent for 2,2-disubstituted malonic acids **1** and the subsequent reaction of **3** with amino acids, esters and peptides **6** takes place under mild reaction conditions with moderate heating and microwave irradiation (50 W, 50 °C).

The structure of product **7f** was confirmed by single-crystal X-ray crystallography (Figure 1). It crystallizes in the orthorhombic space group $P2_12_12_1$ with two molecules in the asymmetric unit that are hydrogen-bonded to one another.

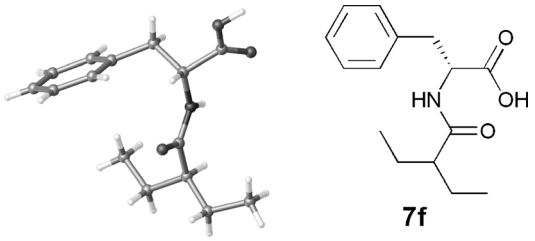
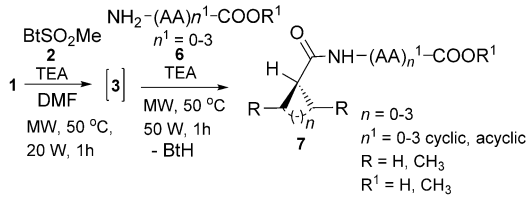


Figure 1. Structure of (2-ethylbutanoyl)-D-phenylalanine **7f**.

Reaction of 2,2-disubstituted malonic acids **1** with 1-(methylsulfonyl)-1*H*-benzo[*d*][1,2,3]triazole **2** using DMF as solvent and excess of TEA as base (50 °C, MW 50 W, 1 h) led to the formation of decarboxylated CO-activated intermediate **3**, which was then reacted in situ with amino acids, their esters, and di- and tripeptides. As such, a library of twelve peptidomimetics, **7a–l**, acylated at the *N*-terminus was synthesized in good to excellent yields (79–90%). Acylation of amino acids and peptides proceeded in situ in DMF using microwave irradiation (50 °C, 70 W, 1 h) (Scheme 3, Table 2). A double excess of amino acid



Scheme 3. Benzotriazolyl-activated decarboxylative acylation of peptides.

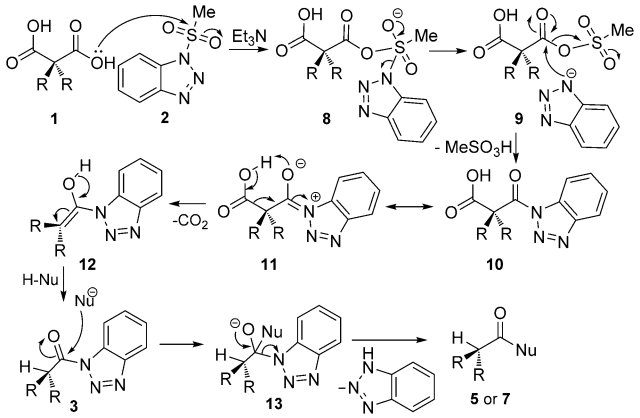
Table 2. Products **7a–l**.

Cmpd	AA	R	*n*	R^1	Yield [%]
7a	Gly	H	0 (acyclic)	OBn	80
7b	Gly	H	1 (cyclic)	OBn	86
7c	L-Leu	H	0 (cyclic)	H	79
7d	L-Val	CH_3	0 (acyclic)	H	85
7e	L-Phe	CH_3	0 (acyclic)	H	80
7f	D-Phe	CH_3	0 (acyclic)	H	84
7g	D,L-Phe	CH_3	0 (acyclic)	H	87
7h	L-Leu-L-Ala	H	1 (cyclic)	H	89
7i	L-Phe-L-Val	CH_3	0 (acyclic)	CH_3	90
7j	L-Ala-L-Leu	H	3 (cyclic)	H	88
7k	β-Ala-L-Cys-*S*-Ala-NH-Cbz	H	3 (cyclic)	H	82
7l	L-Phe-Gly-Gly	H	3 (cyclic)	H	90

was used to synthesize **7c–g** and a 1.5 molar excess of amino ester and peptide was used to synthesize acylated products **7a,b** and **7h–l**. Optical rotation for all the chiral products has been measured (see the Supporting Information). ^{1}H spectra of **7a–l** had an additional multiplet signal at approximately $\delta =$ 4.5 ppm for the proton of the newly formed C–H bond and the ^{13}C NMR spectra revealed a signal between $\delta = 28$–37 ppm.

Analysis of the mechanism of CO_2 loss during the synthesis of acylated nucleophiles and peptidomimetics suggests an eight-step process that begins with the carbonyl group activation of 2,2-disubstituted malonic acids **1** with benzotriazole. We tried several methods of CO-benzotriazolyl activation using thionyl chloride and DCC-mediated COOH/benzotriazole couplings and the highest yields for the final products **5** or **7** were identified when the reaction of malonic acids **1** with 1-(methylsulfonyl)-1*H*-benzo[*d*][1,2,3]triazole **2** was induced by base, heating to 50 °C, and microwave irradiation (Scheme 4).

Activation of **10** occurs through H-bonding between the carboxylic group and the amide carbonyl of the benzotriazolide promoting loss of CO_2 with no requirement for the use of



Scheme 4. Mechanism of: i) monocarbonyl-activation; ii) decarboxylation; iii) acylation for 2,2-disubstituted malonic acids.

strong bases[19,20] or acids.[18,21,22] Formation of the C–H bond of **3** stabilizes the molecule and allows convenient acylation of a broad spectrum of nucleophilic reagents and peptides. Additional HPLC/MS studies of the reaction mixture for **7a** revealed the molecular weight of **7a** (*m/z* $[M+H]^+$ 325.9) present in the mixture and the absence of dicarboxyl malono-intermediates or other products. Isolation of decarboxylated benzotriazole-active intermediates **3a**,**b** agrees with the suggested formation of **3** after CO_2 release from the unstable intermediate **10**. A parallel synthesis where isolated CO-activated intermediate **3a** reacted with benzylamine forming **5a** confirmed loss of CO_2 prior to reaction with nucleophiles.

2,2-Disubstituted malonic acid carbonyl group activation with benzotriazole induces decarboxylation. Malonic acids undergo three steps of mono-carbonyl activation, release of CO_2, and acylation with *N*-, *O*-, *S*-nucleophiles and peptides in one-pot. Retention of chirality in the products, reaction conditions, yields, and reaction mechanisms are reported. This mild decarboxylative acylation represents a convenient pathway for the synthesis of *N*-, *O*-, *S*-conjugates and peptidomimetics.

Experimental Section

All commercial materials were used without further purification. All solvents were reagent grade or HPLC grade. Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected. All microwave-assisted reactions were carried out with a single mode cavity Discover Microwave Synthesizer (CEM Corporation, NC). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, [D_6]DMSO, and CD_3OD using a 300 MHz spectrometer (with TMS as an internal standard). All ^{13}C NMR spectra were recorded with complete proton decoupling. Reaction progress was monitored by thin-layer chromatography (TLC) and visualized by UV light. Dichloromethane was dried and distilled over CaH_2, whereas tetrahydrofuran (THF) was used after distillation over Na-benzophenone.

General procedure for the synthesis of acylated *N*-, *O*-, *S*-nucleophiles 5, amino acids and peptides 7

1-(Methylsulfonyl)-1*H*-benzo[*d*][1,2,3]triazole (0.20 g, 1 mmol) was added to a solution of 2,2-disubstituted malonic acid (1 mmol) in DMF (3 mL) followed by addition of TEA (0.21 mL, 1.5 mmol), and the mixture was subjected to microwave irradiation (20 W, 50 °C) for 1 h. After cooling to room temperature the reaction mixture was treated with the appropriate nucleophile (1.5 mmol for *N*-, *O*-, *S*-nucleophiles and peptides and 2.0 mmol for amino acids) and the mixture was subjected to microwave irradiation for 1 h (50 W, 50 °C). After the reaction was complete, the mixture was added to 4N HCl solution (50 mL) and extracted with ethyl acetate (3× 30 mL). The organic layers were combined, washed with 4N HCl solution (2×50 mL), then dried over $MgSO_4$ to give acylated products **5** and **7**.

Acknowledgements

The authors thank the University of Florida for financial support.

Keywords: acylation · cleavage reactions · conjugates · decarboxylation · peptides

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Received: May 14, 2014
Published online on July 25, 2014