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Self-condensation of activated malonic acid half esters: a model for the decarboxylative Claisen condensation in polyketide biosynthesis

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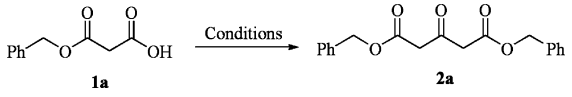
Abstract—The reaction of a malonic acid half oxyester with a *N*-hydroxysuccinimidyl ester-forming reagent resulted in self-condensation to provide the corresponding 1,3-acetonedicarboxylic acid diester. This new method does not require a divalent metal chelator or a coordinating solvent for successful condensation.

The decarboxylative Claisen-type condensation is a fundamental carbon–carbon bond forming reaction for building fatty acids and polyketides in nature.[1] Both catechol and glycouril have been shown to provide good intramolecular frameworks for the biomimetic Claisen condensation.[2,3] Intermolecular condensation of a thiomalonate and a thioester has also successfully been demonstrated, not only for the emulation of the biological process, but also as a practical procedure for building β-ketoesters.[4,5] In these procedures both magnesium cation and imidazole were essential for the efficient intermolecular condensation in coordinating organic solvents such as THF and dioxane.[4] Moreover, fine tuning of the reactivities of carbanion, thiolate leaving group and basic catalyst led to self-condensation of malonic acid half thioesters in a model system for polyketide synthesis.[6] We now report new conditions for self-condensation of malonic acid half oxyesters (MAHOs) via their *N*-hydroxysuccinimidyl (NHS) ester intermediates. The system does not require metal cation, imidazole catalyst or coordinating solvent for successful condensation.

In a search for a good malonylation condition in aqueous solution, we attempted to make NHS esters of MAHOs because such esters had been shown to be

Table 1. Self-condensation of monobenzyl malonate promoted by various NHS ester-forming reagents



1a **2a**

Entry	Conditions	Reaction time	Isolated yield (%)[a]
1	1.2 equiv. NHS, 1.2 equiv. DCC, DMAP, CH_2Cl_2	4 h	78
2	1.2 equiv. DSPP, Et_3N, CH_2Cl_2	3 h	79
3	0.5 equiv. TSTU, DPEA, DMF	30 min	39
4	1.2 equiv. TSTU, DPEA, DMF	10 min	82
5	1.2 equiv. TSTU, DPEA, 80% aqueous DMF	8 h	27
6	1.2 equiv. TSTU, DPEA, 10% aqueous DMF	>24 h	ND[b]
7	1.2 equiv. sulfo-NHS, 1.2 equiv. EDCI, aqueous $NaHCO_3$ solution	>24 h	ND[b]

[a] A mixture of *keto* and *enol* tautomers.
[b] Not detected.

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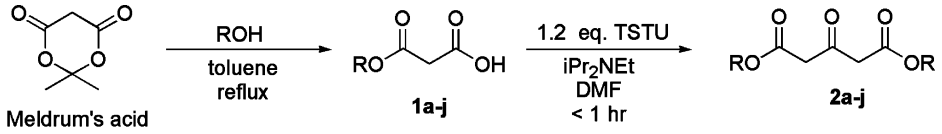
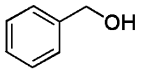
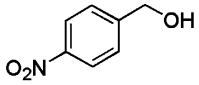
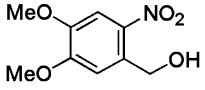
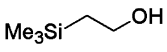
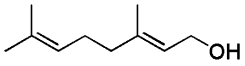
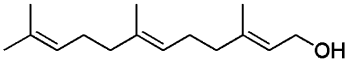
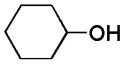
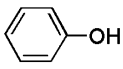
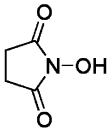
excellent activating groups for peptide formation and crosslinking reactions in water.[7] Initially, the carbodiimide coupling condition was applied to monobenzyl malonate (**1a**). Reaction of **1a** with NHS in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 did not provide any isolable NHS ester of **1a**. Instead, the symmetrical 1,3-acetonedicarboxylic acid dibenzylester (**2a**) was obtained in 78% yield (Table 1, entry 1). A similar result was afforded by the reaction of **1a** with *N*-succinimidyl diphenylphosphate (SDPP) and triethylamine in CH_2Cl_2 (entry 2).[8] Use of a slight excess of *O*-(*N*-succinimidyl)-*N*,*N*,*N*′,*N*′-tetramethyluroniumtetrafluoroborate (TSTU) with *N*,*N*-diisopropylethylamine (DPEA) in DMF also provided **2a** in 82% yield (entry 4).[9] Nevertheless, reduction of the reagent TSTU to a half equivalent resulted in a decrease in the isolated yield to 39% (entry 3). Surprisingly, a slight amount of water in an organic solvent did not totally inhibit the condensation. The reaction of **1a** with TSTU and DPEA in 80% aqueous DMF provided **2a** in spite of a dramatic decrease in yield (27%) and a longer reaction

Table 2. Preparation of various MAHOs and their self-condensation



Entry	ROH	Substrate	Isolated yield of substrate (%)	Product	Isolated yield of product(%)[b]
1		**1a**	CA[a]	**2a**	82
2		**1b**	CA[a]	**2b**	78
3		**1c**	99	**2c**	84
4		**1d**	98	**2d**	84
5		**1e**	91	**2e**	91
6		**1f**	85	**2f**	79
7		**1g**	96	**2g**	90
8		**1h**	CA[a]	**2h**	96
9		**1i**	95	**2i**	82[c]
10		**1j**	54	**2j**	0[d]

[a] Commercially available. [b] A mixture of *keto* and *enol* tautomers with a typical ratio of 4.5:1 on the basis of ^{1}H-NMR. [c] Not very stable and slowly decomposed after isolation. [d] Decarboxylation product was isolated as a major product.

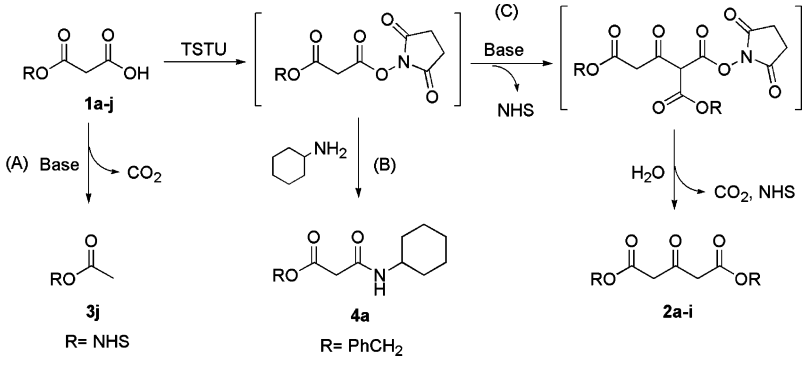
time (entry 5). However, no condensation was observed in 10% aqueous DMF (entry 6). Likewise, the reaction of **1a** with sulfo-NHS and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) in aqueous sodium bicarbonate solution did not produce any condensation product (entry 7).

The results with self-condensation of **1a** led us to investigate the generality of the newly discovered conditions. Thus, several other MAHOs were synthesized and the new conditions applied to them. All the MAHOs, except the commercially available **1a**, **1b** and **1h**, were prepared by reaction of Meldrum's acid with the corresponding alcohols in refluxing toluene.[10,11] For the actual condensation, the use of TSTU in the presence of DPEA in DMF was examined for a series of MAHOs since no large difference was indicated between the several conditions described above. In fact, the new conditions were well suited for a wide range of MAHOs and the corresponding self-condensation products were obtained in moderate to excellent yield as summarized in Table 2.[12,13] First of all, malonic acid 4-nitrobenzyl half ester **1b** was converted to its condensation product **2b** in 78% yield. The self-condensation of malonic acid 6-nitroveratryl half ester (**1c**) provided 1,3-acetonedicarboxylic acid di(6-nitroveratryl)ester **2c** in 84% yield.[14] A good yield of compound **2d** was also obtained by the condensation of malonic acid 2-(trimethylsilyl)ethyl half ester **1d**. Both malonic acid geranyl half ester **1e** and malonic acid farnesyl half ester **1f** were also good substrates for the NHS ester-mediated condensation. Thus, the digeranyl ester (**2e**) and the difarnesyl ester (**2f**) of 1,3-acetonedicarboxylic acid were obtained in 91 and 79% yields, respectively.[15,16] These two C-10 and C-15 isoprenyl systems were introduced for their potential to assist the condensation by self-assembly in aqueous medium.[17] However, many attempts to convert these MAHOs to their corresponding self-condensation products in water were not successful. MAHOs derived from secondary, tertiary and phenolic alcohols were also successfully converted to their corresponding products. Dicyclohexyl ester (**2g**), di(*tert*-butyl) ester (**2h**) and diphenyl ester (**2i**) of 1,3-acetonedicarboxylic acid were produced from their corresponding MAHOs, all in high yield. Malonic acid *N*-hydroxylsuccinimidyl half ester **1j**, which in principle could have led to more extended structures by sequential condensation, however, did not provide any condensation product either in the presence or absence of TSTU. Instead, decarboxylation predominated for this activated ester **1j**, acetyl NHS ester **3j** being obtained as a major product (Path A, Scheme 1).

Although the NHS ester intermediates of MAHOs were never directly isolated in our experiments, the intermediacy of the NHS ester was proven by chemical trapping with a primary amine. Apparently, the cyclohexylamide **4a** was obtained by the reaction of **1a** with TSTU in the presence of cyclohexylamine instead of a tertiary amine such as DPEA (Path B). Therefore, the bimolecular condensation between the NHS ester intermediate generated in situ from each MAHO and the intact MAHO itself was initially considered the mechanism of the newly discovered conditions. However, we subsequently realized that the amount of any NHS ester-forming reagent used for the condensation was generally proportional to the yield of the product, more than one equivalent of the reagent being required for complete conversion in several instances. Thus, we tentatively conclude that NHS ester intermediate undergo a Claisen condensation with each other to form another reactive intermediate, which in turn is decarboxylated either during reaction or work-up to generate the final product (Path C).[18,19] However, the presence of any intermediate other than the NHS ester intermediate, as well as the mechanism of decarboxylation remains to be defined.

Interestingly, unlike most previous biomimetic model systems the new conditions do not require magnesium ion for efficient condensation. It has been suggested that divalent metal chelation may reorient the malonate to its more acidic cyclic structure, which in turn can be easily deprotonated by relatively mild bases such as imidazole or benzimidazoles.[4] In our cases the enhanced acidity was probably achieved by forming a NHS ester which may be readily deprotonated to generate a nucleophilic carbanion intermediate. However, the predominant decarboxylation of **1j** rather than nucleophilic condensation indicates that a subtle balance of the enhanced acidity and nucleophilicity is crucial for successful condensation.[6]

In summary, we have discovered that a NHS ester-forming reagent can mediate the self-condensation of



Scheme 1. A suggested mechanism for the self-condensation of MAHOs.

MAHO to produce the corresponding 1,3-acetonedicarboxylic acid diester. No divalent metal chelator is required and a tertiary amine is sufficient for successful condensation.

Acknowledgements

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11. 2,2-Dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) was heated with an equivalent of an alcohol in refluxing toluene for 4 h. Upon cooling **1c** was precipitated and collected by filtration. Other MAHOs were simply purified by subsequent extraction with saturated aqueous sodium bicarbonate followed by 1N-HCl solution. The structure of each MAHO prepared was confirmed by ^{1}H, ^{13}C NMR spectroscopy and ESI-MS spectrometry. For the new compound **1f**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (br, 1H, COO*H*), 5.35 (t, $J=7.2$ Hz, 1H, vinyl), 5.08 (m, 2H, vinyl), 4.69 (d, $J=7.2$ Hz, 2H, CH_2O), 3.43 (s, 2H, malonyl CH_2), 2.13–1.96 (m, 8H, 4 CH_2), 1.72, 1.68 (2s, 3H each, 2 CH_3), and 1.60 (s, 6H, 2 CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2 (*C*OOH), 167.3 (*C*OO), 143.7, 135.7, 131.5 (3 quaternary vinylic *C*), 124.5, 123.7, 117.5 (3 vinylic *C*H), 63.0 (*C*H$_2$O), 40.9, 39.9, 39.7 (2 *C*H$_2$ and malonyl *C*H$_2$), 26.9, 26.3 (2 *C*H$_2$), 25.9, 17.9, 16.7 and 16.2 (4 *C*H3); HRMS (ESI) calculated for $C_{18}H_{27}O_4^-$ (M–H)$^-$: 307.1915; found: 307.1904.
12. The general procedure for self-condensation of MAHO is as follows: a solution of a MAHO (1 mmol), TSTU (1.2 mmol) and DPEA (3 mmol) in DMF (2 mL) was stirred for 30 min and evaporated in vacuo. The residue was dissolved in chloroform and washed with 1N-HCl solution, dried over $MgSO_4$ and evaporated in vacuo to provide a crude mixture.The pure product was obtained by a silica gel column chromatography.
13. 1,3-Acetonedicarboxylic acid diesters have been extensively used as building blocks for more extended carbocyclic structures such as polyquinenes and steroid skeletons by the Weiss reaction or other condensation reactions. For examples, see: (a) Gupta, A. K.; Fu, X.; Snyder, J. P.; Cook, J. M. *Tetrahedron* **1991**, *23*, 3665; (b) Danishefsky, S.; Crawley, L. S.; Solomon, D. M.; Heggs, P. *J. Am. Chem. Soc.* **1971**, *93*, 2356
14. Data for compound **2c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H, Ph), 7.03 (s, 1H, Ph), 5.56 (s, 2H, benzylic *C*H$_2$), 3.98, 3.94 (2s, 3H each, 2 O*C*H$_3$) and 3.76 (s, 2H, *C*H$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.5 (*C*O), 166.12 (*C*OO), 153.9, 148.6, 139.9, 126.4, 110.6, 108.3 (6 Ph), 64.5 (benzylic *C*H$_2$), 56.8, 55.6 (2 O*C*H$_3$), and 49.2 (*C*H$_2$).
15. Data for compound **2e**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.33 (t, $J=6.9$ Hz, 1H, vinylic), 5.07 (t, $J=6.4$ Hz, 1H, vinylic), 4.65 (d, $J=6.9$ Hz, 2H, C*H*$_2$O), 3.60 (s, 2H, C*H*$_2$CO$_2$), 2.10–2.02 (m, 4H, C*H*$_2$), 1.70, 1.67, and 1.59 (3s, 3H each, 3 CH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6 (*C*O), 166.9 (*C*OO), 143.4, 132.0 (2 quaternary vinylic), 123.8, 117.7 (2 vinylic *C*H), 62.5 (*C*H$_2$O), 49.1 (*C*H$_2$CO), 39.7, 26.4 (2 *C*H$_2$), 25.8, 17.8, and 16.6 (3 *C*H$_3$); HRMS (ESI) calculated for $C_{25}H_{37}O_5^-$ (M–H)$^-$: 417.2646; found: 417.2620.
16. Data for compound **2f**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (t, $J=7.0$ Hz, 1H, terminal vinylic), 5.02 (m, 2H, 2 internal vinylic), 4.59 (t, $J=7.0$ Hz, 2H, C*H*$_2$O), 3.53 (s, 2H, C*H*$_2$CO$_2$), 2.04–1.88 (m, 8H, C*H*$_2$), 1.63, 1.60 (2s, 3H each, 2 C*H*$_3$), 1.52 (s, 6H, 2 C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.7 (*C*O), 167.0 (*C*OO), 143.5, 135.7, 131.5 (3 quaternary vinylic *C*), 124.5, 123.8, 117.7 (3 vinylic *C*H), 62.6 (*C*H$_2$O), 49.1 (*C*H$_2$CO), 39.9, 39.7, 26.9, 26.4 (4 *C*H$_2$), 25.9, 17.9, 16.7 and 16.2 (4 *C*H$_3$); HRMS (ESI) calculated for $C_{35}H_{53}O_5^-$ (M–H)$^-$: 553.3898; found: 553.3831.
17. For reviews of reactions in aqueous amphiphilic self-assembling systems, see: (a) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751; (b) Engberts, J. B. F. N.; Blandamer, M. J. *Chem. Commun.* **2001**, 1701–1708.
18. It is likely that the final product was already formed during the reaction rather than work-up according to a time course study by silica gel thin layer chromatographic analysis.
19. As we could expect from the suggested mechanism, a cross-condensation between two different MAHOs yielded one cross-condensation product and two self-condensation products in almost equal distribution. For instance, a reaction of **1a** and **1h** with TSTU and DPEA in DMF provided 1,3-acetonedicarboxylic acid benzyl *tert*-butyl ester in 34% yield along with **2a** and **2h** in 25 and 26% yield, respectively. A slightly higher yield of the cross-condensation product is probably due to a slight difference in reactivities of two NHS intermediates generated from their corresponding MAHOs.