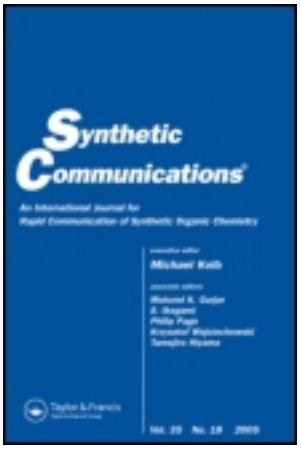

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TMSCL AS A RATE-ACCELERATING ADDITIVE IN ACYLATIONS OF AMINES WITH 5-(α-AMINO-α′-HYDROXY)METHYLENE MELDRUM ACIDS

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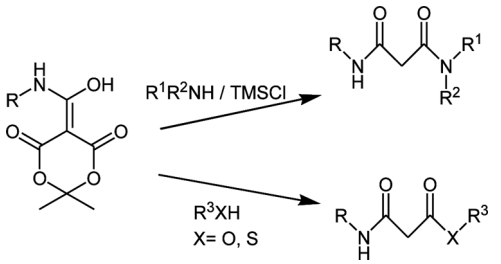
GRAPHICAL ABSTRACT



Abstract *Aspects are presented of the acylation of amines, alcohols, and thiols with 5-(α-amino-α′-hydroxy)methylene Meldrum acids. We placed special emphasis on the acylation reaction of secondary amines with 5-(α-amino-α′-hydroxy)methylene Meldrum acids, which, because of their basicity, caused problems concerning salt formation with a Meldrum acid derivative. We found that secondary amines, which react at the slowest rate and give a poor yield with 5-(α-amino-α′-hydroxy)methylene Meldrum's acid, react quickly and with high yields with the same reagent in the presence 1 to 3 equivalents of TMSCl. Acylation with this derivative of Meldrum acid was optimized for such factors as reaction temperature, solvent polarity, and acidity of the environment. We have prepared a wide range of nonsymmetrical malononic acid diamids, esters, and thioesters of malonamic acid.*

Keywords Acylation; amides; decarboxylation; enols; ketens

INTRODUCTION

Derivatives of malonic acid find broad scope of application in various fields. Among other malonic acid diamids, the structural fragment might be find in retro-inverso-modified pseudopeptides,[1] small molecules of gene regulation,[2] low molecular organogelators,[3] or neuromediator prodrugs[4] and macrocyclic

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compounds,[5] whereas esters of malonamic acid have anti-inflammatory and analgesic effects,[6] anti-ischemic properties,[7] and even ligands for thyroid receptors.[8]

Whereas synthesis of symmetrical malonic acid derivatives is a trivial laboratory procedure[9] synthesis of nonsymmetrical malonamids or esters of malonamic acid require several steps to obtain the final product. The selective classical procedure[10] for preparation of nonsymmetrical malondiamids starting from diethyl malonate require half-hydrolysis, activation of the free carboxyl group, coupling with amine, hydrolysis of ester, another activation, and coupling with a second amine. Even using commercially available alkyl malonyl chloride, it still takes at least four steps to prepare a simple compound. Of course, such a synthetic problem with malonic acid is related to the impossibility of using anhydride in this case.

In the chemical literature over the past few years, several methods have been described that bypass this long procedure. Lopez-Avendano et al.[11] proposed the synthesis of malonamic derivatives based on the reaction of a β-amidothioester with various nucleophiles. They obtain good results, and the β-amidothioester could be prepared quickly as a single-step reaction from isocyanates and commercially available *tert*-butyl acetothiocetate; however, the problem is the cost of *tert*-butyl acetothiocetate.

Another selective procedure[12,13] is based on the use of Meldrum acid as an equivalent of malonic anhydride for the rapid preparation of malonamic acid derivatives, coupled in the next step with another amine under typical conditions. However, while this procedure works well with amino acid esters, with other amines the reaction time is as long as 50 to 70 h,[13] and in some cases it fails to work. We were not able to obtain N,N-dietylmalonamic acid by this procedure.

Apart from these methods, sometimes unselective coupling of malonic acid with amine or amino acid is used, followed by separation of malonamic acid derivative from unreacted malonic acid and diamid.[14]

5-(α-Amino-α′-hydroxy)methylene Meldrum acid, similar to classical acyl-Meldrum[15] acids, are able to generate ketenes upon thermal decomposition. This property underlies the method developed by Lee et al.[16] in which 5-(α-amino-α′-hydroxy)methylene Meldrum acid reacts in boiling solvent with amine in a one-step process, giving the desired unsymmetrical malonamid.

RESULTS AND DISCUSSION

In our laboratory, we needed unsymmetrical malonoamides of secondary amines. Taking into consideration of all the known methods, we decided to adopt the method of Lee et al.[16] as the most promising. However, when we tried to prepare N-phenyl-3-oxo-3-piperidin-1-yl-propionamide (**3aa**) in the reaction of 5-(α-phenylamino-α′-hydroxy)methylene Meldrum acid (**1a**) with piperidine (**2a**) in boling ethylbenzene, we obtained the desired amide with only 34% yield after 20 h of reaction (entry 1, Table 1). Similarly, reaction of **1a** with diethyl amine (**2b**) gave amide (**3ab**) with poor yield (entry 4, Table 1). We repeated these reaction scrupulously again to eliminate any possible experimental errors; however, we still obtained these amides with poor yields. To check if we committed an unknown error, we decided to perform experiments on models very close to these presented by Lee et al. We carried out four of experiments in which **1a** was heated in boiling ethylbenzene respectively

Table 1. Acylation of amines with 5-(α-amino-α′-hydroxy)methylene Meldrum acid (**1**)

Entry	Malonamide **3**	TMSCl eq	Solvent	Time (h)	Yield of **3** (%)
1	**3aa**	0	E	20	34
2[b]	**3aa**	0	E	2	26
3[c]	**3aa**	0	E	1,5	42
4	**3ab**	0	E	1	50
5[c]	**3ab**	0	E	1	43
6	**3ac**	0	E	1	80
7	**3ad**	0	E	1	80
8	**3ae**	0	D	23	70
9	**3ae**	0	C	23	75
10	**3ae**	0	E	1	74
11	**3af**	0	E	1	77
12	**3ag**	0	E	2,5	78
13	**3aa**	1	E	1,5	82
14	**3aa**	3	E	1	85
15	**3aa**	1,5	A	2,5	96
16	**3aa**	1,5	D	2,5	90
17	**3aa**	0	A	2,5	n.r
18	**3aa**	0	B	2,5	n.r
19[d]	**3aa**	0	B	2,5	n.r
20	**3ab**	1,5	B	3	93
21	**3ac**	1,5	B	4	90
22	**3ae**	8	B	3	34
23	**3ae**	3	B	7	73
24	**3af**	3	B	2	86
25	**3ag**	3	B	21	68
26	**3bc**	0	E	1	91
27	**3be**	0	E	1,5	75
28	**3bg**	0	E	1	71
29	**3bc**	1,5	B	24	85
30	**3be**	3	D	23	70
31	**3bg**	3	D	5	75

[a]Equimolar amount of reagent.
[b]2,5 eq of TFA was added.
[c]Reaction mixture was saturated with HCl.
[d]Excess of **1a** was used.
Solvents A = DCM; B = benzene; C = dioxane, D = toluene, E = ethylbenzene.

with 4-methylaniline, benzyl amine, *tert*-butylamine, and isobutylamine. Surprisingly, in these experiments we obtain amides **3ad**, **3ae**, **3af**, and **3ag** with good yields (entries 7, 10, 11, and 12, Table 1). We paid more attention to the reaction of benzyl amine with **1a** because Lee et al. reported that 4-metylbenzyl amine was required for the reaction with 5-(α-amino-α′-hydroxy)methylene Meldrum acid and harsh conditions (refluxing for an hour in boiling o-dichlorobenzene); otherwise they observed only formation of salt of amine with **1**.

When we reacted 2 eq of benzyl amine with 1 eq of **1a** in toluene, the prolonged time of reaction was required and also we observed formation of undissolved salt, which we suspected was a cause of the slow reaction (entry 8, Table 1). Therefore, the next experiment we performed in boiling dioxane; however, the better ability of dioxane to dissolve this salt did not affect the reaction time (entry 9, Table 1).

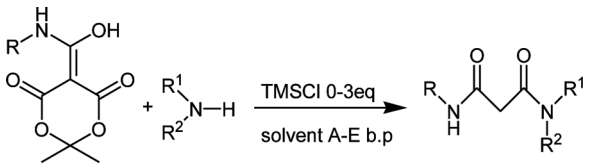
As one can see, there is a rather obvious correlation between the basicity of amines and the yield of malonamides (entries 1, 4 versus 7, 10, 11, 12, Table 1). On the other hand, in experiments performed by Lee et al. the yields were high and the reaction times short, but only weakly basic aromatic amines with electron withdrawing group (EWG) were used. When we attempted to use stronger bases as secondary aliphatic amines, the equilibrium in the formation of salt with **1a** shifted in favor of salt product, resulting in much lower yield of nonsymetrical malonamids and very long reaction time. This result should not be surprising, and taking into account the work of Xu et al.[15a] a correlation between concentration of free acid form of Meldrum derivative and rate of decomposition has been demonstrated.

We tried to improve the yield of reactions of secondary amines with **1a** by creating a more acidic condition for the reaction in accordance with the observations described by Xu et al.[15a] for acyl Meldrum acids.

The addition of 2.5 eq of trifluoroacetic acid (TFA) to the reaction mixture prepared from 1 eq **1a** and 2 eq of piperidine (**2e**) in ethylbenzene accelerated the rate of decomposition of **1a**, although the yield of amide (**3aa**) remained unacceptable (entry 2, Table 1). The application of gaseous HCl to the reaction of piperidine with **1a** or to the reaction of diethylamine with **1a** resulted in a yield that was still comparable to the reaction without any additives (entries 3 and 5, Table 1).

Finally, we checked whether the addition of TMSCl influenced the reaction time or yields, because TMSCl may be at least a convenient source of HCl (Scheme 1). Surprisingly, we obtained significantly better yields when reaction of piperidine with **1a** in boiling ethylbenzene was in the presence of 1 or 3 eq of TMSCl (entries 13 and 14, Table 1). As the next step, we repeated this reaction in lower boiling solvents: toluene and DCM in the presence of 1.5 eq of TMSCl and gave almost quantative yield within 2.5 h. It should be noted that for reaction in DCM the temperature was almost 60 °C lower than for the reaction without TMSCl (entries 15 and 16, Table 1).

Similarly, the reactions of diethylamine and morpholine with **1a** were strongly accelerated in the presence of TMSCl (entries 20 and 21, Table 1). Reactions of



1 a-b **2 a-g** **3 aa-bg**

1	R
a	Ph
b	cyclo-Hex

2	R^1	R^2
a	$-(CH_2)_5-$	
b	Et	Et
c	$-(CH_2)_2-O-(CH_2)_2-$	
d	4-MePh	H
e	Bzl	H
f	tBu	H
g	isoBu	H

Scheme 1. Acylation of amines with 5-(α-amino-α′-hydroxy)methylene Meldrum acid (**1**).

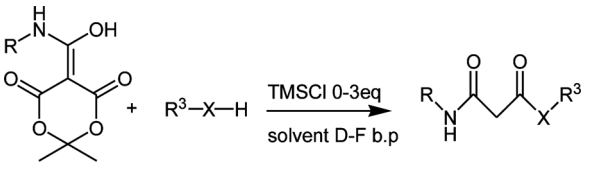
primary amines with **1a** were also accelerated; however, the use of only 1.5 eq of TMSCl gave a reaction of insufficient acceleration, so 3 eq of TMSCl and longer reaction times are required than for secondary amines. When the larger amounts of TMSCl were used, the yield dropped (entries 22–25, Table 1).

To confirm our assumption about the accelerating influence of TMSCl, we carried out two experiments in which **1a** was heated with 2 eq of piperidine in low-boiling solvents, DCM or benzene without TMSCl, and in neither reactions did we observe the formation of malonamide in the specified time (entries 17 and 18, Table 1). We also checked to see whether the use of excess of **1a** to ensure an acidic condition could improve the yield of this reaction, but when we used 1.2 eq of **1a** per 1 eq of piperidine after 2.5 h in boiling benzene, no reaction was observed (entry 19, Table 1).

The influence of TMSCl was less significant when **1b** was used, and for the reactions of **1b** with benzyl amine or with morpholine we did not observe any acceleration of the reaction by TMSCl (entries 29 and 30, Table 1).

Generally, it can be stated that TMSCl significantly accelerates the reaction when a more acidic Meldrum derivative (**1a**) and a more basic secondary amine were used. At this time, we cannot explain the mechanism of reaction in which TMSCl participates with any certainty, but the influence of liberated HCl as a reason for the acceleration could be excluded if saturation with HCl does not change the yield (entries 3 and 5, Table 1).

In subsequent studies, we checked whether **1** can acylate alcohols and thiols (Scheme 2). In the first experiment, we use boiling ethylbenzene to heat **1a** with 2 eq of benzyl alcohol for 3.5 h, obtaining N-phenyl malonamic acid benzyl ester with only 50% yield and N,N′-diphenyl malonamid with 50% yield. The formation of N,N′-diphenyl malonamid was also observed when **1a** was heated alone in ethylbenzene. It appears that, in this case, to ensure a clean reaction it is necessary to use a large excess of alcohol. Use of 20-fold excess of ethyl or allyl alcohol gave malonamic acid esters with good to excellent yields. More importantly, weakly nucleophilic *tert*-butyl alcohol gave malonamic acid *tert*-butyl esters with good yields (entries 3 and 6, Table 2). In a similar way, we examined the reaction of 2 eq of thiols with **1a** and obtained malonamic acid thioesters (entries 7 and 8, Table 2).



1 a-c **4 a-g** **5 aa-cc**

1	R
a	Ph
b	cyclo-Hex
c	Et

4	R^3	X
a	Et	O
b	allyl	O
c	tBu	O
d	Ph	S
e	4-MePh	S

Scheme 2. Acylation of alcohols and thiols with 5-(α-amino-α′-hydroxy)methylene Meldrum acid (**1**).

Table 2. Acylation of alcohols and thiols with 5-(α-amino-α′-hydroxy)methylene Meldrum acid (**1**)

Entry	Malonamic ester **5**	TMSCl (eq)	Solvent	Time (h)	Yield of **5** (%)
1	5aa	0	E	20	81
2	5ab	0	E	2,5	82
3	5ac	0	E	24	68
4	5ba	0	E	24	96
5	5bb	0	E	4	90
6	5cc	0	E	24	94
7	5ad	0	E	2	31
8	5ae	0	D	2,5	45
9	5ae	0	F	4	63
10	5aa	2	E	23	79
11	5ac	2	E	23	63

Note. Solvents D, toluene; E, ethylbenzene; F, acetonitrile.

In the case of ethyl and *tert*-butyl alcohols, the boiling point of a mixture of solvents was approximately 80 °C, which extends the reaction time (entries 1, 3, 4, and 6, Table 2). Based on our experience in reactions between amines and **1**, we checked whether the addition of TMSCl accelerates the process. However, two experiments with the addition of 2 eq of TMSCl (entries 10 and 11, Table 2) showed that reaction of alcohols with **1a** is not accelerated by TMSCl.

CONCLUSION

A method of preparing malonamids was developed to circumvent the problem of the formation of unreactive salt between secondary amines and Meldrum acid derivative (**1a**). The addition of TMSCl allows the process to produce yields in significantly milder condition than was possible before.[16] In addition, we have expanded the scope of use of 5-(α-amino-α′-hydroxy)methylene Meldrum acid to include preparation of malonamic acid esters and thioesters.

EXPERIMENTAL

Reagents were purchased from Sigma-Aldrich. Benzene, toluene, ethylbenzene, and dioxane was distilled from potassium under argon. Dichloromethane (DCM) was distilled from P_2O_5. Acetonitrile was distilled from CaH_2 under argon. Analytical thin-layer chromatography (TLC) was performed on aluminum sheets of silica gel UV-254 Merck. Flash chromatography was carried out using silica gel (40–63 microns) Zeochem. ^1H and ^{13}C NMR were recorded on Varian Gemini 200 and Varian Unity Plus 500 instruments.

5-(α-Phenylamino-α′-hydroxy)methylene Meldrum Acid (1a)

Compound **1a** was prepared according to literature procedure[17] and crystallized twice from AcOEt. Yield 89%, mp 105–107 °C (lit.[17] mp 109–110 °C). Spectral data are in agreement with literature data.

5-(α-Cyclohexylamino-α′-hydroxy)methylene Meldrum Acid (1b)

Et_3N (1.4 ml, 10 mmol) was added to a solution of Meldrum's acid (0.72 g, 5 mmol) in dry DMF (5 ml) in a glass ampoule. Cyclohexylisocyanate (0.751 g, 6 mmol) was added, and the ampoule was sealed. The ampoule was placed in the bath for 20 h at 40 °C. The solution was poured into a 2 M HCl (30 ml) mixture of ice and water. The solid precipitate was filtered and washed with cold water. The precipitate was dissolved in ethyl acetate (30 ml) and dried with $MgSO_4$, and after cooling the solution the precipitate of DCU was removed by filtration. The solvent was removed under reduced pressure. Crystallization from AcOEt/hexane gave 0.795 g (60% yield), mp 103–104.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (m, 1H), 1.40 (m, 4H), 1.64 (m, 1H), 1.73 (m, 6H), 1.78 (m, 2H), 1.98 (m, 2H), 3.81 (m, 1H), 9.22 (s, 1H), 14.91 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.59, 25.42, 26.51, 32.73, 50.09, 73.02, 104.77, 164.60, 169.42, 170.65. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{13}H_{19}NO_5$: 269.1262; found: 269.1266.

5-(α-Ethylamino-α′-hydroxy)methylene Meldrum Acid (1c)

Et_3N (1.4 ml, 10 mmol) was added to a solution of Meldrum's acid (0.72 g, 5 mmol) in dry DMF (5 ml) in a glass ampoule. Ethylisocyanate (0.426 g, 6 mmol) was added, and the ampoule was sealed. The ampoule was placed in the bath for 10 h at 40 °C. The solution was poured into a 2 M HCl (30 ml) mixture of ice and water. The solid precipitate was filtered and washed with cold water. The precipitate was dissolved in ethyl acetate (30 ml) and dried with $MgSO_4$. The solvent was removed under reduced pressure. Crystallization from AcOEt/hexane gave 0.706 g (65% yield), mp 72–74 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (t, 3H, $J = 7.3$ Hz), 1.74 (s, 6H), 3.49 (m, 2H), 9.25 (brs, 1H), 14.98 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.7, 26.4, 35.8, 104.2, 164.1. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_9H_{13}NO_5$: 215.0794; found: 215.0792.

General Procedure for Acylation of Amines with 1

A solution of **1** (2 mmol), the corresponding amine (**2**) (4 mmol), and trimethylchlorosilane (0–8 eq) in anhydrous solvent (10 ml) was stirred under reflux. Amounts of TMSCl, solvent, and reaction time are specified in Table 1. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified.

N-Phenyl-3-oxo-3-piperidin-1-yl-propionamide (3aa)

Purification by flash column chromatography (AcOEt/hex, 5:2), mp 115–117 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.61–1.70 (m, 6 H, CH_2), 3.49 (s, 2H, CH_2), 3.52–3.65 (m, 4H, CH_2), 7.12 (t, $J = 7.32$ Hz, $1H_{arom}$), 7.34 (t, $J = 7.81$ Hz, $2H_{arom}$), 7.60 (d, $J = 7.81$ Hz, $2H_{arom}$), 10.18 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.5, 25.8, 26.7, 40.1, 43.6, 47.5, 120.3, 124.5, 129.2, 138.1, 164.6, 167.0. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{14}H_{18}N_2O_2$: 246.1368; found: 246.1381.

N,N-Diethyl-N′-phenyl-malonamide (3ab)

Purification by flash column chromatography (AcOEt/hex, 3:2), oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05–1.11 (m, 6H, CH_3), 3.25–3.34 (m, 4H, CH_2), 3.39 (s, 2H, CH_2), 6.97–7.0 (m, $1H_{arom}$), 7.18–7.21 (m, $2H_{arom}$), 7.50 (d, $J = 7.8$ Hz, $2H_{arom}$), 10.25 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.8, 14.1, 39.9, 40.9, 42.6, 119.8, 124.0, 128.7, 137.7, 164.3, 167.8. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{13}H_{18}N_2O_2$: 234.1368; found: 234.1346.

N-Phenyl-3-morpholin-4-yl-3-oxo-propionamide (3ac)

Crystallization from AcOEt/hex, mp 126–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.50 (s, 2H, CH_2), 3.61–3.63 (m, 2H, CH_2), 3.71–3.74 (m, 6H, CH_2), 7.13 (t, $J = 7.32$ Hz, $1H_{arom}$), 7.34 (dd, $J = 7.32$ Hz, $J = 7.81$ Hz, $2H_{arom}$), 7.58 (d, $J = 7.81$ Hz, $2H_{arom}$), 9.85 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 40.5, 42.6, 46.8, 66.8, 66.9, 120.3, 124.7, 129.2, 137.9, 164.2, 167.3. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{13}H_{16}N_2O_3$: 248.1160; found: 248.1145.

N-Phenyl-N′-p-tolyl-malonamide (3ad)

Crystallization from AcOEt/hex, mp 223–225 °C; ^{1}H NMR (500 MHz, acetone): δ = 2.08 (s, 3H, CH_3), 3.55 (s, 2H, CH_2), 7.11 (t, $J = 7.32$ Hz, $1H_{arom}$), 7.15 (d, $J = 8.3$ Hz, $2H_{arom}$), 7.35 (t, $J = 7.82$ Hz, $2H_{arom}$), 7.58 (d, $J = 8.3$ Hz, $2H_{arom}$), 7.70 (d, $J = 8.3$ Hz, $2H_{arom}$), 9.61 (s, 1H, NH), 9.70 (s, 1H, NH). ^{13}C NMR (125 MHz, acetone): δ 20.2, 45.0, 119.6, 119.7, 123.9, 129.0, 129.4, 133.3, 136.6, 139.1, 165.4, 165.6. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{16}H_{16}N_2O_2$: 268.1212; found: 268.1191.

N-Benzyl-N′-phenyl-malonamide (3ae)

Crystallization from AcOEt/hex, mp 146–149 °C; alternatively in the cases of entries 22 and 23 in Table 1 the residue was purified by flash column chromatography (AcOEt/hex, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.44 (s, 2H, CH_2), 4.48 (d, $J = 5.38$ Hz, 2H, CH_2), 7.15 (t, $J = 7.32$, $1H_{arom}$), 7.29–7.59 (m, 8H, H_{arom} NH), 7.56–7.58 (m, $2H_{arom}$), 9.55 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 43.9, 44.1, 120.4, 124.9, 128.0, 129.0, 129.1, 129.2, 137.6, 137.8, 165.4, 167.9. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{16}H_{16}N_2O_2$: 268.1211; found: 268.1212.

N-*tert*-Butyl-N′-phenyl-malonamide (3af)

Crystallization from AcOEt/hex, mp 168–171 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (s, 9H, $CH_{3\ (t\text{-}Bu)}$), 3.37 (s, 2H, CH_2), 6.95 (s, 1H, NH), 7.13 (t, $J = 7.32$ Hz, 1 H_{arom}), 7.24 (dd, $J = 7.32$ Hz, $J = 8.3$ Hz, $2H_{arom}$), 7.62 (d, $J = 8.3$ Hz, $2H_{arom}$), 9.81 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.8, 44.9, 52.1, 120.5, 124.7, 129.2, 138.0, 166.2, 167.3. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{13}H_{18}N_2O_2$: 234.1368; found: 234.1340.

N-*iso*-Butyl-N′-phenyl-malonamide (3ag)

Crystallization from AcOEt/hex, mp 147–148 °C; alternatively, in the case of entry 25 in Table 1 the residue was purified by flash column chromatography (AcOEt/hex, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (d, $J = 6.35$ Hz, 6H, CH_3), 1.84 (n, $J = 6.35$ Hz, $J = 6.84$ Hz, 1H, CH), 3.15 (dd, $J = 6.84$ Hz, $J = 6.35$ Hz, 2H, CH_2) 3.46 (s, 2H, CH_2), 7.14 (t, $J = 7.32$ Hz, $1H_{arom}$), 7.27 (s, 1H, NH), 7.34 (t, $J = 7.81$ Hz, $2H_{arom}$), 7.60 (d, $J = 7.81$ Hz, $2H_{arom}$), 9.72 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.4, 28.6, 44.1, 47.4, 47.5, 120.4, 124.8, 129.2, 137.9, 166.0, 168.1. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{13}H_{18}N_2O_2$: 234.1368; found: 234.1392.

N-Cyclohexyl-3-morpholin-4-yl-3-oxo-propionamide (3bc)

Crystallization from AcOEt/hex, mp 101–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.17–1.23 (m, 3H), 1.33–1.40 (m, 2H), 1.59–1.62 (m, 1H), 1.69–1.72 (m, 2H), 1.88–1.90 (m, 2H), 3.31 (s, 2H, CH_2), 3.57–3.59 (m, 2H), 3.64–3.65 (m, 2H), 3.67–3.70 (m, 4H), 3.75–3.80 (m, 1H), 7.25 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.9, 25.7, 33.0, 41.0, 42.5, 46.8, 48.5, 66.9, 164.5, 167.8. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{13}H_{22}N_2O_3$: 254.1630; found: 254.1594.

N-Cyclohexyl-N′-benzyl-malonamide (3be)

Crystallization from AcOEt/hex, mp 136–138 °C; alternatively, in the case of entry 30 in Table 1 the residue was purified by flash column chromatography (AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18–1.24 (m, 3H), 1.32–1.39 (m, 2H), 1.60–1.63 (m, 1H), 1.71–1.74 (m, 2H), 1.87–1.90 (m, 2H), 3.22 (s, 2H, CH_2), 4.43 (d, $J = 5.37$ Hz, 2H, CH_2), 7.12 (s, 1H, NH), 7.27–7.35 (m, $5H_{arom}$), 7.77 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.2, 25.9, 33.1, 43.6, 43.9, 48.9. 127.8, 128.0, 129.0, 138.4, 167.0, 168.1. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{16}H_{22}N_2O_2$: 274.1680; found: 274.1657.

N-Cyclohexyl-N′-isobutyl-malonamide (3bg)

Crystallization from AcOEt/hex, mp 115–116 °C; alternatively in the case of entry 31 in Table 1 the residue was purified by flash column chromatography (AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91 (d, $J = 6.84$ Hz, 6H, CH_3), 1.09–1.38 (m, 5H, CH_2), 1.55–1.90 (m, 6H, CH_2, CH), 3.08 (dd, $J = 6.31$ Hz, $J = 6.51$ Hz, 2H, CH_2), 3.16 (s, 2H, CH_2), 3.71–3.76 (m, 1H, CH), 6.93 (s, 1H, NH), 7.26 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.6, 25.2, 25.9, 28.9, 33.2, 43.7, 47.4, 49.0, 163.5, 164.1. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{13}H_{24}N_2O_2$: 240.1837; found: 240.1796.

General Procedure for Acylation of Alcohols with 1

A solution of **1** (1 mmol), with corresponding alcohol **4** (20 mmol) and trimethylchlorosilane (0–2 eq) in anhydrous solvent (10 ml), was stirred under reflux.

Amount of TMSCl, solvent, and reaction time are specified in Table 2. After completion of reaction, the solvent was removed under vacuum, and the residue was purified.

N-Phenyl-malonamic Acid Ethyl Ester (5aa)

Purification by flash column chromatography (AcOEt/hex, 1:2), oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (t, $J = 7.20$ Hz, 3H, CH_3), 3.47 (s, 2H, CH_2), 4.27 (q, $J = 7.20$ Hz, 2H, CH_2), 7.10–7.17 (m, $1H_{arom}$), 7.26–7.37 (m, $2H_{arom}$), 7.54–7.58 (m, $2H_{arom}$), 9.24 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 41.5, 61.9, 120.1, 124.6, 129.0, 137.5, 162.9, 170.1. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{11}H_{13}NO_3$: 207.0894; found: 207.0882.

N-Phenyl-malonamic Acid Allyl Ester (5ab)

Purification by flash column chromatography (AcOEt/hex, 2:5), oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.51 (s, 2H, CH_2), 4.66 (d, $J = 5.86$ Hz, 2H), 5.27 (dd, $J^2 = 9.77$ Hz, $J^4 = 1.0$ Hz, $1H_{vin}$), 5.35 (dd, $J^2 = 15.63$ Hz, $J^4 = 1.46$ Hz, $1H_{vin}$), 5.87–5.95 (m, $J = 5.86$ Hz, $J = 1.0$ Hz, $J = 9.77$ Hz, $J = 15.63$ Hz, $1H_{vin}$), 7.12 (t, $J = 7.32$ Hz, $1H_{arom}$), 7.31 (t, $J = 7.32$ Hz, $2H_{arom}$), 7.56 (d, $J = 7.33$ Hz, $2H_{arom}$), 9.29 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 42.5, 66.5, 119.4, 120.5, 124.9, 129.2, 131.5, 137.8, 163.9, 169.1. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{12}H_{13}NO_3$: 219.0894; found: 219.0915.

N-Phenyl-malonamic Acid *tert*-Butyl Ester (5ac)

Purification by flash column chromatography (AcOEt/hex, 1:4), mp 75–78 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.54 (s, 9H), 3.41 (s, 2H, CH_2), 7.15 (t, $J = 7.32$ Hz, $1H_{arom}$), 7.29 (s, $1H_{arom}$), 7.36 (t, $J = 7.81$ Hz, $2H_{arom}$), 7.60 (d, $J = 8.3$ Hz, $2H_{arom}$), 9.36 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.5, 43.2, 83.5, 120.6, 124.9, 129.4, 138.1, 164.3, 169.5. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{13}H_{17}NO_3$: 235.1207; found: 235.1204.

N-Cyclohexyl-malonamic Acid Ethyl Ester (5ba)

Crystallization from AcOEt/hex, mp 69–70 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21–1.44 (m, 8H), 1.61–1.73 (m, 3H), 1.91–1.94 (m, 2H), 3.30 (s, 2H, CH_2), 3.80–3.85 (m, 1H), 4.22 (q, $J = 7.30$ Hz, 2H, CH_2), 7.05 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 24.7, 25.5, 32.8, 41.3, 48.2, 61.4, 163.9, 169.7. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{11}H_{19}NO_3$: 213.1365; found: 213.1331.

N-Cyclohexyl-malonamic Acid Allyl Ester (5bb)

Crystallization from AcOEt/hex, mp 45–48 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20–1.29 (m, 3H), 1.34–1.43 (m, 2H), 1.60–1.64 (m, 1H), 1.70–1.74 (m, 2H), 1.90–1.93 (m, 2H), 3.34 (s, 2H, CH_2), 3.79–3.86 (m, 1H), 4.65 (d, $J = 5.86$ Hz, 2H), 5.30 (dd, $J^2 = 9.28$ Hz, $J^4 = 1.0$ Hz, $1H_{vin}$), 5.36 (dd, $J^2 = 16.11$ Hz, $J^4 = 1.46$ Hz,

$1H_{vin}$), 5.89–5.97 (m, $J = 5.86$ Hz, $J = 1.0$ Hz, $J = 9.28$ Hz, $J = 16.1$ Hz, $1H_{vin}$), 6.98 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.9, 25.8, 33.1, 48.4, 66.3, 119.4, 131.6, 163.9, 169.7. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{12}H_{19}NO_3$: 225.1365; found: 225.1367.

N-Ethyl-malonamic Acid *tert*-Butyl Ester (5cc)

Purification by flash column chromatography (AcOEt/hex, 1:2), oil; ^1H NMR (500 MHz, $CDCl_3$): δ 1.19 (t, $J = 7.32$ Hz, 3H, CH_3), 1.49 (s, 9H), 3.23 (s, 2H, CH_2), 3.33–3.36 (m, 2H, CH_2), 7.29 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.1, 28.5, 34.8, 42.5, 82.9, 165.8, 169.5. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_9H_{17}NO_3$: 187.1207; found: 187.1170.

General Procedure for Acylation of Thiols with 1

A solution of **1** (1 mmol), with corresponding thiol (**4**) (2 mmol) and solvent (5 ml), was stirred under reflux. Solvent and reaction time are specified in Table 2. After completion of the reaction, the solvent was removed under vacuum and the residue was purified.

N-Phenyl-thiomalonamic Acid S-Phenyl Ester (5ad)

Purification by flash column chromatography (AcOEt/hex, 1:3), yellow solid, mp 81–83 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 3.81 (s, 2H, CH_2), 7.08–7.53 (m, $10H_{arom}$), 8.70 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 50.1, 120.1, 124.7, 129.0, 129.6, 130.3, 134.6, 137.3, 161.8, 195.1. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{15}H_{13}NO_2S$: 271.0667; found: 271.0637.

N-Phenyl-thiomalonamic Acid S-p-Tolyl Ester (5ae)

Purification by flash column chromatography (AcOEt/hex, 1:3), mp 118–120 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 3.82 (s, 2H, CH_2), 7.13–7.16 (m, $1H_{arom}$), 7.29–7.37 (m, $6H_{arom}$), 7.53–7.55 (m, $2H_{arom}$), 8.79 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9, 50.4, 120.6, 123.3, 125.2, 129.5, 130.9, 135.0, 137.9, 141.2, 162.5, 196.1. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{16}H_{15}NO_2S$: 285.0822; found: 285.0332.

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