Postprint of: Makowiec S., Janikowska K., Tmscl as a rate accelerating additive in acylations of amines with 5-(α-amino- α'-hydroxy)methylene meldrum's acids, SYNTHETIC COMMUNICATIONS, Vol. 42, Iss. 7 (2012), pp. 975 - 988,
DOI: 10.1080/00397911.2010.533805

TMSCl AS A RATE ACCELERATING ADDITIVE IN ACYLATIONS OF AMINES WITH 5-(α-AMINO- α'-HYDROXY)METHYLENE MELDRUM'S ACIDS.

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Received

ABSTRACT: Aspects are presented of the acylation of amines, alcohols and thiols with 5-(α-amino- α'-hydroxy)methylene Meldrum's acids. We placed special emphasis on the acylation reaction of secondary amines with 5-(α-amino- α'-hydroxy)methylene Meldrum's acids, which, due to their basicity, caused problems concerning salt formation with a Meldrum acid derivative. We found that secondary amines, which react at the slowest rate and with a low 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 were optimized for such factors as: reaction temperature, solvent polarity and acidity of the environment. We have prepared a wide range of non-symmetrical malononic acid diamids, esters and thioesters of malonamic acid.

KEYWORDS: amides, acylation, enols, ketens, decarboxylation

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 compounds[5], whereas esters of malonamic acid

include having antiinflammatory and analgesic effect[6], anti-ischemic properties[7] or even having a ligand for thyroid receptor[8].

Whereas synthesis of symmetrical malonic acid derivatives is a trivial laboratory procedures[9], synthesis of non-symmetrical malonamids or esters of malonamic acid require several steps to obtain final product. The selective classical procedure[10] for preparation of non-symmetrical malondiamids starting from diethyl malonate require half-hydrolysis, activation of free carboxyl group, coupling with amine, hydrolysis of ester and 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 last few years several method have been described that bypass this long procedure. Menendez and Avendano[11] has proposed the synthesis of malonamic derivatives based on the reaction of β-amidothioester with various nucleophiles. They obtain good results and 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 insomuch in the case of the other amine the reaction time is as long as 50 to 70 h[13], and have found that in some cases it fails to work and we were not able to obtain N,N-dietylmalonamic acid by this procedure.

Apart from above 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's acid similarly to classical acylmeldrum[15] acids are able to generate ketenes upon thermal decomposition. This property underlies the method developed by Pak[16] in which 5-(α-amino- α'-hydroxy)methylene Meldrum's acid reacts in boiling solvent with amine in a one step process giving the desired unsymmetrical malonamid.

RESULTS NAD DISCUSION

In our laboratory we needed unsymmetrical malonoamides of secondary amines. Taking into consideration of all the known method we decided to adopt the method of Pak[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's acid (**1a**) with piperidine (**2a)** in boling ethylbenzene we obtain desired amide with only 34% yield after 20 hours 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 repeat these reaction scrupulously again to eliminated any possible experimental errors, however we still obtain these amides with low yields. To check if we commit an unknown error, we decided to perform experiments on models very close to these presented by Pak. We carried out four of experiments in which (**1a)** was heated in boiling ethylbenzene respectively with 4-methylaniline, benzyl amine, tert-butylamine and isobutylamine. Surprisingly in these experiments we obtain amides (**3ad), (3ae)**, (**3af)**, (**3ag)** with good yields (Entries 7, 10, 11, 12; Table 1). More attention we put for the reaction of benzyl amine with (**1a)** because Pak has reported that 4-metylbenzyl amine require for the reaction with 5-(α-amino- α'-hydroxy)methylene Meldrum's acid such a harsh condition as refluxing for an hour in boiling o-dichlorobenzene, otherwise they observed only formation of salt of amine with (**1**).

When we done the reaction of 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 perform in boiling dioxane, however better ability of dioxane to dissolve this salt did not affect the reaction time (Entry 9; Table 1).

Scheme 1

Table 1

As one can see, there is rather obvious correlation between the basicity of amines and the yield of malonamides. (Entries 1, 4 ver 7, 10, 11, 12 Table 1). On the other hand, in experiments performed by Pak the yields were high and the reaction times short but only weak basic aromatic amines with 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 favour of salt product, resulting in much lower yield of non-symetrical malonamids and very long reaction time. This result should not be surprising taking into account the work of Grabowski[15a] were 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 Grabowski[15a] for acyl Meldrum acids.

The addition of 2,5 eq of TFA to the reaction mixture prepared from 1eq (**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 the yield was still comparable as for the reaction without any additives (Entries 3, 5 Table 1).

Finally we checked whether the addition of TMSCl influenced the reaction time or yields, since TMSCl may be at least convenient source of HCl (Scheme 1). Surprisingly we obtain significantly higher yields when reaction of piperidine with (**1a)** in boiling ethylbenzene was led in the presence of 1 or 3 eq of TMSCl (Entries 13, 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 obtained almost quantative yield within 2.5 h, it should be noted that for reaction in DCM temperature was almost sixty degrees lower than for reaction without TMSCl (Entries 15, 16, Table 1).

Similarly, reaction with diethylamine and morpholine with (**1a**) were strongly accelerated in the presence of TMSCl (Entries 20, 21, Table 1). Reactions of primary amines with (**1a**) were also accelerated; however, the use of only 1,5 eq of TMSCl gave a reaction giving 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, 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 hours 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, 30, Table1).

Generally it can be stated that TMSCl significantly accelerates the reaction when more acidic Meldrum derivative (**1a)** and a more basic secondary amine was used. At this time we cannot explain the mechanism of reaction in which TMSCl participate 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 (Entry 3, 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 we 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 high yields (Entries 3, 6, Table 2). In a similar way, we examined the reaction of 2 eq of thiols with (**1a**), and obtain malonamic acid thioesters (Entries 7, 8, Table 2).

Scheme 2

Table 2

In the case of ethyl and tert-butyl alcohols, the boiling point of a mixture of solvents were approx. 80°C, what extends the reaction time (Entries 1, 3, 4, 6, Table 2). Based on our

experience in reactions between amines and (**1**), we checked whether the addition of TMSCl accelerate the process. However, two experiments with the addition of 2 eq of TMSCl (Entry 10, 11, Table 2) showed that reaction of alcohols with (**1a**) is not accelerated by TMSCl.

CONCLUSSION

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's acid to include preparation of malonamic acid esters and thioesters.

ACKNOWLEDGMENT

Scientific work financed from funds for science in 2010-2011 as a research project NN204 088338

EXPERIMENTAL

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

5-(α-Phenylamino- α'-hydroxy)methylene Meldrum's acids (1a)

Was prepared according to literature procedure[17], and crystallized twice from AcOEt. Yield 89%, mp 105-107°C (lit.[17] mp109-110°C). Spectral data in agreement with literature.

5-(α-cyclohexylamino- α'-hydroxy)methylene Meldrum's acids (1b)

To a solution of Meldrum's acid (0.72 g, 5 mmol) in dry DMF(5 ml) in glass ampoule was added Et_3N (1.4 ml, 10 mmol). Cyclohexylisocyanate (0.751g, 6 mmol,) was added, and ampoule was sealed. The ampoule was placed in the bath for 20h at 40°C. The solution was poured into 2 M HCl (30 ml) mixture of ice and water. The solid precipitate was filtered and washed with cold water. Precipitate was dissolved in ethyl acetate (30ml) and dried with $MgSO_4$, after cooling the solution the precipitate of DCU was removed by filtration. The solvent was removed under reduced pressure. Crystallization from AcOEt/Hexan gave 0.795g 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's acids (1c)

To a solution of Meldrum's acid (0.72 g, 5 mmol) in dry DMF(5 ml) in glass ampoule was added Et_3N (1.4 ml, 10 mmol). Ethylisocyanate (0.426g, 6 mmol,) was added, and ampoule was sealed. The ampoule was placed in the bath for 10h at 40°C. The solution was poured into 2 M HCl (30 ml) mixture of ice and water. The solid precipitate was filtered and washed with cold water. Precipitate was dissolved in ethyl acetate (30ml) and dried with $MgSO_4$, The solvent was removed under reduced pressure. Crystallization from AcOEt/Hexan gave 0.706g 65% yield mp 72-74 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (t, 3H, J=7,3Hz), 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 (0-8eq) in anhydrous solvent (10 ml) was stirred under reflux. Amount of TMSCl, solvent and reaction time was specified in the Table 1. After completion of reaction the solvent was removed under vacuum, and the residue was purified as follows.

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 case of Entry 22 and 23 in Table 1 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 ºC, ^{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= 8.3Hz, 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 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 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 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 (50MHz, $CDCl_3$): 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 (0-2eq) in anhydrous solvent (10 ml) was stirred under reflux. Amount of TMSCl, solvent and reaction time was specified in the Table 2. After completion of reaction the solvent was removed under vacuum, and the residue was purified as follows.

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 (500MHz, $CDCl_3$): 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 (500MHz, $CDCl_3$): 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 (50MHz, $CDCl_3$): 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, ^{1}H 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) solvent (5 ml) was stirred under reflux under reflux. Solvent and reaction time was specified in the Table 2. After

completion of reaction the solvent was removed under vacuum, and the residue was purified as follows.

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, CDCl3): δ 3.81 (s, 2H, CH2), 7.08-7.53 (m, $10H_{arom}$), 8.70 (s, 1H, NH). 13C NMR (50 MHz, CDCl3): 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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