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Versatile synthesis of malonamic acid derivatives from a β-ketothioester

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Abstract—An efficient synthetic route is described that allows the preparation under mild conditions of several types of malonamic acid derivatives. The *S*-*tert*-butyl acetothioacetate monoanion reacted with aryl or alkyl isocyanates to give β-amidothioesters in one step and 73–87% yield, after spontaneous deacetylation of tricarbonyl intermediates. Treatment of these thioesters with several aliphatic or aromatic alcohols and amines at room temperature in THF or DME and in the presence of silver trifluoroacetate provided, respectively, the corresponding malonamic acid esters and malonamides in 80–100% yield.

β-Dicarbonyl derivatives belonging to the malonamic acid family are very important compounds. More specifically, a wide variety of malonamides and malonamic acid esters have interesting pharmacological properties, including antihypertensive,[1] sedative and anticonvulsant,[2] antiinflammatory,[3] analgesic,[1b,4] and central nervous system-stimulating activities.[5] Their interaction with several important biomolecules, including the M_1 muscarinic[6] and cholecystokinin A[7] receptors, the gramicidin channel[8] and DNA[9] has been also described. Also, the introduction of malonamide substructures is a technique for the design of peptidomimetics.[10,11] Some malonamides are useful as X-ray contrast agents[12] and as non-linear optical materials.[13] Furthermore, the unique chelating properties of β-diamides make them ideal reagents for the extraction and chemical fixation of heavy metal ions,[14] including trivalent lanthanides[15] and actinides,[16] and have thus interesting potential applications in environmental decontamination procedures. These chelating properties are also the basis for a large number of analytical applications as components of chromatographic phases[17] or as metal-selective ionophoric speciating reagents.[18] Finally, several β-amidoesters are used as intermediates in the synthesis of numerous pharmacologically relevant compounds[19–21] or as chiral auxiliaries.[22]

The classical preparation of *N*-symmetrically substituted malonamides involves the high-temperature condensation of diethyl malonate derivatives with amines.[3b] Other methods for the preparation of malonamides and malonamic acid esters start from Meldrum's acid[23] or from malonic acid derivatives such as malonyl chloride,[21] malonyl monoacyl chloride[24] or malonic acid monoethyl ester, which is activated through its conversion into the corresponding acyl chloride (in solution[7] or on a solid support[25]), or via its reaction with DCC,[2] carbonyldiheterocycles[2] or BOP.[11] In most cases, these methods lack generality and give low or moderate yields.

We propose here a new, flexible route to malonamic acid esters and malondiamides that exploits the well-known regioselective reaction of β-ketothioesters with electrophiles at C-2, the easy retro-Claisen degradation of tricarbonyl compounds[26] and the high reactivity of the thioester group towards alcohols and amines in the presence of thiophilic metals.[27] Our route is shown in Scheme 1, and starts by the preparation of β-amidothioesters **3** by treatment of commercially available *tert*-butyl acetothioacetate **1** with sodium hydride and an aryl or alkyl isocyanate in dry dimethoxyethane. Although the intermediate tricarbonyl derivatives **2** could be detected in the crude reaction products, they were deacetylated during workup and purification, a process that was accelerated by the presence of silicagel. Compounds **3** were treated with several amines (including aminoacids), at room temperature in the presence of silver trifluoroacetate,[27] yielding diamides **4** in 80–100% yields. Similar treatment of compounds **3** with alcohols or phenols afforded malonamic acid esters **5**, also in excellent yields.[28]

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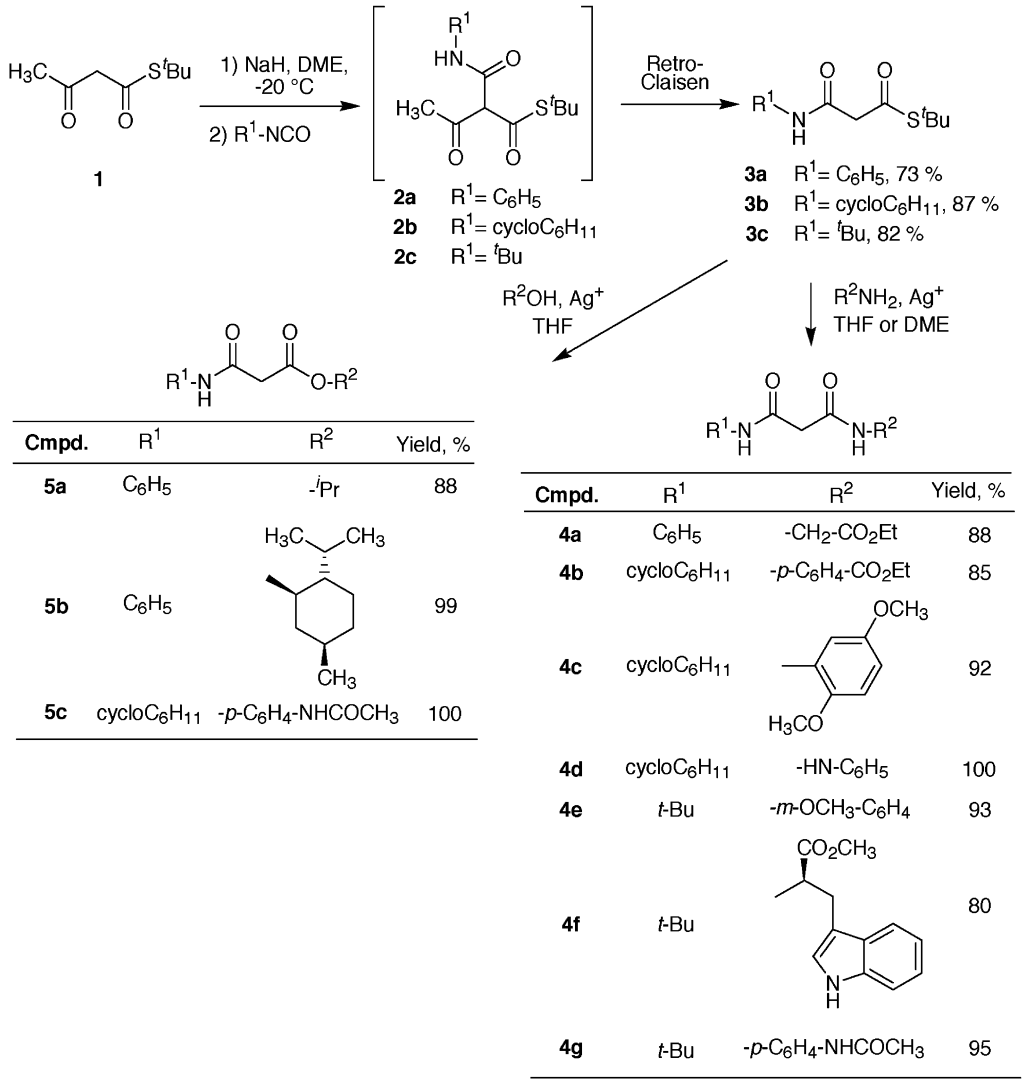
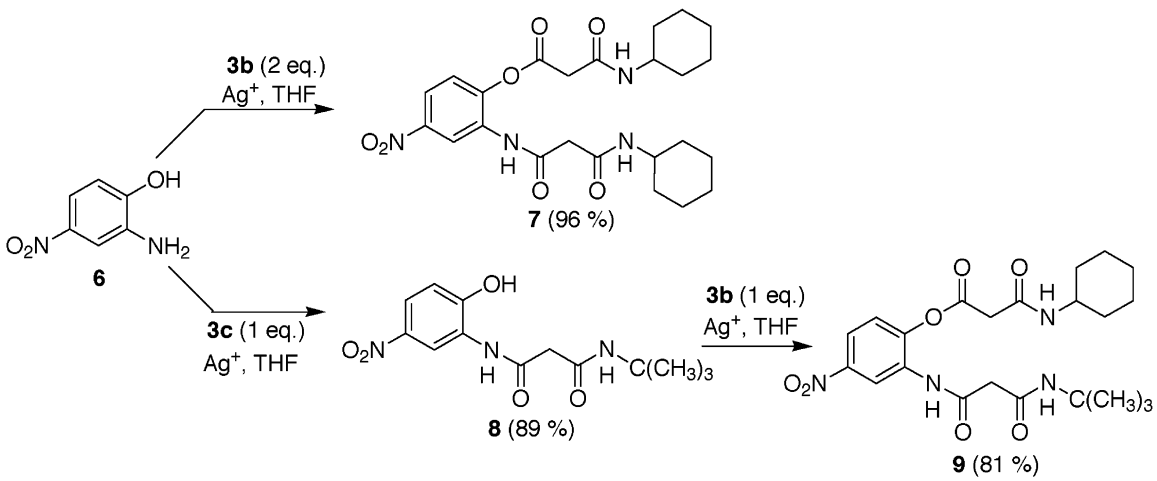


Cmpd.	R^1	R^2	Yield, %
5a	C_6H_5	-^{i}Pr	88
5b	C_6H_5		99
5c	cycloC_6H_{11}	-*p*-C_6H_4-$NHCOCH_3$	100

Cmpd.	R^1	R^2	Yield, %
4a	C_6H_5	-CH_2-CO_2Et	88
4b	cycloC_6H_{11}	-*p*-C_6H_4-CO_2Et	85
4c	cycloC_6H_{11}		92
4d	cycloC_6H_{11}	-HN-C_6H_5	100
4e	*t*-Bu	-*m*-OCH_3-C_6H_4	93
4f	*t*-Bu		80
4g	*t*-Bu	-*p*-C_6H_4-$NHCOCH_3$	95

Scheme 1.

We also briefly examined the acylation of bifunctional substrates by compounds **3**. Treatment of aminophenol **6** with 2 equiv. of amidothioester **3b** gave compound **7** in 96% yield. If only 1 equiv. of the thioester was employed, the reaction could be made chemoselective, as shown by the preparation of **8** from **6** and **3c** (Scheme 2).



Scheme 2.

All new compounds were characterized by spectral analysis (IR, ^{1}H, ^{13}C NMR), and also by other relevant analytical data (mp and [α], in the case of compounds **4f** and **5b**). They all gave satisfactory (±0.30%) combustion microanalyses for CHN.

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28. **Representative experimental procedure**. To a slurry of petroleum ether-washed (2×10 mL) sodium hydride (0.25 g of a 60% dispersion in mineral oil, 6.04 mmol, 1.05 equiv.) in *dry* 1,2-dimethoxyethane (DME) (40 mL) under an argon atmosphere at −20°C, was added dropwise, via cannula, a solution of *S*-*tert*-butyl 3-oxothiobutanoate **1** (1.0 g, 5.75 mmol) in *dry* DME (10 mL). The solution was left to warm to 0°C for 5–10 min, and freshly distilled cyclohexyl isocyanate (0.75 g, 6.04 mmol) was added. After 14 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL), extracted with diethyl ether (2×100 mL) and washed again with aqueous NH_4Cl (50 mL) and brine (2×50 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give an orange oil. Chromatography on silica-gel (gradient from 50% petroleum ether/Cl_2CH_2 to neat Cl_2CH_2) yielded 1.29 g (87%) of *S*-*tert*-butyl cyclohexylcarbamoylthioacetate (**3b**), as white needles. Mp: 59–61°C. IR (KBr): 3289 (NH), 1682 (^{t}BuS-C=O), 1644 (NH-C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 6.66 (d, 1H, J=7.0 Hz, NH), 3.65 (m, 1H, H-1′), 3.29 (s, 2H, H-2), 1.80–1.75, 1.63–1.44 and 1.28–1.02 (3 m, 10H, H-2′,3′,4′,5′,6′), 1.36 (s, 9H, ^{t}Bu). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 195.6 (C-1), 163.5 (CO-NH), 50.9 (C-2), 48.7 ($C(CH_3)_3$), 48.1 (C-1′), 32.6 (C-2′,6′), 29.4 ($C(CH_3)_3$), 25.3 (C-4′), 24.5 (C-3′,5′). Anal. calcd for $C_{13}H_{23}NO_2S$: C, 60.66; H, 9.01; N, 5.44. Found: C, 60.94; H, 9.23; N, 5.63.

To a solution of β-carbamoylthioester **3b** (100 mg, 039 mmol) and 2,5-dimethoxyaniline (65 mg, 0.43 mmol) in dry 1,2-dimethoxyethane (3 mL) was added silver trifluroacetate (94 mg, 0.43 mmol). The reaction mixture was stirred overnight at room temperature. The resulting suspension was poured onto water (25 mL) and extracted with $CHCl_3$ (3×25 mL). The combined organic phases were evaporated under reduced pressure and the residue was chromatographed on silica-gel, eluting with a gradient from neat CH_2Cl_2 to neat Et_2O to yield 114 mg (92%) of compound **4c**, as a white solid. Mp: 97–98°C. IR (KBr): 3337 and 3257 (2 NH), 1662 (2×NH-*C*=*O*) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 9.44 (br. s, 1H, NH′), 8.00 (d, 1H, $J=2.9$ Hz, H-6′), 7.11 (d, 1H, $J=6.8$ Hz, NH″), 6.79 (d, 1H, $J=8.9$ Hz, H-3′), 6.59 (dd, 1H, $J=8.9$ and 2.9 Hz, H-4′), 3.84 and 3.76 (2 s, 2×3H, 2×OMe), 3.76 (m, 1H, H-1″), 3.39 (s, 2H, H-2), 2.00–1.88, 1.74–1.58 and 1.47–1.09 (3 m, 10H, H-2″,3″,4″,5″,6″). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 166.4 and 165.6 (C-1 and C-3), 153.6 (C-5′), 142.9 (C-2′), 127.8 (C-1′), 110.9 (C-3′), 108.7 (C-4′), 106.9 (C-6′), 56.3 and 55.7 (2 OMe), 48.7 (C-1″), 44.2 (C-2), 32.7 (C-2″,6″), 25.4 (C-4″), 24.7 (C-3″,5″). Anal. calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.50; H, 7.67; N, 8.65.