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[A0042]

A general, high-yielding synthesis of b-diamides and b-amidoesters

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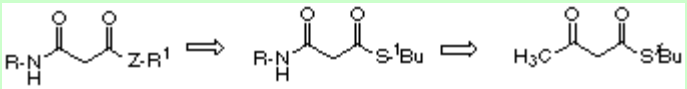
Abstract.- A new and efficient synthetic route to malonamides and malonamic acid esters is described. *S-tert*-Butyl acetothioacetate monoanion reacted with aryl or alkyl isocyanates to give tricarbonyl compounds, which spontaneously deacetylated to the corresponding b-amidothioesters. Treatment of the latter with aliphatic or aromatic amines or alcohols at room temperature in the presence of silver trifluoroacetate provided malonamides or malonamic acid esters, respectively, in excellent overall yields.

Introduction

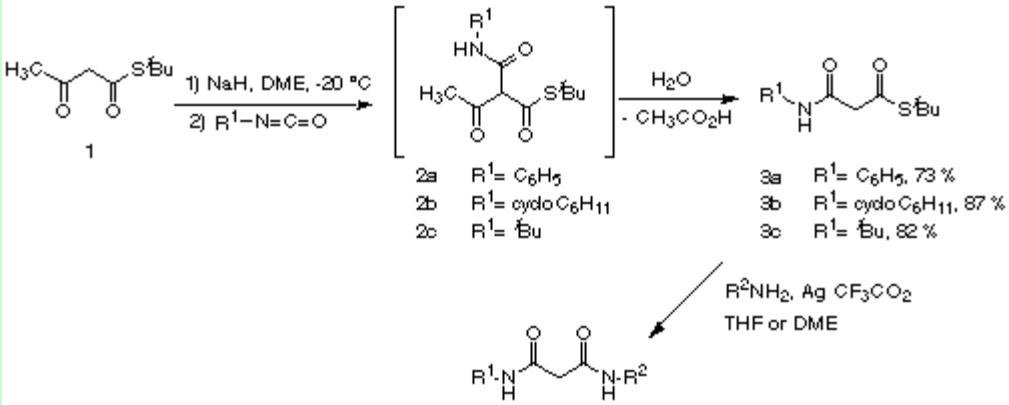
A number of b-dicarbonyl compounds derived from malonic acid, specially malonamides and malonamic acid esters, have interesting pharmacological properties including antihypertensive [1], sedative and anticonvulsant [2], antiinflammatory [3], analgesic [4], M1 selective muscarinic receptor antagonistic [5] activities, among others. Furthermore, the unique chelating properties of some malonamides makes them ideal extracting agents for trivalent lanthanides [6], actinides [7] and other heavy metal ions [8], and has prompted their use as components of chromatographic stationary phases [9]. b-Amidoesters, on the other hand, are also common synthetic intermediates in the preparation of biologically active agents [10] and other interesting organic compounds [11].
The current methods for the preparation of these compounds are normally based on the use of Meldrum's acid [12] or malonic acid monoethyl ester through its conversion into an acyl chloride [5,13] or *via* its reaction with DCC or carbonyldiheterocycles [2]. In most cases, these methods give low or moderate yields. We propose here a new, flexible route to malonamides and malonamic acid esters that exploits the well-known regioselective reaction of b-ketothioesters with electrophiles at C-2, and the high reactivity of the thioester group towards alcohols and amines in the presence of thiophillic metals [14] (Scheme 1).

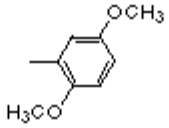
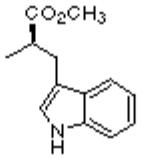


Scheme 1

Results

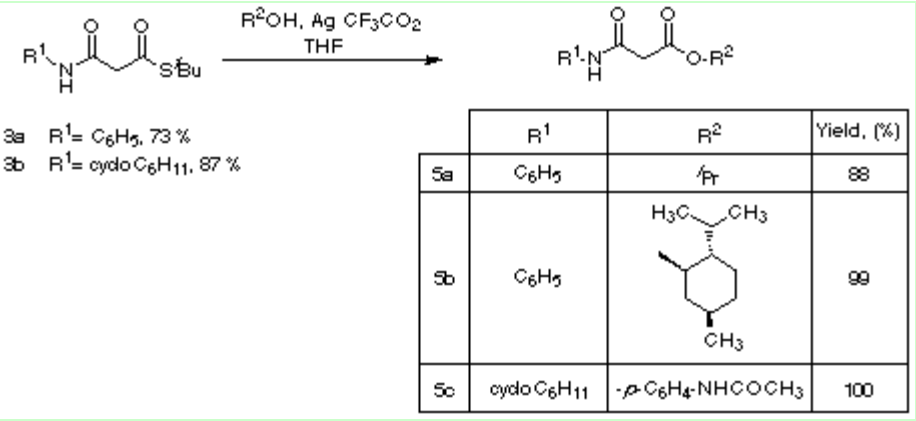
Our route starts by the preparation of b-amidothioesters **3** by treatment of commercially available *tert*butyl acetothioacetate **1** with NaH and an aryl or alkyl isocyanate without isolation of the intermediate tricarbonyl derivatives **2**, which were normally deacetylated during workup and purification. Compounds **3** were treated with several amines in the presence of silver trifluoroacetate [14], yielding diamides **4** in 80-100% yields (Scheme 2).



	R^1	R^2	Yield, (%)
4a	C_6H_5	-CH_2-CO_2Et	88
4b	cydo C_6H_{11}	-*p*-C_6H_4-CO_2Et	85
4c	cydo C_6H_{11}		92
4d	cydo C_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 2

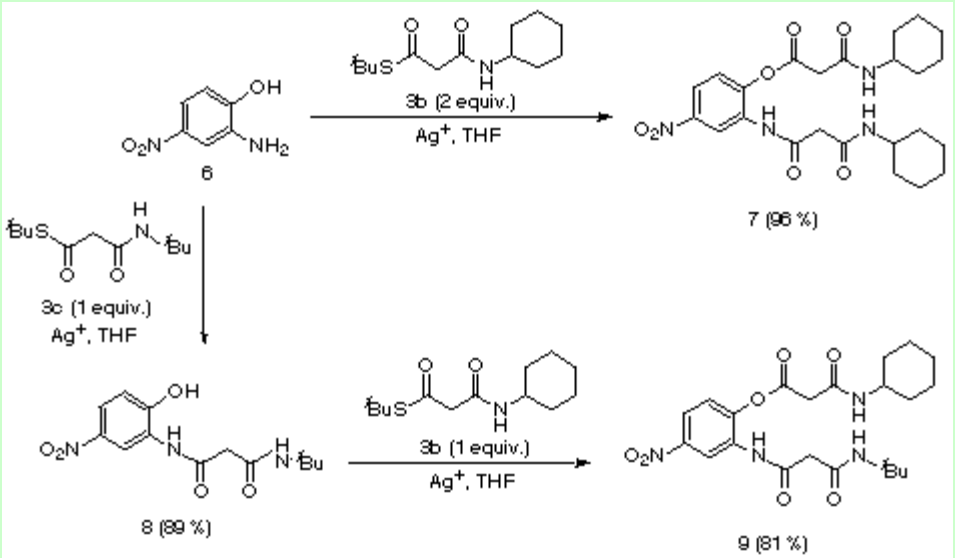
Similar treatment of compounds **3** with several alcohols afforded malonamic acid esters 5, also in excellent yields (Scheme 3).



	R^1	R^2	Yield, (%)
5a	C_6H_5	^iPr	88
5b	C_6H_5		99
5c	cydo C_6H_{11}	-p-C_6H_4-NHCOCH$_3$	100

Scheme 3

Finally, we briefly examined the acylation of bifunctional substrates by compounds **3**. Treatment of aminophenol **6** with 2 equivalents of amidoester **3b** gave compound **7** in 96% yield. If only 1 equivalent of the thioester was employed, the reaction could be made chemoselective, as shown by the preparation of **8** from **6** and **3c** (Scheme 4).



Scheme 4

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