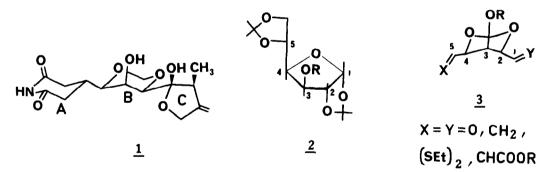
SYNTHESIS OF 4-SUBSTITUTED GLUTARIMIDES BY FREE RADICAL ADDITION OF IODOACETAMIDE TO α,β -UNSATURATED ESTERS

Guerino Sacripante, Charles Tan and George Just* Department of Chemistry, McGill University Montreal, Canada H3A 2K6

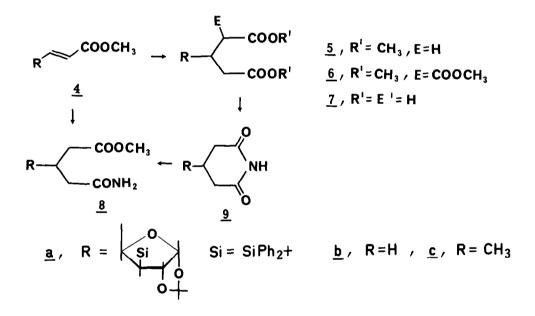
Abstract: Free radical addition of either methyl bromoacetate or iodoacetamide to an α , β -unsaturated ester gave the 4-substituted glutarate or glutarimide respectively, whereas the radical cyclisation of N-bromoacetyl crotonamide gave the 2-substituted succinimide.

Sesbanimide (<u>1</u>), a potent antitumor agent of unknown absolute stereochemistry isolated from *Sesbania drummondii* and *S. punicea* in low yields¹, has been the subject of at least four model studies pertaining to rings A and B². All approaches described derive the central ring B from an appropriately protected glucose (<u>2</u>) or related pentose having the same relative stereochemistry at C-2, C-3 and C-4, where C-1 and C-5 are masked aldehydes. These are then converted to ring system <u>3</u>. In this paper, we wish to describe an efficient approach for the formation of glutarimide ring A from an α , β -unsubstituted ester <u>4</u>, a commonly used precursor for the formation of a 4-substituted glutarimide ring.



In a first conventional approach, the α , β -unsaturated ester <u>4a</u> was treated with the potassium salt of dimethyl malonate, and the resulting triester <u>6a</u> decarbomethoxylated to <u>5a</u>³. Hydrolysis with lithium hydroxide⁴ gave the diacid <u>7a</u> which upon heating at 165°C with 2-4 eq of urea⁵ gave glutarimide <u>9a</u> in 80% yield, based on diester <u>5a</u>. Because of the relative cumbersomeness of the procedure, we sought another approach.

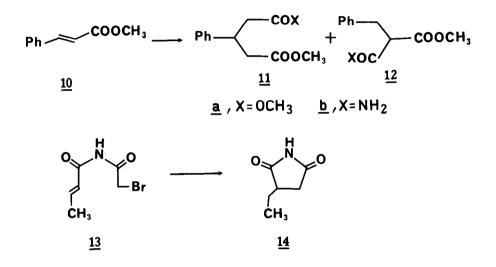
The use of excess methyl acrylate or acrylonitrile to trap organic radicals yielding the corresponding 1,4-addition products has been well documented by several workers⁶. In order to make this type of reaction synthetically useful for the formation of 4-substituted glutarimides, we studied conditions for the addition of organic radicals generated in situ with tributyltin hydride, using α , β -unsaturated esters as substrates. Thus, when the α , β -unsaturated ester <u>4a</u> and a twenty fold excess of methyl bromoacetate were heated at 80°C with catalytic amounts of azobisisobutyronitrile (AIBN) and slow addition of Bu₃SnH over a 15 h period (syringe pump), a 30% yield of glutarate <u>5a</u> was obtained with recovery of over 60% starting material. Removal of the stannanes⁷ and recycling of the crude mixture employing the same conditions yielded 56% diester <u>5a</u> and 8% starting material. It should be noted that with more rapid addition of Bu₃SnH, or dilution with solvent, the yield of <u>5a</u> was vanishingly small.



Addition of methyl bromoacetate to methyl acrylate $\underline{4b}$ or methyl crotonate $\underline{4c}$, using the conditions described, gave 85 and 77% yield of glutarates $\underline{5b}$ and $\underline{5c}$ without recycling.

More interestingly, when the above reaction was carried out with excess iodoacetamide as the radical precursor, and <u>4a</u> as the unsaturated ester component, and the mixture irradiated with a tungsten lamp at $80-90^{\circ}$ C, a mixture of amido ester <u>8a</u> and glutarimide <u>9a</u> was obtained after recycling once. Further heating of this mixture at 120°C gave 64% of glutarimide, with a 5% recovery of <u>4a</u>. Higher yields could be obtained by cyclising the isolated amido ester <u>8a</u> by known methods⁸. A similar glutarimide has been converted to the A/B rings of sesbanimide^{2b}. The iodoacetamide addition to methyl acrylate and crotonate <u>4b</u>, <u>4c</u> gave similarly mixtures of amido esters <u>8b</u>, <u>8c</u> and glutarimide <u>9b</u>, <u>9c</u> in 87 and 85% combined yield respectively. Further heating provided glutarimide <u>9b</u>, <u>9c</u> in good yields without recycling. In all of these reactions, no product of 1, 2-addition was detected.

When methyl cinnamate <u>10</u> was submitted to the action of methyl bromoacetate or iodoacetamide, an approximately 1:1 mixture of <u>11a</u> and <u>12a</u> or <u>11b</u> and <u>12b</u> was obtained, together, in the case of iodoacetamide, with some product of cyclisation.



Finally, the imide <u>13</u>, derived from crotonamide and bromoacetic anhydride gave, not unexpectedly⁹, exclusively 2-ethyl succinimide <u>14</u> derived from a 5-exo-trig addition of the radical to the olefinic bond, with some product of reduction.

General Procedure (9a):

To 100 mg of ester $\underline{4a}$ and 830 mg of iodoacetamide (20 eq) in 0.5 ml of absolute ethanol at 80-90°C under N₂ and irradiation (tungsten lamp), was added 1.3 g of Bu₃SnH over a 15 h period (syringe pump). After removal of the stannanes⁷, the crude mixture was dissolved in CH₂Cl₂, washed with water, dried, and concentrated by rotary evaporation. Recycling of this crude mixture employing the same conditions, followed by heating to 120°C in toluene, gave after the usual work-up and chromatographic separation, a 64% yield of glutarimide $\underline{9a}$ and 5% starting material.

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