Communications to the Editor

[Chem. Pharm. Bull. 31(8)2955—2956(1983)]

AN EASY SYNTHESIS OF MONOMETHYL MALONATE DERIVATIVES[1)]

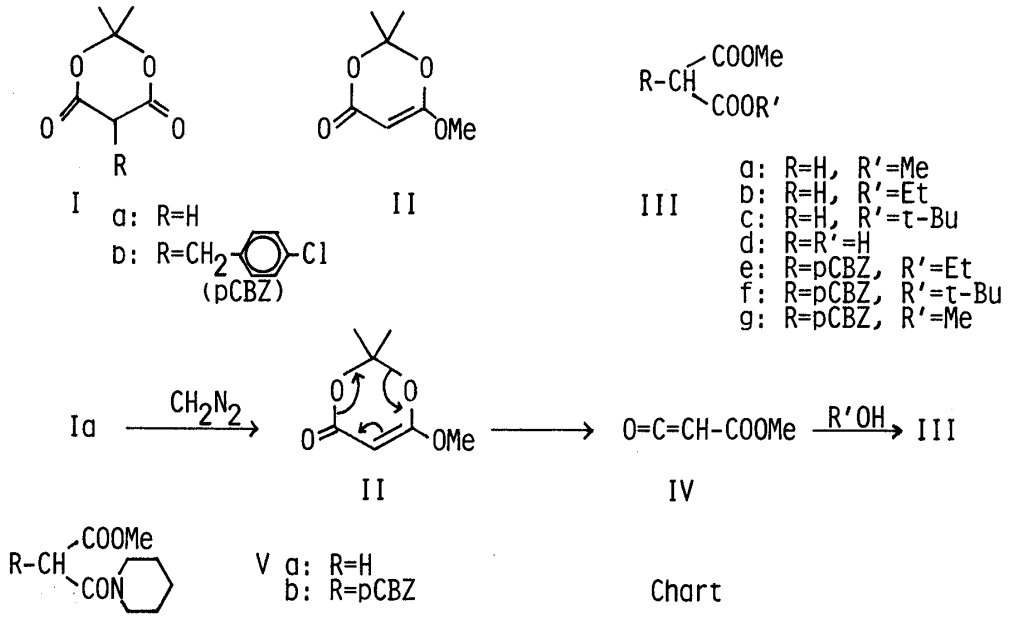
Katsuhide Matoba* and Takao Yamazaki
Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani, Toyama 930-01, Japan

Monomethyl malonates(IIIa-c and Va) were synthesized from Meldrum's acid(Ia) by treating with an excess of diazomethane in the corresponding alcohols and piperidine, respectively, in quantitative yields. In a similar manner, 5-p-chlorobenzyl Meldrum's acid(Ib) afforded the corresponding monomethyl malonate derivatives(IIIe, f, and Vb). The mechanism proposed for this reaction is described.

KEYWORDS ——— Meldrum's acid; monomethyl malonate; half ester; ketene ester; 4,6-dioxo-1,3-dioxane

Meldrum's acid (2,2-dimethyl-4,6-dioxo-1,3-dioxane, Ia) was widely used in organic syntheses because of its ambiphilic reactivity.[2)] On the other hand, Ia has strong acidity (pKa 4.97) as well as acetic acid (pKa 4.76) or dimedone (pKa 4.85) attributable to the resonance stability of the conjugate base.[3)] If Ia gave the methyl vinylogous ester(II) by treatment with diazomethane(CH_2N_2) as well as dimedone, a new chemistry might be developed for Ia.

In the case of the addition of CH_2N_2 to the suspension of Ia in ether, the evolution of nitrogen gas was scarecely observed. On the other hand, when this reagent was added to the methanolic solution of Ia, nitrogen gas evolved violently and dimethyl malonate(IIIa) was obtained in quantitative yield. Ethyl methyl malonate (IIIb) and t-butyl methyl malonate(IIIc) were obtained in almost pure states by treatment of Ia with CH_2N_2 in ethanol and t-butanol, respectively. The structures of IIIa-c were determined by comparison with authentic samples[4)] using GC and NMR spectra. The proposed mechanism for the formation of these methyl malonates is shown in the chart, that is, the vinylogous ester(II) formed as an intermediate would decompose at ambient temperature into ketene methyl ester(IV), which was further attacked by appropriate alcohols to give expected products. Junek et al. reported that monophenyl or monocycloalkyl malonates were obtained by warming the mixture of Ia and phenols or cycloalkanols at 100°C for 90min.[5)] A similar reaction was examined using methanol in our laboratory. Although the major product was IIId, the reaction did not proceed smoothly and about half of the starting material, Ia, remained unchanged even after refluxing for 4 h. This fact also suggests the proposed mechanism described above. And also, it is well known that the alkyl half esters of malonic acid are subject to disproportionation of ester group during storage to give a mixture of dialkyl malonates and malonic acid. From these points of view, this synthetic method of monomethyl malonates has greater advantage than the method known earlier.



Chart

In a similar manner, CH_2N_2 was added to the solution of Ia in piperidine to give N-(methoxycarbonylacetyl)piperidine(Va) in 59.4% yield. Thus it was revealed that the method could be applied to the synthesis of half malonate amide.

Next, to apply this method to other Meldrum's acid, 5-p-chlorobenzyl Meldrum's acid(Ib) was prepared from p-chlorobenzyl malonic acid. The conditions for the preparation of Ib has not been optimized. Ib: mp 140-141°C(needles from aq. acetone). NMR($CDCl_3$): 1.57 and 1.74(each 3H, s), 3.46(2H, d, J=4Hz), 3.74(1H, t, J=4Hz), 7.24 (4H, s). In the case of ethanol and piperidine, the corresponding methyl malonates (IIIe and Vb) were obtained in quantitative and 95.0% yields, respectively. The new compounds(Ib, IIIe, and Vb) gave satisfactory elemental analyses. But when Ib was treated with this reagent in t-butanol, t-butyl methyl p-chlorobenzylmalonate(IIIf) and dimethyl p-chlorobenzylmalonate(IIIg) were obtained in about 67 and 17% yields, respectively. These structures were confirmed by the NMR spectrum and the elemental analyses and the yields were determined by the GC and GC-Mass spectra. In this case, the sterically hindered ketene methyl ester corresponding to IV would be attacked with difficult by bulky t-butanol, and water containing in ether would attack to produce methyl p-chlorobenzylmalonic acid, which was further converted to IIIg with an excess of CH_2N_2.

ACKNOWLEDGEMENT The authors wish to express sincere gratitude to Tateyama Kasei Co. Ltd. for the supply of malonic acid and p-chlorobenzylmalonic acid. We are also grateful to Mr. M. Ogawa for the elemental analyses.

REFERENCES AND NOTES

1) A part of this work was presented at the 59th Meeting of the Hokuriku Branch of the Pharmaceutical Society of Japan, Kanazawa, June 1983. 2) Y. Oikawa, H. Hirasawa, and O. Yonemitsu, Tetrahedron Lett., 1978, 1759. 3) K. Pihlaja and M. Seilo, Acta Chem. Scand., 23, 3003 (1969). 4) H. Staudinger and H. Schneider, Ber., 56B, 699(1923). 5) H. Junek, E. Ziegler, U. Herzog, and H. Kroboth, Synthesis, 1976,332.

(Received June 23, 1983)