Tetrahedron Letters No. 40, pp 4071 - 4074, 1972. Pergamon Press. Printed in Great Britain.

ALLYLIC FUNCTIONALIZATION OF α-METHYLMUCONATES: A NEW SYNTHESIS OF 2,5-DIHYDRO-2,4-DISUBSTITUTED THIOPHENES, FURANS, AND PYRROLES

Philip L. Stotter (1a), Steven A. Roman (1b), and Charles L. Edwards (1c)
Department of Chemistry, The University of Texas at Austin, Austin, Texas, 78712

(Received in USA 25 July 1972; received in UK for publication 1 September 1972)

In an earlier communication (3), the preparation and dienophilic character of methyl 4-carbomethoxy-2,5-dihydro-2-thiopheneacetate 2a were demonstrated as part of a new stereospecific synthesis of (cis-1,2-dialkyl)cyclohexanecarboxylic acids and angularly substituted polycyclic systems. As an alternative preparation of 2a, as well as of its oxygen and nitrogen analogues (2b, 2c), we have devised a general synthesis involving a novel, internal Michael-type addition (2). Since the substituents at C-2 and C-4 offer the possibility of further modification, these preparations of compounds 2a,b,c provide access to the title compounds of generalized structure 3.

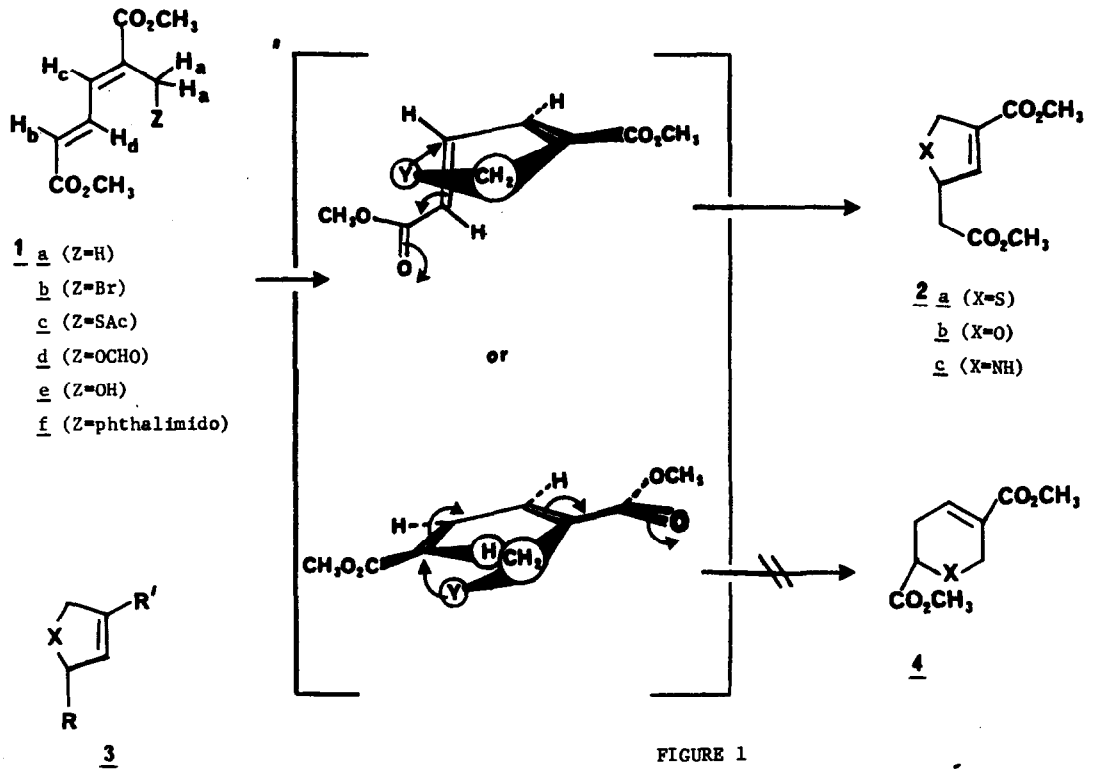


FIGURE 1

The starting material chosen for these syntheses of 2 was the known dimethyl trans,trans-α-methylmuconate 1a (Z=H)(4, 5). Although a variety of preparations of 1a have been reported, we have found it most convenient to prepare 1a via a Wittig reaction of methyl fumaraldehydate(6) and α-carbomethoxyethylidene triphenylphosphorane(7)(refluxing benzene for 2.5 hours). Recrystallized 1a, mp 54-55°C (from ether-hexane), was isolated in 85% yield; its physical constants and spectral data are consistent with those previously reported(4, 5) for the trans,trans structure indicated above, the isomer expected from such Wittig reactions(7). Using a modification of the procedure previously reported(5), molar quantities of 1a could reproducibly be brominated at the allylic methyl in greater than 50% yield (n-bromosuccinimide with benzoyl peroxide in refluxing chlorobenzene), producing 1b, mp 96-98°C (from ether), reported(5) 97-98°C.

Direct nucleophilic substitution of this allylic bromide readily led to desired crystalline sulfur, oxygen, and nitrogen derivatives(8). Exposure of 1b to potassium thiolacetate in dry dimethylformamide (15 minutes at room temperature, followed by 10 minutes at 65°C) produced 1c (Z=SAc) in 67% yield, mp 88.5-89.5°C (from ether-petroleum ether). Similarly, a solution of sodium formate and 1b in dry dimethylformamide (70°C for three hours) formed formate ester 1d (Z=OCHO) in 91% yield, mp 70-71°C (from ether-petroleum ether). This formate was easily hydrolyzed (without cyclization to 2b) by the action of excess potassium carbonate in aqueous tetrahydrofuran (65°C for 3.5 hours). The crystalline alcohol 1e (Z=OH), isolated in 88% yield, was easily recrystallized from ether, mp 65°C. Finally, as reported(5), from 1b

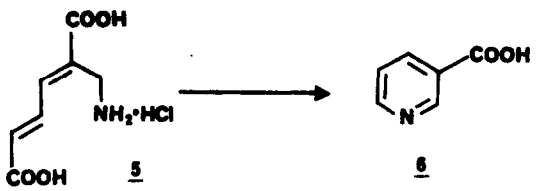
TABLE 1. Pertinent Spectral Data for Compounds 1

	$CHCl_3$ λ max EtOH λ max(log ε)	NMR: as δ from TMS, solvent $CDCl_3$. J in Hz H_a	H_b	H_c	H_d	methyl esters	other protons
1a (Z=H)	5.85, 6.23μ 275mμ(4.43)	2.03 (3H)d. J=1.5	6.05 (1H)d. J=14	7.07 (1H)d. of q. J=12,1.5	7.42 (1H)d. of d. J=14,12	3.69 (3H)s. 3.71 (3H)s.	
1b (Z=Br)	5.87, 6.23μ 279mμ(4.42)	4.40 (2H) broad s.	6.32 (1H)d. J=14	7.31 (1H)d. J=12	7.65 (1H)d. of d. J=14,12	3.79 (3H)s. 3.83 (3H)s.	
1c (Z=SAc)	5.84, 6.23μ 276mμ(4.38)	4.01 (2H) broad s.	6.20 (1H)d. J=15	7.25 (1H)d. J=12	7.75 (1H)d. of d. J=15,12	3.79 (6H) broad s.	2.31 (3H)s. $SCOCH_3$
1d (Z=OCHO)	5.82, 6.22μ 269mμ(4.47)	5.15 (2H)d. J=1	6.31 (1H)d. J=14.5	7.48 (1H)d. J=12	7.72 (1H)d. of d. J=14.5,12	3.80 (3H)s. 3.83 (3H)s.	8.11 (1H)t. J=1 OCHO
1e (Z=OH)	2.73, 5.85, 6.21μ 270mμ(4.48)	4.52 (2H) broad s.	6.25 (1H)d. J=15	7.27 (1H)d. J=12	7.70 (1H)d. of d. J=15,12	3.78 (3H)s. 3.81 (3H)s.	5.35 (1H)s. OH
1f (Z= phthalimido)	5.72, 5.82, 6.21μ 2.19mμ(4.65) 2.22mμ(4.36) 2.30mμ(4.33) 2.73mμ(4.41)	4.79 (2H)s.	6.38 (1H)d. J=15	7.43 (1H)d. J=12	7.95 (1H)d. of d. J=15,12	3.78 (3H)s. 3.81 (3H)s.	7.78 (4H)m. aromatic

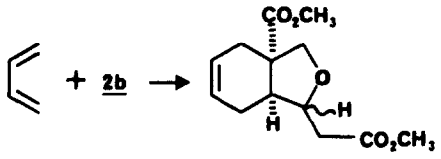
and potassium phthalimide in dry dimethylformamide (overnight at room temperature, then 30 minutes at 60°C) the phthalimido derivative 1f was prepared; dilution of the reaction mass with water produced a copious precipitate (greater than 85% yield) which could be recrystallized from ether, mp 132-133°C, reported (5) 134°C. Spectral data for compounds 1 summarized in Table 1 suggest that for all these structures the disubstituted olefin has maintained a trans configuration (J_{b-d}=14 to 15 Hz). However, isomerization of the trisubstituted olefin during allylic bromination and/or subsequent nucleophilic displacement cannot be ruled out by these data. That these reactions have occurred without double bond isomerization, at least in the preparation of 1c, was demonstrated conclusively by X-ray crystallographic determination (9) of 1c as the trans,trans isomer.

Cyclized structures 2 were readily prepared from 1 via an internal 1,4-addition as indicated in figure 1. Methanolysis of 1c (catalytic sodium methoxide in methanol for one hour at room temperature) provided, via an intermediate mercaptide which cyclized as it was formed, the dihydrothiophene 2a in 71% yield; this material was identical in all respects to that decribed earlier (3). Similarly, the action of catalytic potassium t-butoxide in t-butanol (one hour at 45°C) cyclized alcohol 1e to the liquid dihydrofuran 2b (in 90% yield), bp 97-99°C/0.5 mm. The spectral properties of this heterocyclic diester were consistent with structure 2b and were appropriately similar to those reported for 2a. Conversion of phthalimido derivative 1f to the unstable dihydropyrrole 2c was effected in 48% yield by removing the phthaloyl group as phthalhydrazide (exposure for four hours to one equivalent anhydrous hydrazine in refluxing methanol-methylene chloride, 4:1); the intermediate primary amine cyclized under these conditions and the oily secondary amine was isolated from the cooled reaction mass by addition of one equivalent sodium methoxide, removal of the solvent, and extraction of the amorphous ionic residue with ether. Crude 2c showed spectral properties consistent with its assigned structure and appropriately similar to 2a. It was readily converted into a stable crystalline derivative, its N'-phenyl thiourea (from phenyl isothiocyanate in carbon tetrachloride) in high yield, mp 129-131°C (from ether).

It is not surprising that these in vitro cyclizations of appropriately functionalized α-methylmuconates produce exclusively five-membered heterocycles 2, rather than six-membered heterocycles 4 (via 1,6-conjugate addition). The latter cyclization would have necessitated intramolecular nucleophilic addition at the δ-carbon of a near-planar, conjugated, cisoid diene ester (see fig. 1); its transition state would thus have required significantly more steric constraint and steric compression than does that of the observed 1,4-conjugate addition. However, it should be noted that 1,6-addition of this type has been postulated (5) as an intermediate step in the apparent in vivo conversion of amino acid 5 to nicotinic acid 6 by cultures of Xanthomonas pruni.



Compound 2b has been shown to react effectively and in good yield with butadiene under conditions similar to those required for cycloadditions of 2a (3). However, under these same conditions, no stable adducts of butadiene and 2c, or its N-formyl derivative (from chloral in chloroform (10) on 2c) could be obtained; and, in fact, the nitrogen heterocycles were themselves destroyed.



Acknowledgements

The authors wish to acknowledge support of this research from the National Science Foundation, the Robert A. Welch Foundation (Grant F-345), and Research Corporation. The principal author also wishes to thank Professor Gilbert Stork for his sound advice in the early stages of this work.

References and Footnotes

1. (a) Author to whom correspondence should be addressed at The University of Texas at Austin.
   (b) Robert A. Welch Foundation Postdoctoral Fellow, 1969; present address: Shell Development Co., Modesto, California.
   (c) Robert A. Welch Foundation Predoctoral Fellow, 1971.
2. The principal investigator began the initial investigation of this project at Columbia University.
3. G. Stork and P. L. Stotter, J. Amer. Chem. Soc., 91, 7780 (1969).
4. M. Ohno, Y. Inouye and T. Sugita, Bull. Inst. Chem. Res., Kyoto University, 38, 9 (1960).
5. J. O. Harris and F. Binns, Nature, 179, 475 (1957).
6. (a) R. Rambaud and M. Vessiere, Bull. Soc. Chim. France, 1567 (1961).
   (b) Prepared most easily by selective ozonolysis of methyl sorbate. Details will be described in a communication now in preparation.
7. H. O. House and G. H. Rasmusson, J. Org. Chem., 26, 4278 (1961).
8. Satisfactory analytical data were obtained for all new crystalline compounds and distillable liquids.
9. The authors wish to thank Mr. G. L. Cupper and Professor R. E. Davis of the University of Texas at Austin for performing this X-ray structure determination.
10. For procedure see: F. F. Blicke and Chi-Jung Lu, J. Amer. Chem. Soc., 74, 3933 (1952).