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INTERCEPTION OF [2+2] CYCLOADDUCTS IN THE ZINC BROMIDE MEDIATED REACTION OF DI-TERT-BUTYL METHYLENEMALONATE WITH SIMPLE ENOL ETHERS

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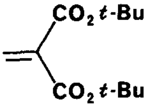
Abstract: Di-tert-butyl methylenemalonate combines efficiently with simple enol ethers at -78°C in the presence of zinc bromide to give [2+2] cycloadducts.

Recently we reported a convenient synthesis of di-tert-butyl methylenemalonate (DBMM, 1),[2] which is considerably more stable than simpler congeners and suitable for synthetic exploration. Because of the potential for activation of 1 via metal ion chelation, initial experiments have focused on its behavior as an acceptor in Lewis acid mediated Michael reactions. As developed by Mukaiyama, the latter conventionally includes an aqueous workup and isolation of the classical Michael adduct.[3] In some variations, however, products of silyl transfer[4] and formal [2+2][5] and [4+2][5c,6] cycloaddition have been isolated. We record here that DBMM, in zinc bromide[7] mediated reactions with simple enol ethers at low temperature, characteristically gives rise to cyclobutanes in good to excellent yields.

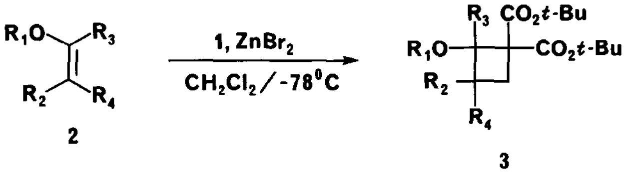


1

When excess n-butyl vinyl ether (2a, Table 1) was added to a 1:1 mixture of DBMM and zinc bromide in dichloromethane at -78°C and the reaction quenched with water after 0.5h, cycloadduct 3a was obtained in good yield.[8,9] Especially diagnostic in identifying 3a as a cyclobutane and eliminating other possibilities were saturated ester carbonyl absorption at 1724 cm^{-1}, the lack of C=C absorption near 1650 cm^{-1}, proton NMR absorption characteristic of a saturated monoether, and ^{13}C NMR absorption consistent with a saturated four-membered ring carbon framework.[10] Under the same conditions, dihydropyran (2b) cleanly afforded 3b in comparable yield.

In contrast to these results, when ketone-derived substrates 2c and 2e were subjected to

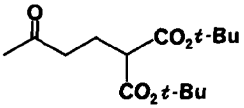
Table 1. Cyclobutanes from DBMM and Enol Ethers



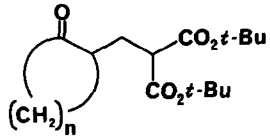
	R1	R2	R3	R4	%
a	n-Bu	H	H	H	72
b	$-(CH_2)_3-$		H	H	80
c	CH_3	H	CH_3	H	71[a]
d	CH_3	H	$-(CH_2)_3-$		67
e	CH_3	H	$-(CH_2)_4-$		90
f	CH_3	H	$-(CH_2)_5-$		89
g	CH_3	H	$-(CH_2)_6-$		(90)[b]

[a] Contains ~ 4% ketomalonate 4. [b] Crude yield

the same protocol, Michael adducts 4 and 5a were isolated in 60 and 76% yields, respectively. Closer scrutiny of these reactions revealed, however, that local heating effects and stringency of workup conditions were very likely responsible for this divergence in behavior. When reactants were first combined at -130°C, warmed to -78°C, and the reaction then worked up by quenching with pyridine at -78°C,[11] cycloadducts 3c and 3e were obtained very cleanly. This procedure was then used to prepare the remaining adducts in Table 1.[12]



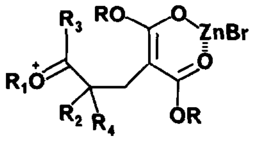
4



5a, n = 4
5b, n = 6

The foregoing reactions are remarkably efficient, the cycloadducts being the only detectable product except for 3c which was accompanied by ~4% of 4. The stability of the small ring β-alkoxymalonate moiety varied considerably with structure, a feature which was revealed especially in the fragility of 3c and 3g. Each of the latter has thus far defied purification because of rapid breakdown on silica gel and neutral alumina and, in the case of 3g, rapid decomposition upon attempted distillation.[13] Characterization was effected spectroscopically and through acid catalyzed hydrolysis to ketomalonates 4 and 5b.

The foregoing results reveal the potency of zinc complexed 1 as an electrophile and the propensity of presumed intermediate 6 to undergo 1,4-closure. Evidently complexation forecloses a nucleophilic role for carbonyl oxygen and directs reaction essentially completely towards carbon-carbon bond formation.[14] This behavior contrasts with the observation that enecarbonyl systems α-substituted with carbonyl or other electron withdrawing π-functionality generally combine directly with electron rich alkenes via inverse electron demand Diels-Alder cycloaddition to give dihydropyrans.[6a,15] Further elaboration of this chemistry as a new variation of thermal [2+2] cycloaddition as well as development of the aforementioned adducts as masked aldehydo- or ketomalonates are in progress.



6 (R = *t*-Bu)

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7. For recent examples of chelation-controlled conjugate addition using zinc salts, see: (a) Posner, G. H.; Hulce, M.; Mallamo, J. P.; Drexler, S. A.; Clardy, J. *J. Org. Chem.* 1981, *46,* 5244; (b) Posner, G. H.; Mallamo, J. P.; Hulce, M.; Frye, L. L. *J. Am. Chem. Soc.* 1982, 104, 4180; (c) Posner, G. H.; Frye, L. L.; Hulce, M. *Tetrahedron* 1984, *40,* 1401; (d) Posner, G. H.; Frye, L. L. *Isr. J. Chem.* 1984, *24,* 88; (e) Posner, G. H.; Kogan, T. P.; Haines, S. R.; Frye, L. L. *Tetrahedron Lett.* 1984, *25,* 2627.

8. (a) IR, ^{1}H NMR, and ^{13}C NMR spectra of all new compounds, and compositional analyses of those stable enough to be purified (vide infra) were consistent with assigned structures; (b)

Control experiments established the necessity of the Lewis acid. In the absence of the latter 1 was inert toward enol ethers at ambient temperature and produced only polymer-like material on heating.

9. **3a**: bp 110-111°(0.05 mm Hg, short path distillation); IR (neat) ν_{max} 1724 cm^{-1}(s); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.91(t, J = 7.0 Hz, 3H), 1.30-1.39 (m, 4H), 1.46 (s, 9H), 1.49(s, 9H), 1.57-1.66 (m, 1H), 2.04-2.17 (m, 2H), 2.35-2.44 (m, 1H), 3.40-3.44 (m, 1H), 3.60-3.71(m, 1H), and 4.37(t, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ13.87(q), 19.25(t), 21.07(t) 25.70(t), 27.45(q), 28.04(q), 31.77(t), 62.62(s), 69.75(t), 75.63(d), 80.73(s), 81.28(s), 167.88(s), and 170.42(s); Found: C, 66.00; H, 9.90.

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11. The same technique was used to isolate products of silyl transfer: ref. 4.

12. The preparation of **3e** exemplifies the general procedure: A suspension of 248 mg (1.10 mmol) of dry $ZnBr_2$ in 2.5 mL of dry CH_2Cl_2 was placed under argon and cooled in a liquid nitrogen/pentane bath (~ -130°C). A solution of 267 mg of DBMM (94% purity, 1.10 mmol) in 2.5 mL of CH_2Cl_2 was added via syringe followed by a solution of 148 mg (1.32 mmol) of 1-methoxycyclohexene in 2.5 mL of CH_2Cl_2. The flask was warmed to -78°C and stirred magnetically for 0.5h. The reaction was then quenched by adding a precooled (-78°C) solution of 348 mg (4.4 mmol) of pyridine in 2.5 mL of CH_2Cl_2. After warming to ambient temperature, the solution was washed twice with 5 mL of saturated aqueous Na_2EDTA, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residue was evaporatively distilled at 0.02 mm Hg and the product collected as an oil which gradually solidified. Yield: 337 mg (90%), mp 79.0-80.5°C(uncor.).

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