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AN ANIONIC 3+2 CYCLIZATION-ELIMINATION ROUTE TO CYCLOPENTENES

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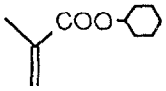
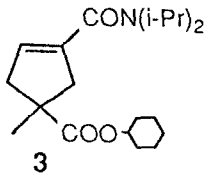
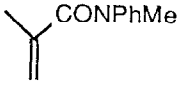
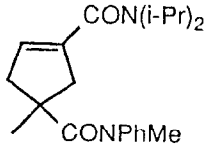
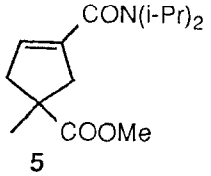
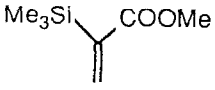
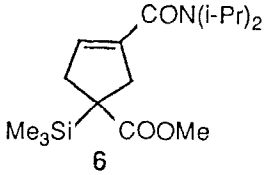
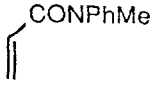
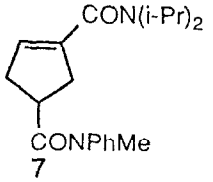
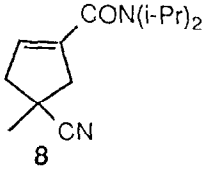
Summary: Anionic 3+2 cyclization-elimination reactions between 1-benzenesulfonyl-2-(N,N-diisopropyl)carboxamidoallyllithium (2) and electron-deficient olefins provide the 4-substituted-N,N-diisopropylcyclopent-1-ene carboxamides 3-8 in yields of 22-89%.

The formal $\pi_s^4 + \pi_s^2$ cycloaddition of an allyl anion and an olefin to give a cyclopentyl anion, the anionic 3+2 cyclization, is one of the most straightforward routes to the five membered carbocyclic ring. Early investigations of this approach by Böche, Kauffmann, and Ford revealed the reaction can occur in appropriately substituted systems albeit as a stepwise process.[1] We have reported the β'-lithiation of tertiary methacryl amides give 1-alkyl-2-carboxamidoallyllithium reagents and noted their use and limitations in anionic 3+2 cyclizations.[2] Recently Tanaka and coworkers have reported the formation of the formal dianion 1-benzenesulfonyl-2(N-lithio-N-phenyl)carboxamidoallyllithium and its use as a β-lithio-methacrylic acid and β'-lithiohydroxymethacrylic acid synthetic equivalent.[3] We wish to report methodology in which the benzenesulfonyl group not only activates the β' hydrogen of tertiary methacryl amides for lithiation and directs the incoming electrophile to the sulfonyl substituted carbon, but also acts as a leaving group to provide an anionic 3+2 cyclization-elimination sequence which is useful for the synthesis of cyclopentenes.[4] The overall sequence is shown in Scheme I and summarized in Table I.

Initial lithiation of 1 at -78°C with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) to give 2 is followed by dropwise addition of 1.1 equivalents of the electron-deficient olefin all in tetrahydrofuran (THF). After 1 h at -78°C, and 24 h at room temperature the cyclopentene products are obtained as shown in Table I.[5,6] The proposed intermediates are outlined in Scheme I and no more than a few percent of the alternative regioisomeric products can be present. We believe the reaction to be stepwise, based on analogy,[1,2] but that has not yet been established.

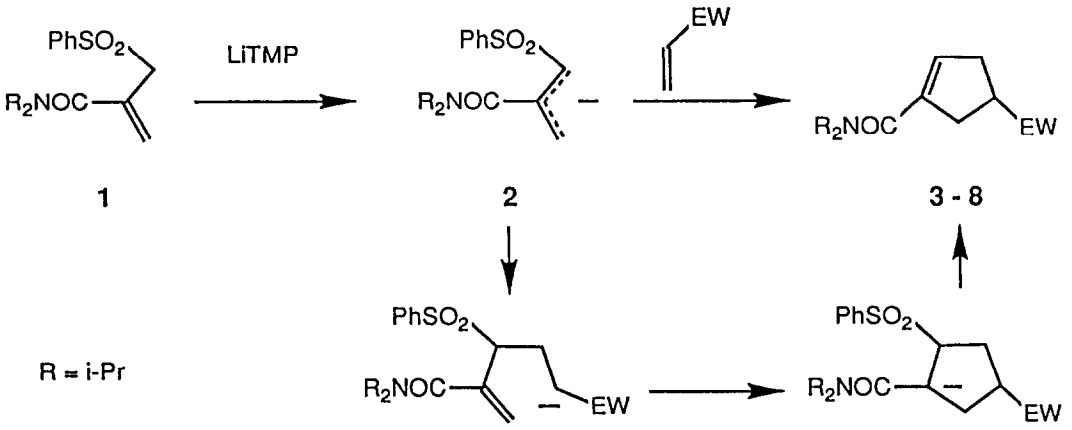
Table I. Reaction of 1-Benzenesulfonyl-2-(N,N-diisopropyl)carboxamidoallyllithium (2) with Electron-Deficient Olefins.[a]

Olefin	Product	Yield[b]
	 **3**	89%
	 **4**	65%
	 **5**	59%
	 **6**	57%
	 **7**	33%
	 **8**	22%

[a]1. 1.1 eq of olefin, THF, -78°C; 2. Ambient temperature 24 h.

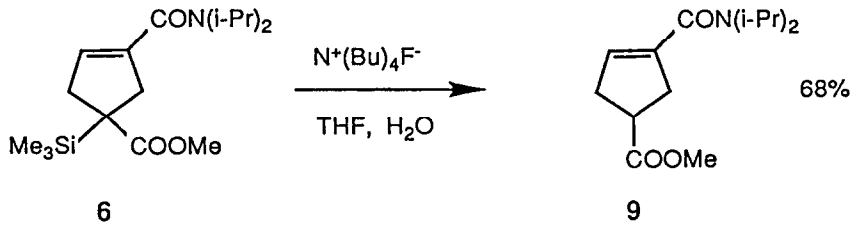
[b]Yields are for analytically pure material.

Scheme I



Electron-deficient olefins without alpha substituents give poor yields of cylopentene products as shown for 7. Therefore, we have used two steps in order to synthesize the cyclopentene 9. First cyclopentene 6 is formed in 57% yield via the cyclization reaction between 2 and methyl 2-trimethylsilylpropenate. Then 6 is treated with tetrabutylammonium fluoride in wet THF to give cyclopentene 9 in 68% yield as shown in Scheme II. A one-pot variant of this reaction provides 9 in 55% yield.

Scheme II



In summary this work provides a formal 3+2 cyclization-elimination sequence which appears to be a synthetically useful one-pot reaction for the synthesis of various substituted cyclopentenes. We are currently investigating the scope and mechanism of the reaction as well as the extension of the approach to other functionalities.

Acknowledgement. We are grateful to the National Institutes of Health for support of this work.

References and Notes

1. For a summarizing review see T. Kauffmann, Top. Curr. Chem., 92, 109 (1980).

2. a) P. Beak, D. J. Kempf, and K. D. Wilson, J. Am. Chem. Soc., 107, 4745 (1985).
   b) P. Beak and K. Wilson, J. Org. Chem. (1986), in press.

3. K. Tanaka, H. Yoda, A. Kaji, Tetrahedron Lett., 26, 4747 (1985); K. Tanaka, H. Yoda, and A. Kaji, Ibid., 26, 4751 (1985).

4. For a recent discussion and leading references about cyclopentane synthesis see B. M. Trost and T. N. Nanninga, J. Am. Chem. Soc., 107, 1293 (1985).

5. Compound 1 is prepared in 30% yield by the reaction of 2-bromomethylacrylic acid and the sodium salt of benzenesulfinic acid in methanol containing 1 equiv. of NaOH followed by treatment with thionyl chloride and then diisopropylamine: mp 93-[illegible]°C. NMR δ ($CDCl_3$): 7.52-7.98 (m, 5 H), 4.5 (b, 1 H, $-C\underline{H}(CH_3)_2$), 4.49 (s, 2 H, $=CH_2$), 4.15 (s, 2 H, $-C\underline{H}_2SO_2Ph$), 3.45 (b, 1 H, $-C\underline{H}(CH_3)_2$), 1.33 (bd, 12 H, $CON(i\text{-}Pr)_2$). All products are characterized by ^1H NMR, mass spectrometry, IR, and elemental analysis. The experimental and analytical data for cyclopentene 5 is provided as a representative example. To a stirred solution of LiTMP (1.29 mmol) in 40 ml THF at -78°C was added a solution of 1 (0.4 g, 1.29 mmol) in 15 ml THF and the resulting mixture was stirred for 5 min at -78°C. A solution of methyl methacrylate (0.15 ml, 1.42 mmol) in 40 ml of THF was then added dropwise and the mixture was stirred for 1 h at -78°C and then warmed to RT for 24 h. Workup and purification by medium pressure liquid chromatography on silica gel using EtOAc/hexane as eluent gave 203.9 mg (59%) of 5: ^1H NMR δ (360 MHz, $CDCl_3$): 5.59 (m, J = 2 Hz, 1 H, =CH), 4.1 (b, 1 H, $C\underline{H}(Me)_2$), 3.70 (s, 3 H, COOMe), 3.4 (b, 1 H, $C\underline{H}(Me)_2$), 3.14 (dm, J = 16.4 Hz, 1 H, $C\underline{H}H$), 3.0 (dm, J = 17.1 Hz, 1 H, $C\underline{H}H$), 2.50 (dm, J = 16.4 Hz, 1 H, $C\underline{H}H$), 2.35 (dm, J = 17.1 Hz, 1 H, $C\underline{H}H$), 1.37 (s, 3 H, CCH_3), 1.3 (b, 12 H, $CON(i\text{-}Pr)_2$). ^{13}C NMR δ ($CDCl_3$): 178.0 (COOMe), 168.1 ($CON(i\text{-}Pr)_2$), 138.3 ($=CR_2$), 126 (=CHR), 52.1 ($COO\underline{C}H_3$), 49.5 (b, $CH(Me)_2$), 48.0 ($R_2\underline{C}MeCOOMe$), 45.8 (CH_2), 44.5 (CH_2), 25.8 (CH_3), 21.0 ($CON(i\text{-}Pr)_2$). Mass Spectrum: M^+ = 267. Anal. Calc for $C_{15}H_{25}O_3N$: C, 67.38; H, 9.43; N, 5.24. Found: C, 67.68; H, 9.25; N, 5.16. IR (Nujol Mull): 1730, 1618 cm^{-1}.

6. The use of β-alkyl-α,β-unsaturated esters and amides as acceptor olefins under these conditions has resulted in recovery of starting materials.

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