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1-BROMO-1-ETHOXYCYCLOPROPANE: A NEW REAGENT FOR CYCLOBUTANONE SYNTHESIS

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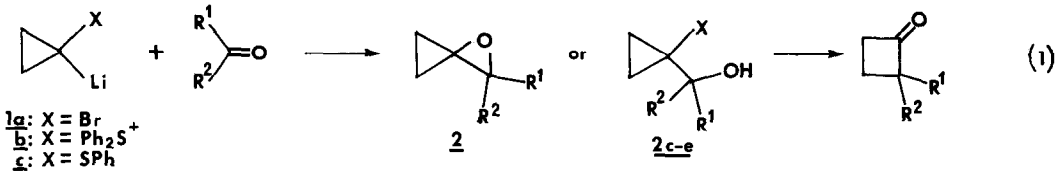
Summary: A variety of of cyclobutanones have been prepared in high yield from 1-bromo-1-ethoxycyclopropane via lithiation, addition to aldehydes or ketones, and mild acid-catalyzed rearrangement of the adducts.

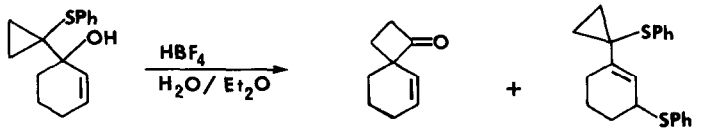
Cyclobutanones have attained a position of considerable synthetic importance in recent years. They serve as useful precursors of five-,[1] six-,[2] and eight-membered[3] rings, as well as a wide variety of highly functionalized acyclic fragments.[4,5] A number of methods are available for the synthesis of cyclobutanones, and one of the most general is the acid-catalyzed ring expansion of oxaspiropentanes (2) or heteroatom-substituted cyclopropyl carbinols (2c-e), which in turn are usually prepared by the addition of cyclopropyl carbanions (1) to carbonyl compounds (eq 1).[6]



(1)

1a: X = Br
b: X = Ph_2S^+
c: X = SPh
d: X = SePh
e: X = OMe

Although a number of heteroatom-substituted cyclopropyl carbanions have been introduced as reagents for cyclobutanone synthesis, each suffers from some drawback. 1-Bromocyclopropyllithium (1a)[7] reacts with ketones to give modest yields of cyclobutanones (via oxaspiropentane intermediates), but fails with aldehydes. Cyclopropyl diphenylsulphonium ylide (1b)[8] produces cyclobutanones in good yield from both saturated aldehydes and ketones (again via an oxaspiropentane) but undergoes 1,4- rather than 1,2-addition with enones and enals. 1-Phenylthiocyclopropyllithium (1c)[9] undergoes exclusive 1,2-addition, but the derived carbinols (2c) undergo rearrangement with difficulty, and thiophenol produced during the rearrangement often reacts to give by-products. For example, in this laboratory, fluoboric acid-catalyzed rearrangement of 3 produced low yields of cyclobutanone 4 along with substantial amounts of the thiophenol adduct 5 (eq 2).[10] Lithiocyclopropyl selenides (1d)[11] have also been investigated, but seem to offer no advantage over the sulfide reagents.

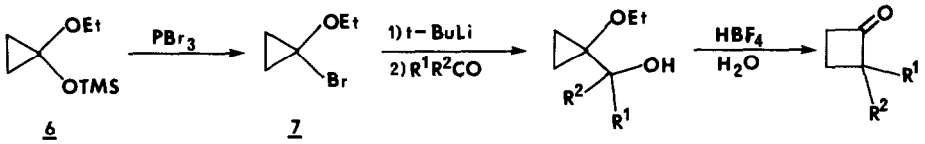


(2)

1-Methoxycyclopropyllithium (1e), introduced by Cohen,[12] is an improvement over the sulfur-based variants in that rearrangement of the derived adducts (2e) are, as expected, greatly accelerated and much cleaner. However, preparation of 1-methoxy-1-phenylthiocyclopropane (the precursor to 1e) requires a four-step synthesis from 1,3-dibromopropane or a two-step synthesis from commercially available, but expensive, phenylthiocyclopropane.

An alternative approach to formation of an alkoxycyclopropyllithium reagent would be lithiation of an alkoxybromocyclopropane via metal-halogen exchange with t-BuLi. Although reports of the synthesis of various alkoxyhalocyclopropanes have appeared in the literature,[13] there appears to be no synthetically useful procedure available. It has been found, however, that 1-bromo-1-ethoxycyclopropane (7) can be conveniently prepared in good yield by reaction of PBr_3 with 1-ethoxy-1-trimethylsiloxycyclopropane (6, eq 3) in the absence of pyridine or solvent. This cyclopropyl ketal can in turn be prepared in one step from inexpensive ethyl 3-chloropropionate.[14]

Lithiation of 7 occurs rapidly upon treatment with t-BuLi in ether at -78°, and reaction of the derived 1-ethoxycyclopropyllithium with a wide variety of aldehydes and ketones occurs cleanly and in high yield. After simple extractive work-up and removal of volatile components, cyclopropyl carbinols of greater than 90% purity can be isolated, often in quantitative yield. Rearrangement occurs under very mild conditions, often within minutes at room temperature after addition of a small amount of 48% aqueous HBF_4 to an ether solution of the adduct. Although conversion of aldehydes and ketones to cyclobutanones can be carried out in one pot by quenching the organolithium reaction with excess HBF_4, the overall yields of cyclobutanones from this method are 10-20% lower than from the two-step procedure.



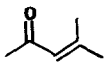
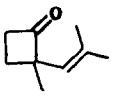
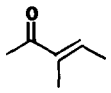
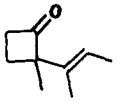
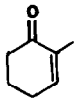
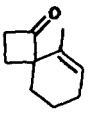
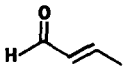
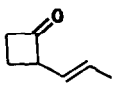
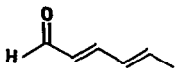
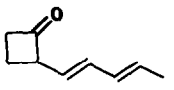
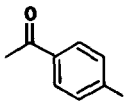
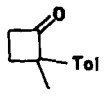
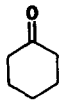
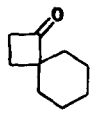
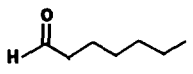
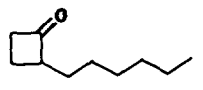
6 7 (3)

Table 1 lists a variety of cyclobutanones which have been prepared using this new reagent. Yields are uniformly high, and a variety of both saturated and unsaturated aldehydes and ketones have been utilized. The rates of rearrangement of the intermediate adducts generally parallel carbocation stabilities, with the adducts from α,β-unsaturated carbonyls rearranging fastest, and those from saturated aldehydes rearranging slowest.

Thus it has been shown that 1-bromo-1-ethoxycyclopropane is an extremely useful reagent for the synthesis of a wide variety of monocyclic cyclobutanones. It has a considerable practical advantage over 1-methoxy-1-phenylthiocyclopropane in that it can be prepared in only two steps from inexpensive starting materials. Efforts are currently underway to apply this methodology to the synthesis of substituted cyclobutanones and bicyclo[n.2.0] ketones. Experimental procedures follow for the preparation of 1-bromo-1-ethoxycyclopropane and its use in cyclobutanone synthesis.

1-Bromo-1-ethoxycyclopropane: 1-Ethoxy-1-trimethylsiloxycyclopropane[14] (3.13g, 3.64 mL, 0.0180 mole) and PBr_3 (3.58g, 1.24 mL, 0.0132 mole) were mixed and allowed to stand at room temperature for 6 hours. Direct Kugelrohr distillation at 60° and 25 Torr afforded a mixture of the product and TMSBr. Pentane (20 mL) was added to this mixture and this solution was washed with 10 mL of saturated Na_2CO_3 solution. The aqueous layer was extracted twice with

Table 1. Conversion of Aldehydes and Ketones to Cyclobutanones

Carbonyl Compound	Cyclobutanone Product	Rearrangement[a] Conditions	Overall[b] Yield(%)
		0.5 eq, 10 min	69
		0.5 eq, 60 min	83
		0.5 eq, 20 min	78
		0.5 eq, 10 min	81
		0.5 eq, 10 min	91
		2.0 eq, 2 h	82
		2.0 eq, 30 min	81
		4.0 eq, 48 h	81

a. Equivalents of 48% aqueous HBF_4 used and time needed for complete rearrangement of the intermediate adducts. b. Yield of pure material isolated by Kugelrohr distillation.

10 mL portions of pentane, and the combined organic phases were dried with $MgSO_4$. The pentane was removed by distillation at atmospheric pressure, and the residue was distilled to afford 1.62g of product (55% yield), BP_{25} = 48-50°. NMR (CCl_4) δ 3.60 (2H, q, J = 7 Hz), 1.15 (5H, m). 1-Bromo-1-ethoxycyclopropane is somewhat unstable at room temperature, but can be stored at -20° for weeks without decomposition.

Synthesis of cyclobutanones (general procedure): 1-Bromo-1-ethoxycyclopropane (0.264g, 0.197 mL, 1.60 mmole) was added to t-BuLi (2.35 M in pentane, 1.30 mL, 3.00 mmole) in 5 mL of dry ether at -78° under nitrogen. After 5 min at -78°, 1.00 mmole of the aldehyde or ketone was added as a solution in 2 mL of dry ether (pre-cooled to -78°) via stainless steel cannula using nitrogen pressure. After an additional 10 min at -78°, the reaction was warmed to 0° in an ice bath and 1 mL of saturated NH_4Cl solution was added. The phases were separated, and the aqueous phase was extracted twice with 5 mL of ether. The combined organic phases were dried ($MgSO_4$) and condensed under vacuum to yield the cyclopropyl carbinol. This adduct

was dissolved in 10 mL of ether (ca. 0.1 M solution), and 0.5 to 4.0 equivalents (see Table 1) of 48% aqueous HBF_4 (ca. 7.4 M) were added After TLC analysis indicated that all of the carbinol had rearranged, the reaction was washed with 1.2 equivalents of 1 M Na_2CO_3 solution. The aqueous phase was extracted twice with 5 mL portions of ether, and the combined organic phases were dried ($MgSO_4$) and concentrated under vacuum. The cyclobutanones produced were isolated by Kugelrohr distillation.

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Literature Cited

1) Gadwood, R.C. J. Org. Chem. 1983, 48, 2098, and references therein.

2) Wilson S.R.; Mao, D.T. J. Chem. Soc., Chem. Commun. 1978, 479; Danheiser, R.L.; Martinez-Davila, C.; Sard, H. Tetrahedron 1981, 37, 3943; Cohen, T.; Bhupathy, M.; Matz, J.R. J. Am. Chem. Soc. 1983, 105, 520; Bhupathy, M.; Cohen, T. J. Am. Chem. Soc. 1983, 105, 6978.

3) Gadwood, R.C.; Lett, R.M. J. Org. Chem. 1982, 47, 2268; Paquette, L.; Andrews, D.R.; Springer, J.P. J. Org. Chem. 1983, 48, 1147.

4) Trost, B.M. Accnts. Chem. Res. 1974, 7, 85; Trost, B.M.; Bogdanowicz, M.J.; Kern, J. J. Am. Chem. Soc. 1975, 97, 2218; Trost, B.M.; Preckel, M.; Leichter, L.M. ibid. 1975, 97, 2224.

5) For selected references to other uses of cyclobutanones in synthesis, see: Trost, B.M.; Ornstein, P.L. J. Org. Chem., 1983, 48, 1131.

6) Cyclobutanones can also be prepared from vinylic and acetylenic cyclopropanols and from 1-aminomethylcyclopropyl amines: Wasserman, H.H.; Clagett, D.C. J. Am. Chem. Soc. 1966, 88, 5368; Wasserman, H.H.; Cochoy, R.E.; Baird, M.S. ibid. 1969, 91, 2375; Wasserman, H.H.; Hearn, M.J.; Haveaux, B; Thyes, M. J. Org. Chem. 1976, 41, 153; Wasserman, H.H.; Hearn, M.J.; Cochoy, R.E. ibid. 1980, 45, 2874.

7) Hiyama, J.; Takehara, S.; Kitatani, K.; Nozaki, H. Tetrahedron Lett. 1974, 3295; Braun, M.; Dammann, R.; Seebach, D. Chem. Ber. 1975, 108, 2368.

8) Trost, B.M.; Bogdanowicz, M.J. J. Am. Chem. Soc. 1973, 95, 5311; Trost, B.M.; Bogdanowicz, M.J. ibid. 1973, 95, 5321.

9) Trost, B.M.; Keeley, D.E.; Arndt, H.C.; Rigby, J.H.; Bogdanowicz, M.J. J. Am. Chem. Soc. 1977, 99, 3080; Trost, B.M.; Keeley, D.E.; Arndt, H.C.; Bogdanowicz, M.J. ibid. 1977, 99, 3088.

10) For additional discussion and a partial solution to this problem, see: Trost, B.M.; Jungheim, L.N. J. Am. Chem. Soc. 1980, 102, 7910.

11) Halazy, S.; Zutterman, F.; Krief, A. Tetrahedron Lett. 1982, 23, 4385.

12) Cohen, T.; Matz, J.R. J. Am. Chem. Soc. 1980, 102, 6900; Cohen, T.; Matz, J.R. Tetrahedron Lett. 1981, 22, 2455.

13) van der Vecht, J.R.; Steinberg, H.; de Boer, Th.J. Recl. Trav. Chim. Pays-Bas 1977, 96, 313; Jorritsma, R.; Steinberg, H.; de Boer, Th.J. ibid. 1981, 100, 194; van Tilborg, M.W.E.M.; van Doorn, R.; Nibbering, N.M.M. J. Am. Chem. Soc. 1979, 101, 7617; Smith, N.P.; Stevens, I.D.R. Tetrahedron Lett. 1978, 22, 1931; Moss, R.A.; Shieh, W.-C. ibid. 1978, 22, 1935.

14) Ruhlmann, K. Synthesis 1971, 236.

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