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C-Alkylation of Phenylthio Aziridine Carboxylates†

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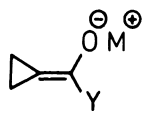
The N-*t*-butyl and N-benzyl aziridine carboxylic acid phenylthiol esters are deprotonated in the α-carbonyl position and alkylated by alkyl halides, by aldehydes, and by nitrostyrene. The diastereoselectivities in the additions to trigonal centers range from 72 to 88% (rel. topicity *lk* with benzaldehyde).

The enolates of cyclopropane carboxylic acid derivatives are not readily generated and, once formed, they are highly reactive. Actually, they may not have an enolate structure 1 (*i-strain*) but be the tautomeric α-metallo carbonyl derivatives 2. For a general discussion and leading references see our previous papers on such species,[1] on related compounds,[2] and on the structure of "normal" lithium enolates.[3]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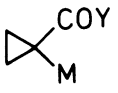
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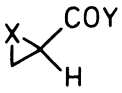
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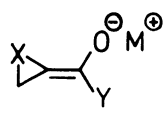
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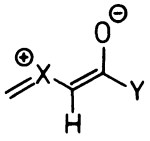
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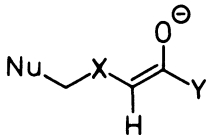
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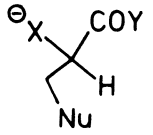
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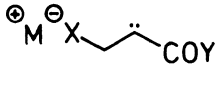
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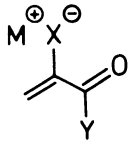
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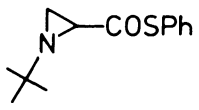
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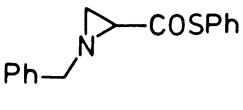
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Deprotonation of oxirane and aziridine carboxylic acid derivatives 3 → 4 (X = O or NR) is expected to be additionally hampered by ring opening, which may occur thermally[4] (→ 5) or by nucleophilic attack on the precursor 3 (→ 6 or 7)[5,6] or else by α- or β-elimination in the desired intermediate (→ 8 or 9).[7-10] On the other hand, base catalyzed epimerization of aziridyl ketones[11,12] and some electrophilic substitutions on oxirane and aziridine carbon atoms, which take place through

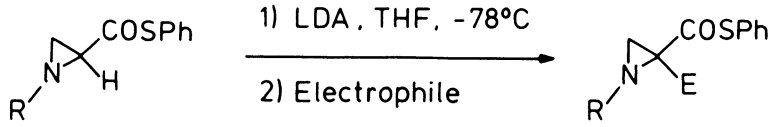
† *Warmly dedicated in admiration to Professor Teruaki Mukaiyama at the occasion of his 60th birthday.*

anionoid intermediates without ring opening, have been described in the literature.[7,10a,13-15]

In our attempts to generate metallated three-membered heterocyclic derivatives such as 4, we have now found that the phenylthiol esters 10 and 11[16] are readily deprotonated and alkylated (→ 12 - 18). This is especially surprising since thiol esters are known to be highly efficient acylating reagents for amines;[17] under the same conditions the corresponding methyl or ethyl esters decomposed.

Treatment of the thiol ester 10 with LDA in THF at -78°C for 30 min. followed by the addition of a carbonyl compound or nitrostyrene at -100°C gave the corresponding products 12 - 14 in good yields and moderate diastereoselectivities (88:12 to 72:28) (Table 1). If methyl iodide was used as the electrophile, DMPU[18] was required as cosolvent to give 15 in 60%. Without cosolvent only starting material and decomposition products were isolated. With benzyl bromide as the electrophile no product was obtained, with or without cosolvent. The thiol ester 11 could also be deprotonated and converted to the products 16 - 18, the reaction with benzaldehyde again showed moderate diastereoselectivity (77:23), and with benzylbromide/DMPU the desired product was obtained.

Table 1. Yields and diastereoselectivities of products 12 - 18

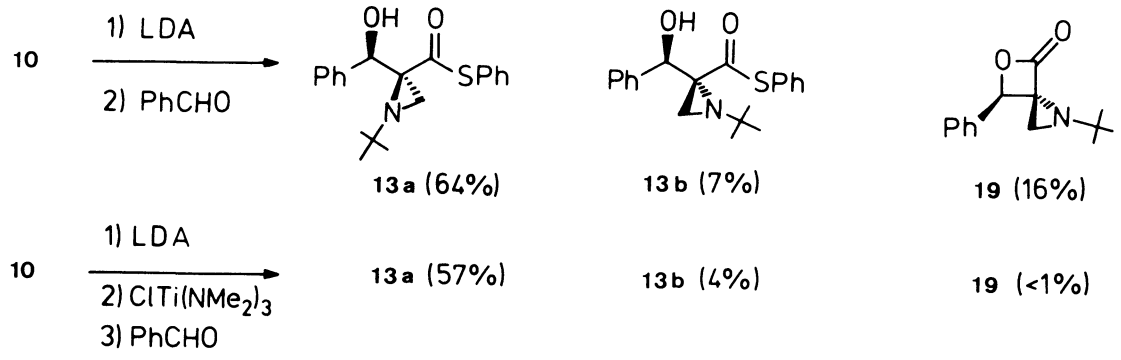


10, 11 **12 - 18**

R	Electrophile	E	Product	% Yield	Diastereosel.[a]
t_{Bu} (10)	CH_3CHO	$CH_3CH(OH)$	12	70	88:12[b]
	PhCHO	PhCH(OH)	13	87[c]	74:26[d]
	nitrostyrene	$NO_2CH_2CH(Ph)$	14	75	72:28
	CH_3I/DMPU	CH_3	15	60	---
Bn (11)	PhCHO	PhCH(OH)	16	71	77:23[b]
	CH_3I/DMPU	CH_3	17	61	---
	$PhCH_2Br$/DMPU	$PhCH_2$	18	62	---

a) Determined by ^{1}H-NMR. b) Diastereoisomers not separated. c) Includes 16% of lactone 19. d) Corrected for lactone 19.

In the reaction of the lithium enolate of 10 with benzaldehyde the lactone 19 was isolated as a minor product besides the two diastereomers 13a and 13b (see Scheme 1). The relative configuration of 19 follows from a NOE experiment. The isomer 13b was converted into the lactone 19 by treatment with LDA in THF at -78°C and warming the solution to -30°C.



Scheme 1.

To improve the diastereoselectivity of the reaction, a solution of the lithium enolate of 10 was first treated with one equivalent of $ClTi(NMe_2)_3$ and then with benzaldehyde. In this way the product was obtained in 61% yield with a diastereoselectivity of 93:7 (see Scheme 1). Furthermore, formation of the lactone 19 was almost completely suppressed.

This work provides a new and attractive access to derivatives of aziridine-2-carboxylic acid. Considering the fact that aziridines represent an important class of alkylating agents with cytotoxic properties,[6a,19] it might give rise to new compounds possessing biological activity. We are now doing experiments aimed at the deprotonation of non-racemic 11 and at the incorporation of products of type 12 - 18 into peptides[20] using the thiol ester moiety directly for N-acylation.

In a typical procedure a solution of 0.94 g (4.0 mmol) of thiol ester 10 in 2 mL of THF was added dropwise to a solution of 4.4 mmol of LDA in 10 mL of THF under argon at -78°C. After 30 min the yellow solution was cooled to -100°C and a solution of 0.53 g (5.0 mmol) of benzaldehyde in 2 mL of THF was added dropwise. The reaction mixture was allowed to warm to -78°C within 30 min and was stirred for another 30 min. After quenching with 5 mL of sat. aq. NH_4Cl and warming to room temperature, workup with ether and flash chromatography (pentane/ether) gave 13a (0.87 g, 64%, mp 110-111°C), 13b (0.10 g, 7%, mp 135-136°C) and 19 (0.15 g, 16%, mp 38-39°C).

References

1) R. Häner, Th. Maetzke, and D. Seebach, Helv. Chim. Acta, 69 (1986), in press; R. Häner and D. Seebach, Chimia, 39, 356 (1985).
2) Y. Kai, P. Knochel, S. Kwiatkowski, J.D. Dunitz, J.F.M. Oth, D. Seebach, and H.-O. Kalinowski, Helv. Chim. Acta, 65, 137 (1982); H.-U. Wagner and G. Boche, Helv. Chim. Acta, 66, 842 (1983).
3) Review: D. Seebach, Proceedings of the Robert A. Welch Foundation Conference on Chemical Research. XXVII. Stereospecificity in Chemistry and Biochemistry, Houston, Texas, Nov. 7-9, 1983, published in the proceedings of the above conference, Welch Foundation, Houston, 1984, p. 93; Th. Laube, J.D. Dunitz, and D. Seebach, Helv. Chim. Acta, 68, 1373 (1985).
4) Ph. DeShong, D.A. Kell, and D.R. Sidler, J. Org. Chem., 50, 2309 (1985), and

refs. cited therein.

5) Cf. the corresponding cyclopropane ring opening: S. Danishefsky, Acc. Chem. Res., 12, 66 (1979).

6) a) O.C. Dermer and G.E. Ham, "Ethylenimine and other Aziridines," Academic Press, New York (1969); J.A. Deyrup, "The Chemistry of Heterocyclic Compounds," ed by A. Hassner, J. Wiley and Sons, New York (1983), Vol. 42, Part 1; b) M. Bartok and K.L. Lang, "The Chemistry of Heterocyclic Compounds," ed by A. Hassner, J. Wiley and Sons, New York (1985), Vol. 42, Part 3.

7) J.J. Eisch and J.E. Galle, J. Am. Chem. Soc., 98, 4646 (1976); J. Organomet. Chem., 121, C10 (1976).

8) J.K. Crandall, W.H. Machleder, and M.J. Thomas, J. Am. Chem. Soc., 90, 7346 (1968); J.K. Crandall and W.H. Machleder, J. Am. Chem. Soc., 90, 7347 (1968); R.L. Camp and F.D. Greene, J. Am. Chem. Soc. 90, 7349 (1968).

9) Cf. also the decarboxylation during Darzens' reaction; see e.g. E.P. Blanchard, Jr. and G. Büchi, J. Am. Chem. Soc., 85, 955 (1963).

10) a) P. Tarburton, D.K. Wall, and N.H. Cromwell, J. Heterocyclic Chem., 13, 411 (1976); ibid. 15, 1281(1978); b) A.E. Pohland, M.C. McMaster, R.C. Badger, and N.H. Cromwell, J. Am. Chem. Soc., 87, 2510 (1965); c) A. Padwa and W. Eisenhardt, J. Org. Chem., 35, 2472 (1970).

11) R.E. Lutz and A.B. Turner, J. Org. Chem., 33, 516 (1968), and refs. cited therein.

12) P. Tarburton, A. Chung, R.C. Badger, and N.H. Cromwell, J. Heterocyclic Chem., 13, 295 (1976), and refs. cited therein.

13) I. Hasan and Y. Kishi, Tetrahedron Lett., 21, 4229 (1980); T.H. Chan, P.W.K. Lau, and M.P. Li, Tetrahedron Lett., 1976, 2667.

14) H.O. House and R.S. Ro, J. Am. Chem. Soc., 80, 2428 (1958).

15) Cf. the Haller-Bauer cleavage of cyclopropyl phenyl ketone: A. Haller and E. Benoist, Ann. Chim., 17, 25 (1921).

16) Originally 10 was prepared as described in the literature: R.A. Gorsky, J. Dagli, V.A. Patronik, and J. Wemple, Synthesis, 1974, 811. We found that it can be prepared equally well from the corresponding ethyl ester and diethylaluminium thiophenoxide (77% yield); see: R.P. Hatch and S.M. Weinreb, J. Org. Chem., 42, 3960 (1977), and refs. cited therein. Thiolester 11 was prepared by the same method in 77% yield.

17) T. Kömives, A.F. Marton, and F. Dutka, J. Prakt. Chem., 318, 248 (1976); B. Boopsingh and D.P.N. Satchell, J. Chem. Soc., Perkin Trans. 2, 1972, 1702.

18) T. Mukhopadhyay and D. Seebach, Helv. Chim. Acta, 65, 385 (1982); M. Eyer and D. Seebach, J. Am. Chem. Soc., 107, 3601 (1985). For a general discussion of the replacement of HMPT by DMPU see: Chimia, 39, 147 (1985).

19) W.A. Remers, "Antineoplastic Agents," Vol. 3 of "Chemistry and Pharmacology of Drugs," J. Wiley and Sons, New York (1984).

20) Introduction of derivatives of aziridine-2-carboxylic acid into peptides has been thoroughly studied; for a review see: K. Okawa, K. Nakajima, and T. Tanaka, Yuki Gosei Kagaku Kyokai Shi, 42, 390 (1984).

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