Tetrahedron Letters,Vol.25,No.37,pp 4141-4144,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain 

# INTRAMOLECULAR ACYLATION OF α-SULFINYL CARBANION
## A NEW GENERAL ROUTE TO 5-METHYLENE-2-CYCLOPENTENONES

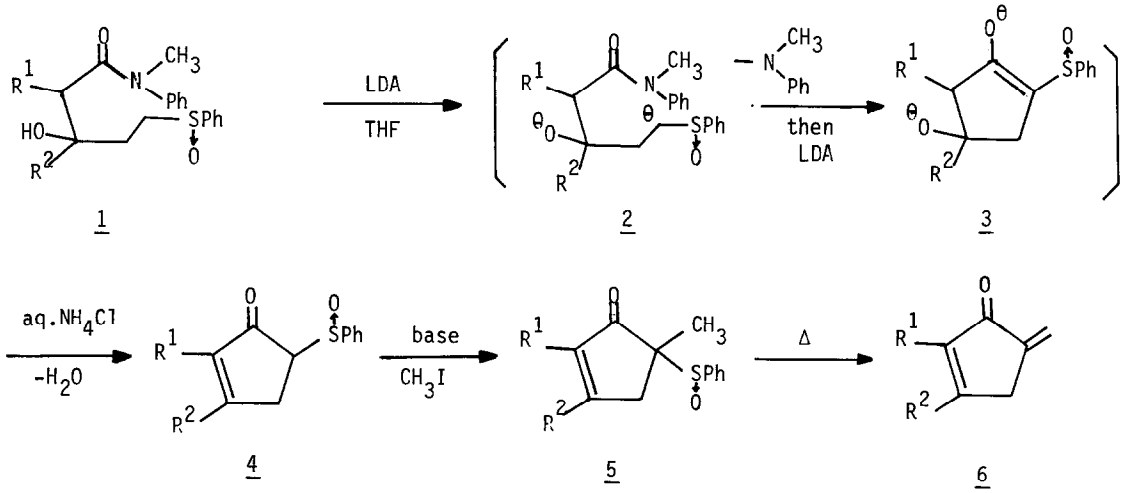
Manat Pohmakotr* and Sirirat Chancharunee

Department of Chemistry, Faculty of Science, Mahidol University,
Rama VI Road, Bangkok 10400, THAILAND

Summary: A convenient synthesis of 5-methylene-2-cyclopentenones including Methylenomycin B involving the intramolecular acylation of α-sulfinyl carbanion followed by methylation and pyrolysis is described.

5-Methylene-2-cyclopentenone unit occurs widely in natural products, particularly the cyclopentenoid antibiotics such as methylenomycin B[1] and deepoxy-4,5-didehydromethylenomycin A[2] which were isolated from the culture broth of *Streptomyces* species. For the synthesis of such products,[3,4] the development of general methods for the preparation of 5-methylene-2-cyclopentenones is a particular desirable objective.[4] Recently, we reported a general synthesis of 5-substituted 2-cyclopentenones based on the intramolecular acylation reactions of α-sulfinyl carbanions followed by elimination of benzenesulfenic acid.[5] This cyclisation appears to be a convenient route for preparation of functionalised cyclopentenones which could be used as intermediates for the synthesis of 5-methylene-2-cyclopentenones. To demonstrate the synthetic potential of the intramolecular acylation of α-sulfinyl carbanions, we report here a new general approach to the synthesis of 5-methylene-2-cyclopentenones. The general strategy is depicted in Scheme I.

Scheme I




1 2 3 4 5 6

The prerequisite hydroxy sulfoxides 1 could be easily prepared by treatment of the enolate anions derived from the corresponding amides (LDA/THF, 0°C, 1 hr) with 3-phenylthio-1-propanal[6] or 4-phenylthio-2-butanone[6] (-78°C, 1 hr) followed by oxidation of the resulting hydroxy sulfides with m-chloroperbenzoic acid[7] ($CH_2Cl_2$, -78°C) (see Table). The reaction of the hydroxy sulfoxide 1 (1 equiv.) with 3.0-3.2 equivalents of lithium diisopropylamide (LDA) in THF (10 ml/1 mmol of 1) at -78°C for 1 hr and then at 0°C for an additional hour gave the cyclisation product 4 in moderate to good yield as diastereomeric mixtures after quenching with saturated ammonium chloride solution. The reaction proceeded *via* the intramolecular acylation reaction of the initially formed α-sulfinyl carbanion 2 leading to the intermediate 3 which upon hydrolysis afforded the functionalised cyclopentenone 4. Having the functionalised cyclopentenone 4 in hand we then next explored the synthesis of 5-methylene-2-cyclopentenone 6 by employing the sequential methylation of 4 and elimination of benzenesulfenic acid of the resulting methylated product 5. At the beginning of our investigation, we tried to trap the enolate anion intermediate 3a or 3e with an equimolar amount of methyl iodide (or even with an excess amount ca. 3 equiv. in the presence of HMPA) at 0° → RT overnight, unfortunately the reaction gave the desired product 5a or 5e in low yields (25-30%). Methylation (1.2-1.5 equiv. of $CH_3I$) of 4a and 4e (1 equiv. each) using LDA (1 equiv.) as base in THF at -78°C → RT also gave unsatisfactory yields of 5a and 5e (28-35%). We observed that the reaction led to many other side products as indicated by TLC and $^1$H-NMR

Table Preparation of 5-methylene-2-cyclopentenones 6.

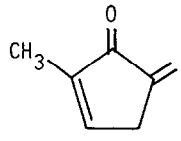
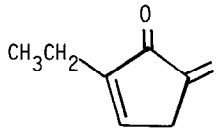
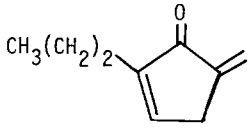
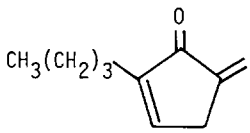
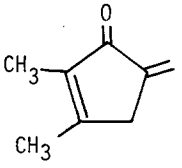
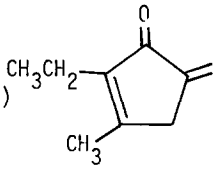
| 1 (%)[a,b] | 4 (%)[a,b] | 5 (%)[a,b] | 6 (%)[a] |
|---|---|---|---|
| 1a, $R^1$=$CH_3$; $R^2$=H (66) | 4a (77) | 5a (65) |  6a (84) |
| 1b, $R^1$=$CH_3CH_2$; $R^2$=H (77) | 4b (75) | 5b (51) |  6b (77) |
| 1c, $R^1$=$CH_3(CH_2)_2$; $R^2$=H (51) | 4c (66) | 5c (85) |  6c (74) |
| 1d, $R^1$=$CH_3(CH_2)_3$; $R^2$=H (45) | 4d (65) | 5d (84) |  6d (89) |

Table (cont.)

| 1 (%)[a,b] | 4 (%)[a,b] | 5 (%)[a,b] | 6 (%)[a] |
|---|---|---|---|
| 1e, $R^1=R^2=CH_3$ (74) | 4e (73) | 5e (78)  | 6e (95) |
| 1f, $R^1=CH_3CH_2$; $R^2=CH_3$ (71) | 4f (73) | 5f (71)  | 6f (79) |

a) Yields of isolated products: the spectral data of these products are fully consistent with the assigned structures.

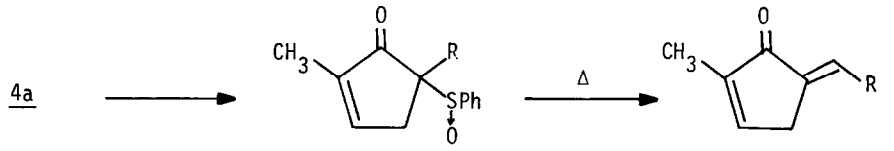
b) These products have been obtained as diastereomeric mixtures.

analyses: only small amount of the unreacted 4a and 4e could be recovered. We assume that this may be due to the instability of the lithium dienolate anions desired from 4a and 4e. However, good yields of the methylated products 5a-f were achieved by employing the phase transfer catalytic conditions. Thus, treatment of 4a-f (1 equiv.) with methyl iodide (1.1 equiv.) in dichloromethane (20 ml/1 mmol of 4) in the presence of 50% aq.NaOH (1.1 equiv.) and benzyltrimethylammonium chloride (1 equiv.) at $0^0 \rightarrow$ RT overnight furnished the expected methylated products 5a-f as diastereomeric mixtures in good yields (see Table). Pyrolysis of the diastereomeric mixture of the methylated β-ketosulfoxides 5 gave the desired 5-methylene-2-cyclopentenones 6 in high yields.[8] This was carried out by heating neat at 110-110°C under reduced pressure (0.02-0.05 torr) followed by direct distillation during which the distillate was trapped at -78°C. The results are summarized in Table.

Having established the general approach for the synthesis of 5-methylene-2-cyclopentenones 6, we examined briefly the preparation of some 5-alkylidene-2-cyclopentenones 8a-c using the same reaction sequence. Thus, alkylation ($CH_3CH_2I$, $CH_2=CH_2-CH_2Br$, $PhCH_2Br$) of 4a using the standard conditions as above afforded the alkylated sulfoxides 7a-c which were converted into 5-alkylidene-2-cyclopentenones 8a-c in high yields by heating neat under reduced pressure (100-110°C, 0.02-0.05torr). The results are summarized in Scheme II.

In conclusion, the results described herein offer a general procedure for the synthesis of 5-methylene- and 5-alkylidene-2-cyclopentenones starting from common amides. Thus, the method provides a simple synthesis of methylenomycin B (6e).

Scheme II




7a, R=$CH_3CH_2$- (40%)[a] 8a, R=$CH_3$- (71%)[a]

7b, R=$PhCH_2$- (quant.)[b] 8b, R=Ph- (66%)[c]

7c, R=$CH_2$=CH-$CH_2$- (98%)[b] 8c, R=$CH_2$=CH- (62%)[c]

a) Yields of isolated products. b) Yields of crude products. c) Overall yields from 4a.

References


1. T. Haneishi, N, Kitihara, Y. Takiguchi, M. Rai, and S. Sugawara, J. Antibiot. 27, 386 (1974); T. Haneishi, A. Terahara, M. Rai, T. Hata, and C. Tamura, ibid., 27, 394(1974).
2. U. Hornemann and D.A. Hopwood, Tetrahedron Lett., 2977(1978).
3. J. Jernow, W. Tautz, P. Rosen, and J.F. Blount, J. Org. Chem., 44, 4210(1979); J. Jernow, W. Tautz, P. Rosen, and T.H. Williams, ibid., 44, 4212(1979); J.N. Marx and G. Minaskanian, Tetrahedron Lett., 4175(1979); R.K. Broeckman, Jr., P.C. Naegeley, and S.D. Arther, J. Org. Chem 45, 752(1980); M.Koreeda and Y.P.L. Chen, Tetrahedron Lett., 22, 15(1981); R.M. Scarborough, Jr., B. Toder, and A.B. Smith, III, J.Amer.Chem.Soc., 102, 3904 (1980); D. Boschelli, M.R. Scarboroug Jr., and A.B. Smith,III, Tetrahedron Lett., 22, 19(1981); Y. Takahashi, H. Kosugi, and H. Uda, J.Chem.Soc., Chem.Commun., 496(1982); G.M. Strunz and G.S. Lal, Can.J.Chem., 60, 2528(1982); M. Mikolajczyk, S. Grzejsczak, and P. Lyzwa, Tetrahedron Lett., 23, 2237(1982); P. Pauson and D.C. Billington, Organomet., 1, 1560(1982); E. Negishi and J.A. Miller, J.Amer.Chem.Soc., 105, 6761(1983).
4. T. Siwapinyoyos and Y. Thebtaranonth, J.Org.Chem., 47, 598(1982).
5. M. Pohmakotr and P. Phinyocheep, Tetrahedron Lett., 25, (1984), in press.
6. cf. B.M. Trost and D.E. Keeley, J.Org.Chem., 40, 2013(1975).
7. B.M. Trost, T.N. Salzmann, and K. Hiroi, J.Amer.Chem.Soc., 98, 4887(1976).
8. Pyrolysis of pure isolated diastereomers of 5a or 5e gave the 5-methylene-2-cyclopentenones 6a or 6e in comparable yields.


(Received in UK 28 June 1984)