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A NEW SYNTHETIC METHOD FOR β,γ-UNSATURATED KETONES AND A TOTAL SYNTHESIS OF EGOMAKETONE

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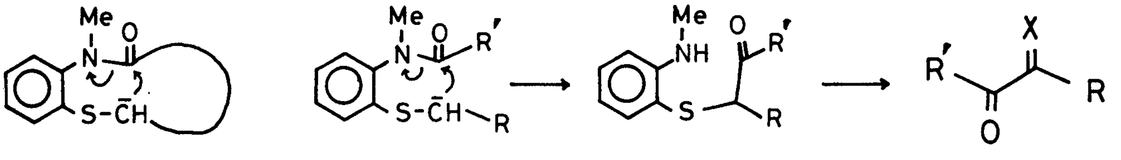
A new method for preparing β,γ-unsaturated ketones based on the intramolecular acyl N to C transfer of 2-carboxamidephenylsulfides is described including a total synthesis of egomaketone using this method.

KEYWORDS——Intramolecular acyl transfer; β,γ-unsaturated ketone; 2-N-methylaminobenzenethiol; amide sulfide; amide sulfone; β-keto sulfide; β-keto sulfone; egomaketone

In the course of a study to develop a general method for the preparation of medium membered ketones[1] based on the intramolecular cyclization of large membered lactam sulfides **1**, we carried out a model experiment using the amide sulfides **2**, the open chain analogue of **1**, and found that an acyl transfer actually took place to afford a variety of β-keto sulfides **3**. Conversion of **3** (R= phenyl, R'= isopropyl) into the simple ketone **4a** or variously functionalized ketones **4** has also been achieved.[2]



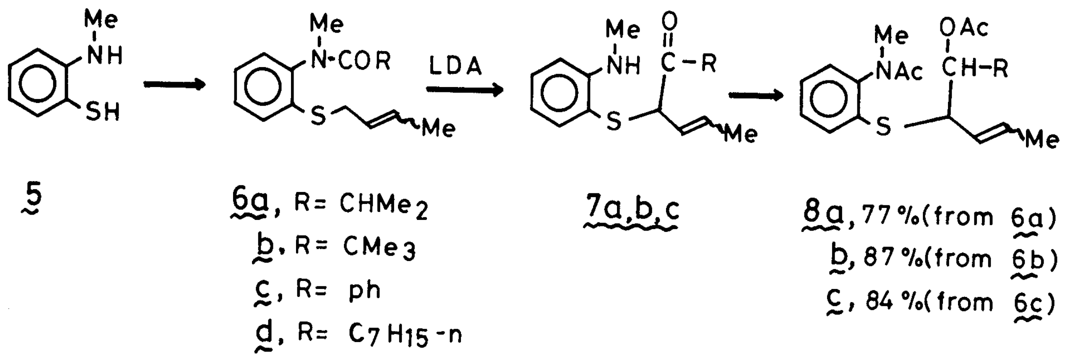
1

2

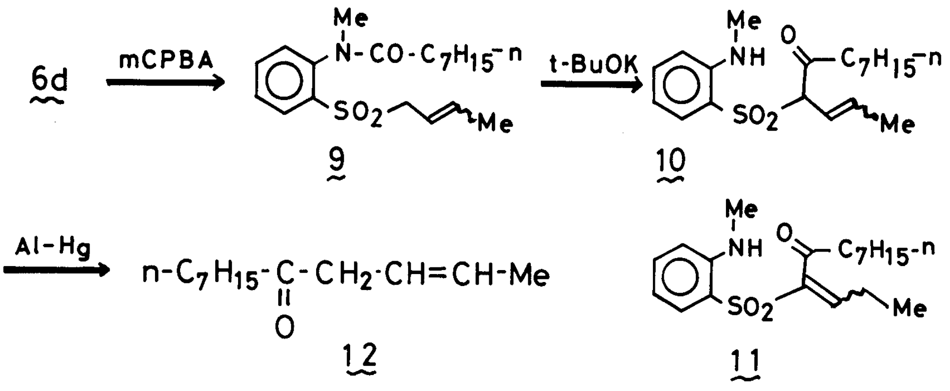
3, R=ph,Sph,CO_2Et
R'=$CHMe_2$,CMe_3,ph

4, R=ph,R'=$CHMe_2$
a,X= H_2
b,X= $<^{OH}_{H}$, $<^{Cl}_{H}$, O

We now report that β,γ-unsaturated ketones can be prepared by the above method without producing any α,β-unsaturated ketones.[3,4] The amide sulfides[5] **6a,b,c** were readily prepared by treatment of 2-N-methylaminobenzenethiol (**5**) with crotyl bromide in the presence of NaOEt, followed by N-acylation with acid chlorides. When **6a,b,c** were treated with 2.2 eq of lithium diisopropylamide (LDA) (-78°C, 30 min, then 0°C, 30 min), protons were abstracted from the active methylene followed by an intramolecular attack by the resulting carbanion on the amide carbonyl. The α-(2-N-methylaminophenylthio)-β,γ-unsaturated ketones

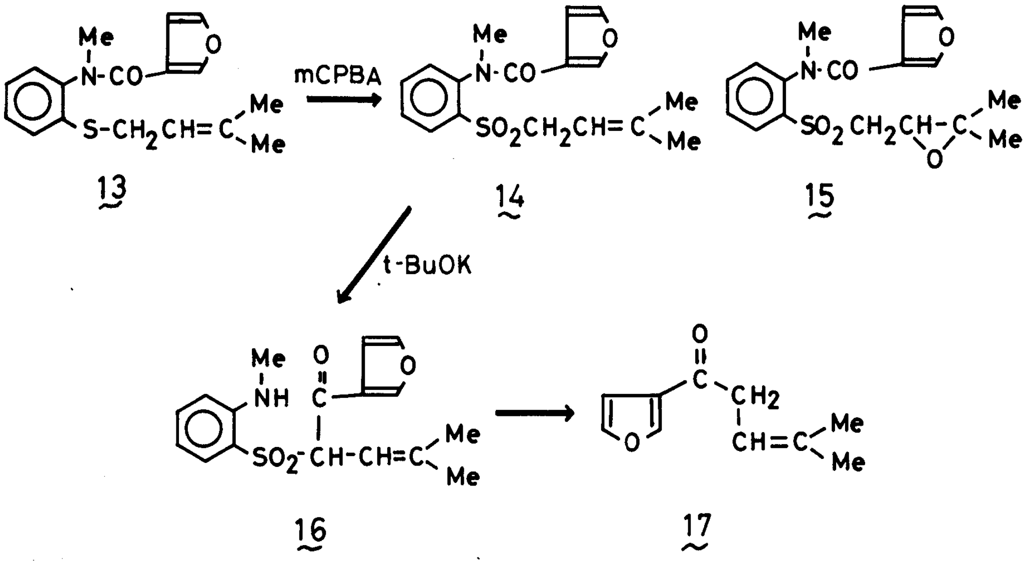


7a,b,c, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3380, 1710-1687, PMR(CDCl$_3$) δ: 4.2-4.95 (m, S-$\overset{|}{C}\underline{H}$-CO), 5.45-5.8 (m, C$\underline{H}$=C$\underline{H}$), were produced in essentially quantitative yield. The structures of 7a,b,c were confirmed after conversion into 8a,b,c, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1745, 1670, PMR(CDCl$_3$) δ: 3.7-4.3 (m, S-$\overset{|}{C}\underline{H}$-CH=), 4.8-5.3 (m, C$\underline{H}$-OAc), because 7a,b,c were found to be susceptible to decomposition.$^{6)}$ However, when R is n-heptyl (6d), the reaction did not take place at all. Therefore, to increase the acidity of the methylene proton adjacent to sulfur, the sulfide 6d was converted into the sulfoxide (NaIO$_4$), but again the starting material was recovered unchanged. However, when the corresponding sulfone 9, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1660, 1327, PMR(CDCl$_3$) δ: 3.68-4.26 (m, SO$_2$-C$\underline{H}_2$-CH=), prepared by the oxidation of 6d with mCPBA (2 eq, 85% yield), was subjected to reaction with t-BuOK (3 eq, THF/DMSO, 4:1), as a base in this case, the desired ketone 10, mp 74-5°C, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3390, 1715, PMR(CDCl$_3$) δ: 4.45-4.7 (m, SO$_2$-$\overset{|}{C}\underline{H}$-CH=), 5.2-6.1 (m, C$\underline{H}$=C$\underline{H}$), was obtained in quantitative yield. Here, addition of DMSO was found to be essential for the completion of the reaction. It should be emphasized that t-BuOK which was less basic than LDA was sufficient to initiate the reaction and even if an excess of still strongly basic t-BuOK was present in the reaction mixture, none of the conjugated unsaturated compound 11 could be detected. Reductive desulfurization of 10 with Al-Hg (THF/H$_2$O) produced the β,γ-unsaturated



ketone 12, bp 138°C (14 mmHg), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1720, PMR(CDCl$_3$) δ: 1.68 (d, =CH-C$\underline{H}_3$), 2.13-2.66 (m, CO-C$\underline{H}_2$-CH=), 5.08-5.86 (m, C$\underline{H}$=C$\underline{H}$), in 78% yield.

In order to examine the applicability of the present method for natural product synthesis, a total synthesis[3i,3l)] of egomaketone (17), isolated from a form of <u>Perilla frutescens</u> Brit.[7)] and known to have the β,γ-unsaturated ketone system, was undertaken. The starting amide sulfide 13 was prepared as usual from 5, methallyl chloride and 3-furoyl chloride. However, all attempts to convert 13 and the sulfoxide obtained by NaIO$_4$ oxidation of 13 into the corresponding β-keto sulfide or sulfoxide failed, although there was no hydrogen atom that could be abstracted by base treatment adjacent to their amide carbonyls.[8)] Therefore, the reaction was accomplished with the sulfone 14. The sulfone 14, mp 87-9°C, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1645, 1325, PMR(CDCl$_3$) δ: 3.6-4.13 (m, SO$_2$-C$\underline{H}_2$-CH=), 4.78-5.45 (m, C$\underline{H}$=C), was obtained in 66% yield by the oxidation of 13 using 2 eq of mCPBA at room temperature. Although mCPBA oxidation of the sulfide 6d containing a disubstituted double bond afforded the sulfone 9 in 85% yield as mentioned above, the sulfide 13 containing a trisubstituted double bond gave an appreciable amount of the epoxy sulfone 15 (13% yield), PMR(CDCl$_3$) δ: 2.88-3.30 (m, SO$_2$-CH$_2$-$\overset{O}{\underline{\mathrm{C}\mathrm{H}}\text{-}\mathrm{C}}$), along with the desired sulfone 14. Several methods have been reported for the conversion of sulfides into sulfones in the presence of disubstituted double bonds.[9)] However, in the present system involving trisubstituted double bonds which are presumed to be more susceptible to oxidation than disubstituted double bonds, the sulfone 14 was always accompanied by the over oxidation product (15). Intramolecular acyl N to C transfer[10)] proceeded this time smoothly by t-BuOK treatment (THF/DMSO, room temp., 5 min) of the sulfone 14 to afford the β-keto sulfone 16, mp 83-5°C, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3240, 1685, 1330, PMR(CDCl$_3$) δ: 5.2-5.75 (m, SO$_2$-$\overset{|}{\mathrm{C}}\underline{\mathrm{H}}$-C$\underline{H}$=), in quantitative yield. Reductive desulfurization of 16 afforded egomaketone (17)[11)] in 80% yield (Raney Ni) or in 58% yield (Al-Hg).



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1) Y. Ohtsuka and T. Oishi, Tetrahedron Lett., 1979, 4487.

2) The details will be described in a forthcoming paper.

3) For the preparation of β,γ-unsaturated ketones, see a) V.A. Smit, A.V. Semenovskii, O.V. Lywbinskaya and V.F. Kucherov, Dokl. Akad. Nauk. SSR, 203, 604 (1972); b) R. Clas, J. Dunoques, J.-P. Pillot, C. Biran, F. Pisciotti and B. Arreguy, J. Organomet. Chem., 85, 149 (1975); c) M. Kosugi, Y. Shimizu and T. Migita, ibid., 129, C36 (1977); d) H.M. Hoffman and T. Tsushima, J. Am. Chem. Soc., 99, 6008 (1977); e) B. Cazes and S. Julia, Tetrahedron Lett., 1974, 2077; f) J.L.C. Kachinski and R.G. Salomon, ibid., 1977, 3235; g) D. Seebach, Synthesis, 1969, 17; h) B.-T. Gröbel and D. Seebach, ibid., 1977, 357 and references cited therein; i) A. Hoppman and P. Weyerstahl, Tetrahedron, 34, 1723 (1978); j) S. Masson, M. Saquet and A. Thuillier, ibid., 33, 2949 (1977); k) P. Gosselin, S. Masson and A. Thuillier, Tetrahedron Lett., 1978, 2717; l) P. Gosselin, S. Masson and A. Thuillier, J. Org. Chem., 44, 2804 (1979); m) G. Cahiez, A. Alexakis and J.F. Normant, Synthetic Commun., 9, 639 (1979); n) G. Rousseau and J.M. Cania, Tetrahedron Lett., 1981, 649.

4) Satisfactory elemental analysis and spectral data were obtained for all newly isolated compounds.

5) Commercial crotyl bromide which contains about 14% isomeric 3-bromo-1-butene was directly used for allyl sulfide formation, but none of the sulfide derived from the isomer could be detected in the products. The amide sulfides 6a,b,c,d were all accompanied by small amounts of the isomeric compounds around the double bond. The structural studies of these double bond isomers were not pursued further.

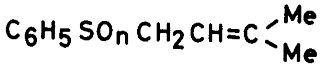
6) The compounds 8a,b,c were obtained as a mixture of diastereoisomers (the ratios, ca. 1:1).

7) T. Uda and Y. Fujita, Chem. Ind. (London), 1962, 1618.

8) The α-hydrogen of the furan ring can be abstracted by LDA, which may be related to the present failure of the LDA induced N to C acyl transfer in 13 and its sulfoxide.

9) a) L. Kuhnen, Angew. Chem., 78, 937 (1966); b) B.M. Trost and D.P. Curran, Tetrahedron Lett., 1981, 1287.

10) Attempted intermolecular acylation of 18 (n= 0, 1 or 2) with 3-furoic acid amide or ester using LDA or t-BuOK as a base were all unsuccessful.



$C_6H_5SO_nCH_2CH{=}C\begin{smallmatrix}Me\\ Me\end{smallmatrix}$

18

11) Spectral data (IR, PMR) of 17 were identical with those of the reported values of synthetic egomaketone[3i] and the melting point of 2,4-DNP of 17, mp 145-6°C, was also the same as that of the natural egomaketone.[7]

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