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Regiospecific Procedure for the Preparation of Silyl Enol Ethers from α-(N-Alkoxycarbonylamino)Ketones

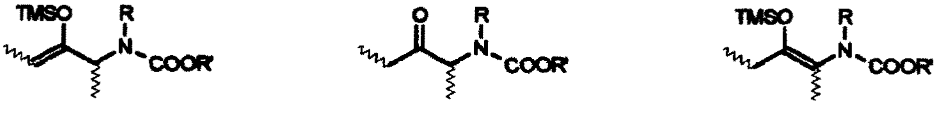
Luciana Rossi and Angelo Pecunioso*

Glaxo Research Laboratories
GLAXO Spa, via Fleming 4, 37100 Verona, Italy

Abstract: *A general procedure for the conversion of cyclic and acyclic α-(N-alkoxycarbonylamino)ketones into the corresponding "kinetic" silyl enol ethers in the presence of trimethylsilyltriflate and a tertiary amine is described. The advantage of the present method consists of an almost complete regioselectivity obtained under mild reaction conditions.*

In the course of our recent studies we required a highly regioselective procedure for the preparation of "kinetic"[1] silyl enol ethers (1) from α-(N-alkoxycarbonylamino)ketones (2) (FIGURE 1).

FIGURE 1



1

2

3

The formation of silyl enol ethers from α-(N-alkoxycarbonylamino)ketones (2) was previously studied by Garst et al[2] who showed that, when subjected to classical kinetic enolisation conditions,[3] ketones such as 2 enolize to give predominantly the "thermodynamic" regioisomer 3 (FIGURE 1).

Despite of these discouraging evidences, we looked for alternative procedures that could improve the "kinetic"/"thermodynamic" ratio in the silylation reaction of the ketones 2. In this context, we found promising the versatile procedure described by Simchen and coll. to silylate a number of different carbonyl derivative.[4]

Under these reaction conditions, α-alkyl substituted ketones reacted with triethylamine and trimethylsilyltriflate gave a variable degree (30-80%) of "kinetic" regioselectivity.[4b] Therefore, we expected that the steric hindrance of N-alkoxycarbonyl group could drive, at least in part, the reaction of ketones 2 toward the "kinetic" silyl enol ethers 1.

As shown in the Table, some cyclic and acyclic α-(N-alkoxycarbonylamino)ketones (2a-h)[5] were reacted under mild temperature conditions (0°C) with a moderate excess of trialkylamine/trialkylsilyltriflate.[6,7] The conversion of 2 was generally complete in 30-60 min. and, after the removal of the trialkylamine and the trialkylsilyltriflate salts[7], the crude reaction products were analysed by 300 MHz or 400 MHz ^{1}H-NMR spectroscopy to determine the regioisomeric composition (1 / 3 ratio, see Table). Surprisingly, we observed that both the carbocyclic (2a-d) and the acyclic substrates (2g and 2h) gave in very good yields the corresponding pure "kinetic" silyl enol ethers.[8] Only the 3-piperidinone derivatives 2e and 2f showed a different trend yielding a mixture of "kinetic" and "thermodynamic" regioisomers. The reaction worked without appreciable differences with both trimethylsilyl- or *t*.butyldimethylsilyltriflate or when the triethylamine was substituted with N-ethylpiperidine. On the other hand, the reactions with the more sterically hindered diisopropylethylamine showed a remarkable and unpredictable substrate dependence, working effectively with the ketones 2c and 2f but failing to give any conversion into silyl enol ethers in the case of the ketones 2a and 2h (Table).

It is also to be stressed that the nature of the substituents R and R' on the carbamate group (FIGURE 1) does not seem to have remarkable influence both on the recovered yields and on the 1 / 3 ratio (Table).

Although the trend emerging from the reported data (Table) indicates a strong preferential deprotonation on the least substituted carbon atom α to the carbonyl group, it is not certain whether the obtained excellent regioselectivity can be attibuted to steric effects alone. In fact, under similar reaction conditions, various α-alkyl substituted monocyclic or acyclic ketones failed to give a very high "kinetic" regioselectivity.[4b,9]

In summary, we have described a mild and highly regioselective procedure for the conversion of α-(N-alkoxycarbonylamino)ketones (2) into the corresponding of "kinetic" silyl enol ethers (1). These latter compounds cannot be efficiently obtained by means of classical kinetic enolisation conditions.[2,3]

Further studies are required to determine the sources of the observed selectivity as well as the scope and limitations of this silylation procedure.

ACKNOWLEDGMENT

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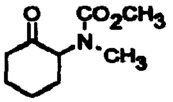
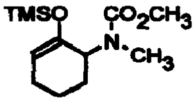
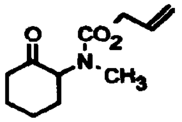
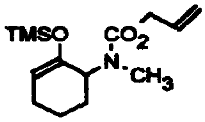
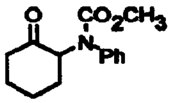
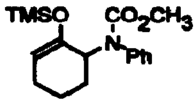
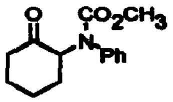
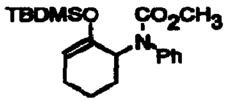
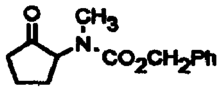
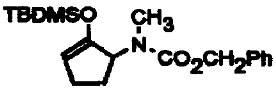
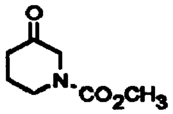
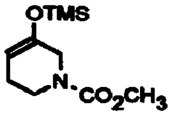
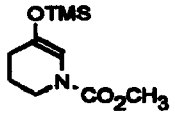
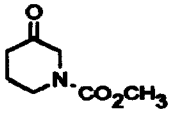
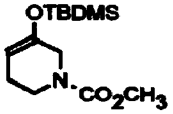
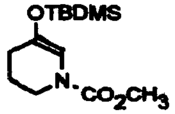
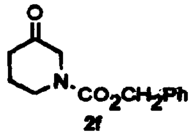
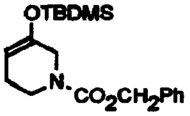
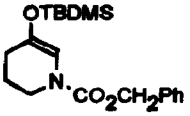
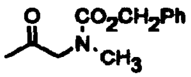
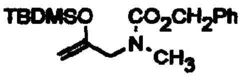
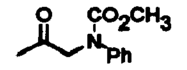
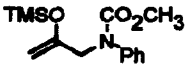
TABLE

KETONES	SILYL ENOL ETHERS (a)	BASE (b)	YIELD% (c) (1/3 ratio)
 2a	 1a	TEA DIPEA	85 no reac.
 2b	 1b	TEA	80
 2c	 1c	TEA DIPEA	90 82
 2c	 1c'	TEA	70
 2d	 1d	TEA NEP	92 89
 2e	 1e  3e	TEA	15 (d) (70:30)
 2e	 1e'  3e'	TEA	91 (48:52)

 **2f**	 **1f**  **3f**	NEP TEA DIPEA	99 (55:45) 97 (55:45) 93 (54:46)
 **2g**	 **1g**	TEA NEP	94 97
 **2h**	 **1h**	TEA DIPEA	80 no reac.

a) TMS=Trimethylsilyl-; TBDMS=*t*.Butyldimethylsilyl- . b) TEA=Triethylamine; NEP=N-ethylpiperidine; DIPEA=Diisopropylethylamine. c) Isolated yields. Unless otherwise specified, only the "kinetic" silyl enol ether was observed in the reaction mixture. d) The product decomposed in part during the work-up.

REFERENCES AND NOTES

1. In this work we use the terms "Kinetic" and "Thermodynamic" to describe respectively the regioisomeric silyl enol ethers 1 and 3 (FIGURE 1).
2. a) Garst, M.E., Bonfiglio, J.N. *Tetrahedron Lett.* 1978, *19*, 2671; b) Garst, M.E., Bonfiglio, J.N. *J. Org. Chem.* 1980, *45*, 2307.
3. House, H.O., Czuba, L.J., Gall, M., Olmstead, H.D., *J. Org. Chem.*, 1969, *34*, 2324.
4. a) Simchen, G. et al., *Synthesis*, 1982, 1 and references cited therein; b) Emde, H., Gotz, A., Hofmann, K., Simchen, G., *Liebigs Ann. Chem.*, 1981, 1643; c) Simchen, G., Kober, W., *Synthesis*, 1976, 259.
5. The α–(N-alkoxycarbonylamino)ketones (2) were prepared from the corresponding aminoalcohos protecting the amino group with the suitable alkylchloroformate and then converting the hydroxy group into the carbonyl functionality by means of the Swern oxidation protocol.
6. Since it was reported (ref. 4b) that the trimethylsilyltriflate causes the isomerisation of the "kinetic" isomer into the "thermodynamic" isomer, in our experiment we precautionally used a 0.2 equivalent excess of trialkylamine base with respect to trimethylsilyltriflate to prevent any possible conversion of 1 to 3.
7. In a tipical procedure, trialkylsilyltriflate (12 mmol) was added to a cooled (0^0C) solution of the α–(N-alkoxycarbonylamino)ketone (10 mmol) and trialkylamine (14 mmol) in dichloromethane (30 mL). When the reaction was complete (thin layer chromatography), ethyl ether (40 mL) was added and the organic phase washed with cold NH_4Cl. The organic layer was dried over anhydrous sodium sulphate and the solvents evaporated under vacuum to give a crude oil which was then purified by means of flash chromatography on a short silica gel column. The obtained yields of the purified silyl enol ethers (1 or 1+3 mixture) are reported in the Table. All new compounds gave satisfactory ^1H-NMR, IR, and MS spectra analysis.
8. The structure of the "kinetic" silyl enol ethers were assigned on the basis of the ^1H-NMR signals of the vinilic protons (4.80-5.05 ppm range).
9. Mander, L.N., Sethi, S.P., *Tetrahedron Lett.*, 1984, *25*, 5953.

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