

C-Glycosylation of Cyclic N-Acyliminium Ions with Trimethylsilyloxyfuran

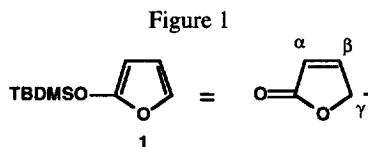
Marianne Pichon, Bruno Figadère*, André Cavé

Laboratoire de Pharmacognosie, associé au CNRS (BIOCIS), Université Paris-Sud, Faculté de Pharmacie, rue J. B. Clément, 92296 Châtenay-Malabry (France)

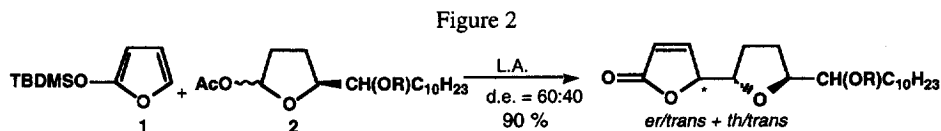
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Abstract: C-glycosylation of 2-methoxy-5-alkoxycarbonyl pyrrolidines with trimethylsilyloxyfuran allows us to obtain the corresponding pyrrolidines contiguous to a α,β -unsaturated butyrolactone. Copyright © 1996 Published by Elsevier Science Ltd

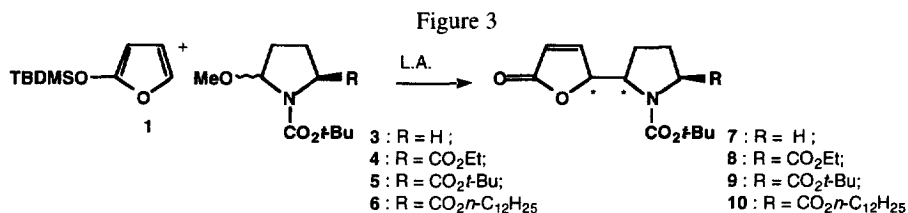
Use of trimethylsilyloxyfuran (TMSOF) **1** has been of particularly great interest as a α,β -unsaturated butyrolactonic nucleophile equivalent (Fig. 1). In numerous reports it has been shown that the reactive anion is located at the γ position, related to the carbonyl¹. The use of this reagent allows one to obtain the butenolide adducts which can be used as building blocks for the preparation of more elaborated products.



A few years ago, we have reported² that TMSOF can also react with cyclic oxonium ions affording the corresponding butyrolactonic tetrahydrofurans in high yields and good stereoselectivities, since among the four possible stereomers only two of them were formed (Fig. 2). We next applied with success this strategy to the stereoselective preparation of oligo-tetrahydrofurans³.



We want now to report our findings concerning the reaction of TMSOF with cyclic N-acyliminium ions for elaboration of 2,5-disubstituted pyrrolidines (Fig. 3). Further chemical transformations (e.g. oxidations, hydrogenation and opening of the lactone ring) could lead to natural products of biological interests.



2,5-disubstituted pyrrolidines are naturally occurring bioactive products⁴. Furthermore, these heterocycles may serve as homochiral catalyst in stereoselective reactions⁵. Therefore high yielding and stereoselective syntheses of such valuable chiral products are needed⁶.

Several authors have shown that N-acyliminium derivatives obtained from pyrrolidines are very convenient starting materials for the preparation of 2,5-disubstituted pyrrolidines by addition of nucleophiles in the presence of Lewis acids^{7a-g}. Martin and Corbett⁸ have reported that TMSOF **1** reacts at low temperature with N-benzyloxycarbonyl-2-ethoxy-pyrrolidine in the presence of BF₃.OEt₂ to give a separable mixture (5:1) of the *threo* and *erythro* adducts in 79 % yield, but did not study the reaction with substituted pyrrolidines. In order to optimize the reaction conditions, we first studied the influence of the Lewis acid, as well as the temperature, both on the stereoselectivity and the yield of the reaction in CH₂Cl₂ of TMSOF **1** with unsubstituted N-*tert*-butyloxycarbonyl-2-methoxy-pyrrolidine **3**. N-Boc-2-methoxy-pyrrolidine **3**, as well as N-Boc-2-methoxy-5-alkoxycarbonyl pyrrolidines **4-6** were first prepared from the corresponding pyrrolidinones through standard procedures⁹.

Table 1

entry	2-methoxy pyrrolidines	Lewis acid	Temperature (°C)	Adduct yield (%)	d.r. ^b
1	3 (R=H)	BF ₃ .OEt ₂	-78	7 72	44:56
2	3 (R=H) ^a	BF ₃ .OEt ₂	-78	7 79	1:5
3	4 (R=CO ₂ Et)	BF ₃ .OEt ₂	-78	8 32	15:7:22:56
4	4 (R=CO ₂ Et)	TrClO ₄	-10	8 30	20:2:20:58
5	4 (R=CO ₂ Et)	Sc(ClO ₄) ₃	-10	8 25	24:11:20:45
6	4 (R=CO ₂ Et)	TiCl ₄	-78	8 10	14:8:19:58
7	4 (R=CO ₂ Et)	SnCl ₄	-78	8 38	15:10:18:55
8	5 (R=CO ₂ <i>tert</i> -Bu)	BF ₃ .OEt ₂	-78	9 49	15:0:18:66
9	6 (R=CO ₂ <i>n</i> -C ₁₂ H ₂₅)	Sc(ClO ₄) ₃	-10	10 28	20:11:16:53

a) with N-benzyloxycarbonyl-2-ethoxy-5-ethyloxycarbonyl pyrrolidine: ref.8;

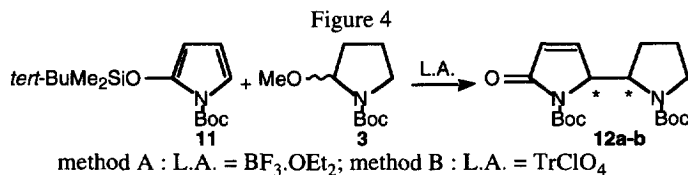
b) d.r. (*er:th:er:th*) by NMR

The relative configuration of the adducts was then assigned on the base of the NMR data^{8,10}. It is worth noting that the *threo* and *erythro* adducts **7a,b** could not be separated by usual flash chromatography on silica gel. These results are quite astonishing, since in the case of the N-benzyloxycarbonyl protected compounds, they have been separately characterized⁸. Furthermore, surprisingly these results show that N-*tert*-butyloxycarbonyl-2-methoxy-pyrrolidine **3**, when reacted with **1** in the presence of BF₃.OEt₂, afforded a 44:56 mixture of the *erythro*/*threo* adducts **7a,b** (entry 1), whereas N-benzyloxycarbonyl-2-ethoxy-pyrrolidine gave a 1:5 ratio, as reported by

Martin *et al* (entry 2). We have no explanations for such a dramatic effect of the protecting groups of the nitrogen atom on the diastereomeric ratio so obtained. Then influence of the Lewis acid (TrClO_4 , $\text{Sc}(\text{ClO}_4)_3$, TiCl_4 , SnCl_4) was examined (yields) and we can now conclude that the best one was obtained with $\text{BF}_3 \cdot \text{OEt}_2$ (72 %, entry 1) whereas the diastereoselectivity was very poor and did not depend on the nature of the Lewis acid used.

Next we studied the reaction of TMSOF **1** with the N-Boc-2-methoxy-5-alkyloxycarbonyl-pyrrolidines **4-6**. In these reactions, two new stereocenters are created, thus four possible diastereomers are expected. When **4** reacted with **1** in the presence of a Lewis acid in CH_2Cl_2 , the expected adducts are formed but yields are lower, whatever the Lewis acids are (entries 3-7), compare to the precedent case (with unsubstituted pyrrolidine derivative **3**). Therefore an alkyloxycarbonyl substituent at C-5 seems to decrease the reactivity of the cyclic N-acyliminium ions toward **1**. It is also worthnoting that the all four stereomers **8a-d** are obtained in all cases and are not separable by usual flash chromatography on silica gel. In a related reaction, Koert has shown that TMSOF **1** when reacted with 2-acetoxy-5-trimethylsilyloxymethyl furan, the four stereomers were also formed¹¹ (d.r. *er-trans:th-trans:th+er-cis* = 31:10:59). However, when the substituent at C-5 was more sterically demanding (see Fig. 2), the only two *trans* isomers were obtained². We thus decided to use N-Boc-2-methoxy-5-*tert*-butyloxycarbonyl pyrrolidine **5** as starting material and were pleased to observe that only three unseparable diastereomers **9a-c** were obtained (entry 8). However, with the N-Boc-2-methoxy-5-dodecyloxycarbonyl pyrrolidine **6**, we again formed all four unseparable isomers **10a-d** (entry 9).

In a related case we then wanted to apply this strategy to the coupling reaction between the aza-analogue of TMSOF **1**, N-Boc-2-*tert*-butyldimethylsilyloxy-pyrrole (TBSOP) **11** and the pyrrolidine **3** (Fig. 4). TBSOP **11** was prepared from pyrrolidinone in 4 steps as described¹². It is worthnoting that Casighari studied the addition of TBSOP **11** on aldehydes for the synthesis of aza-sugars¹³, but did not apply this strategy to the addition with cyclic N-acyliminium derivatives. Therefore, we submitted a mixture of **11** and **3** in CH_2Cl_2 to either 1 eq. of $\text{BF}_3 \cdot \text{OEt}_2$ at -78°C (method A) or to 0.5 eq. of TrClO_4 at -10°C (method B). The results show that the cross coupling products **12a,b** were obtained in low yields (38 %) and with a 25:75 diastereomeric ratio for method B, whereas method A gave a slightly better diastereomeric ratio (12:88) in similar yields (40 %).



In conclusion TMSOF, when it reacts with cyclic N-acyliminium derivatives, has shown to be a useful reagent for the formation of 2,5-disubstituted pyrrolidines. Furthermore, the use of TMSOF aza-analogue such as TBSOP allowed us to have an access to the cross coupling products with good diastereoselectivity, and therefore to oligopyrrolidines¹⁴. We are now working on the

improvement of the diastereomeric ratio of the reaction and the application to the preparation of oligo-pyrrolidines as well as mixed (tetrahydrofuran-pyrrolidine)_n compounds.

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References and notes

- 1 Casiraghi, G.; Rassa, G.; *Synthesis*, **1995**, 607-626.
- 2 Figadère, B.; Chaboche, C.; Peyrat, J.-F.; Cavé, A.; *Tetrahedron Lett.*, **1993**, *34*, 8093-8096.
- 3 Peyrat, J.-F.; Figadère, B.; Cavé, A.; Mahuteau, J.; *Tetrahedron Lett.*, **1995**, *36*, 7653-7656.
- 4 a) Massiot, G.; Delaude, C.; "The Alkaloids", A. Brossi, Ed., Academic Press, New-York, **1986**, vol. 27, pp 269-322; b) Jones, T. H.; Blum, M. S.; *Tetrahedron*, **1982**, *38*, 1949-1958; c) Daly, J. W.; Spande, T. F.; Whittaker, N.; Highet, R. J.; Feigl, D.; Nishimori, N.; Tokoyama, T.; Myerl, C. W.; *J. Nat. Prod.*, **1986**, *49*, 265-280; d) Wright, W. G.; *J. Chem. Soc. (C)*, **1967**, 284-285; e) Welter, A.; Jadot, J.; Dardenne, G.; Marlier, M.; Casimir, J.; *Phytochemistry*, **1976**, *15*, 747-749; f) Shinagawa, S.; Maki, M.; Kintaka, K.; Imada, A.; Asai, M.; *J. Antibiotics*, **1984**, *38*, 17-23; g) Schwartz, R. E.; Liesch, J.; Hensens, O.; Zitano, L.; Honeycut, S.; Garrity, G.; Frontling, R. A.; Oniski, J.; Monaghan, R.; *J. Antibiotics*, **1988**, *42*, 1775-1779.
- 5 For a recent example, see : Shi, M.; Satoh, Y.; Makihara, T.; Masaki, Y.; *Tetrahedron Asymmetry*, **1995**, *6*, 2109-2112.
- 6 Pichon, M.; Figadère, B.; *Tetrahedron Asymmetry*, **1996**, *7*, 927-964.
- 7 a) Thaning, M.; Wistrand, L.-G.; *Helv. Chim. Acta*, **1986**, *69*, 1711-1717; b) Barret, A. G.; Pilipanskas, D.; *J. Org. Chem.*, **1991**, *56*, 2787-2800; c) Ahman, J.; Somfai, P.; *Tetrahedron*, **1992**, *48*, 9537-9544; d) Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S.; *Tetrahedron Lett.*, **1993**, *34*, 5743-5746 e) Langlois, N.; Rojas, A.; *Tetrahedron*, **1993**, *49*, 77-82; f) Altmann, K.-H.; *Tetrahedron Lett.*, **1993**, *34*, 7721-7724; g) Skrinjar, M.; Wistrand, L.-G.; *Tetrahedron Lett.*, **1990**, *31*, 1775-1778.
- 8 Martin, S. F.; Corbett, J. W.; *Synthesis*, **1992**, 55-57.
- 9 N-Boc-2-methoxy-pyrrolidine **3** was prepared from pyrrolidinone by protection with (Boc)₂O in the presence of 1 eq. of Et₃N and 1 eq. of DMAP, in CH₂Cl₂ at room temperature in 96 % yield, followed by Dibal-H reduction at -78 °C and subsequent treatment by a methanolic solution of PTSA (1 g/L) leading to the desired product **3** in 85 % yield for the last two steps. N-Boc-2-methoxy-5-alkyloxycarbonyl pyrrolidines **4-6** were prepared from L-pyrroglutamic acid (obtained by heating L-glutamic acid at reduced pressure), which either after treatment with EtOH in the presence of thionyl chloride led to the corresponding ethyl ester in 90 % yield or treated with *tert*-butyl acetate and perchloric acid at room temperature to give the corresponding *tert*-butyl ester in 60 % yield or treated with C₁₂H₂₅OH in the presence of PTSA, leading to the desired dodecyl ester in 54 % yield. Then esters were treated by (Boc)₂O in the same conditions as described above to give the corresponding protected compounds in 90, 71, and 65% yield, respectively. Dibal-H reduction of the latters, as described above, followed by treatment with PTSA solution in methanol (1 g/L) yielded the desired N-Boc-2-methoxy-5-alkyloxycarbonyl pyrrolidines **4-6** in 73, 57, and 65 % yield for the last two steps, respectively.
- 10 Baussanne, I.; Royer, J.; *Tetrahedron Lett.*, **1996**, *37*, 1213-1216.
- 11 Koert, U.; Stein, M.; Harms, K.; *Tetrahedron Lett.*, **1993**, *34*, 2299-2302.
- 12 Rassa, G.; Pinna, L.; Spanu, I.; Ulgheri, F.; Casiraghi, G.; *Tetrahedron Lett.*, **1994**, *35*, 4019-4022.
- 13 For addition of TBSOP on a sugar, see : Rassa, G.; Zanardi, F.; Battistini, L.; Casiraghi, G.; *Tetrahedron Asymmetry*, **1995**, *6*, 371-374.
- 14 For a recent stereospecific synthesis of a bipyrrrolidine, see : Kotsuki, H.; Kuzume, H.; Gohda, T.; Fukuhara, M.; Ochi, M.; Oishi, T.; Hiram, M.; Shiro, M.; *Tetrahedron Asymmetry*, **1995**, *6*, 2227-2236.

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