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Diastereoselection of the addition of silyloxyfurans to five-, six- and seven-membered *N*-acyliminium ions

Maria da Conceição F. de Oliveira, Leonardo Silva Santos and Ronaldo Aloise Pilli*

Instituto de Química, UNICAMP, PO Box 6154, 13083-970 Campinas, SP, Brazil

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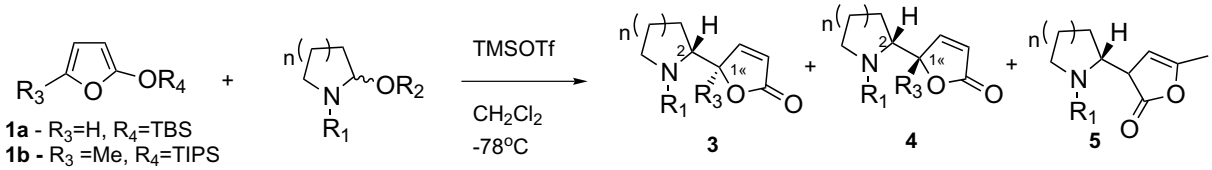
Abstract—The addition of silyloxyfuran **1a** to five-, six- and seven-membered *N*-acyliminium ions **2** afforded *threo*-**3** as the major isomers (the structures of **3a**, **3g** and **3m** were determined by X-ray analysis). The diastereoisomeric ratio increased with bulkier carbamate groups (Boc>Cbz>CO_2Me) with the five- and seven-membered *N*-acyliminium ions more selective than the six-membered ones. However, *erythro*-**4** isomers predominated when 5-methylsilyloxyfuran **1b** was employed (the structures were determined by NOE studies on the corresponding bicyclic lactams **6a**,**b** and **7a**,**b**) and the formation of regioisomer **5** was observed for *N*-acyliminium ions with Boc (seven-membered series) and Cbz (six- and seven-membered series) groups.

Over the last few years 2-trialkylsilyloxyfurans[1] have been used as versatile reagents for the preparation of enantiomerically pure compounds of biological interest, among which homopumiliotoxins and *Stemona* alkaloids have attracted our interest.[2] We have investigated the nucleophilic addition of carbon nucleophiles to cyclic *N*-acyliminium ions and found the relevant role played by the *N*-acyliminium ring size in the stereochemical outcome of the reaction.[3] As studies involving the intermolecular nucleophilic addition of 2-trialkylsilyloxyfurans to cyclic *N*-acyliminium ions are so far restricted to five-membered *N*-acyliminium ion rings and mainly to *N*-carbobenzyloxy derivatives,[4] we decided to extend these studies to six- and seven-membered rings containing Boc and CO_2Me groups as well.



1a - R_3=H, R_4=TBS
1b - R_3 =Me, R_4=TIPS

n=3 - **2a** - R_1=Boc, R_2=Et
2b- R_1=CBz, R_2=Et
2c - R_1=CO_2Me, R_2=Et

n=2 - **2d** - R_1=Boc, R_2=Et
2e - R_1=CBz, R_2=Me
2f - R_1=CO_2Me, R_2=Me

n=1 - **2g** - R_1=Boc, R_2=Et
2h - R_1=CBz, R_2=Me
2i - R_1=CO_2Me, R_2=Me

n=3 **3a/4a/5a** - R_1=Boc, R_3=H
3b/4b/5b - R_1=CBz, R_3=H
3c/4c/5c - R_1=CO_2Me, R_3=H
3d/4d/5d - R_1=Boc, R_3=Me
3e/4e/5e - R_1=CBz, R_3=Me
3f/ 4f/5f - R_1=CO_2Me, R_3=Me

n=2 **3g/4g/5g** - R_1=Boc, R_3=H
3h/4h/5h - R_1=CBz, R_3=H
3i/ 4i /5i - R_1=CO_2Me, R_3=H
3j/ 4j/ 5j - R_1=Boc, R_3=Me
3k/4k/5k - R_1=CBz, R_3=Me
3l/ 4l/ 5l - R_1=CO_2Me, R_3=Me

n=1 **3m/4m/5m** - R_1=Boc, R_3=H
3n/4n/5n - R_1=CBz, R_3=H
3o/4o /5o - R_1=CO_2Me, R_3=H

Figure 1. Addition of **1a**,**b** to **2a**–**i** catalyzed by TMSOTf.

* Corresponding author. E-mail: pilli@iqm.unicamp.br

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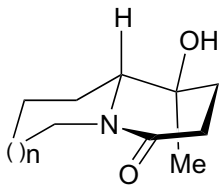
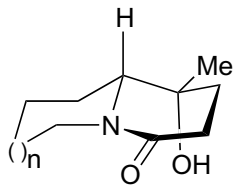
The reactions involving the addition of 2-trialkylsilyloxyfurans **1a**,**b** to cyclic *N*-acyliminium ions **2a**–**f** were carried out in CH_2Cl_2 at −78°C using a catalytic amount (10 mol%) of TMSOTf under an inert atmosphere (Fig. 1).[5] The results are summarized in Table 1. The relative configurations of the major stereoisomers **3a** and **3g**, obtained from non-substituted 2-silyloxyfuran **1a**, were determined by X-ray diffraction analysis[6] and the 2*R**,1′*R** configuration agrees nicely with the one determined previously for the addition to five-membered *N*-acyliminium ions.[4a,b] Compounds **3b**,**c** or **3h**,**i** were assigned the same relative configuration as **3a** and **3g**, respectively, after chemical correlation: Boc deprotection of **3a** and **3g** followed by reprotection with benzyl or methyl chloroformate afforded **3b**,**c** and **3h**,**i**, respectively. Interestingly, *N*-Boc derivatives always provided the best diastereoselectivities despite the ring size of the *N*-acyliminium ion involved.

Motivated by the influence of the nature of the carbamate group in the stereochemical outcome of the reaction, we decided to investigate the corresponding addition of **1a** to **2g**–**i**. In fact, the highest diastereoisomeric ratio in this series was observed for Boc derivative **2g** (**3m**:**4m** = 19:1), which represents a significant improvement over the results described by Figadère and co-workers under different experimental conditions.[4c] The 2*R**,1′*R** relative configuration of **3m** was established by X-ray analysis.[6] As expected, lower selectivities were observed for the carbomethoxy and carbobenzyloxy derivatives **2h** and **2i**.

In the series derived from 5-methyl-2-silyloxyfuran **1b**, the 2*R**,1′*S** relative stereochemistry of the major isomer was established through NOE experiments on the corresponding bicyclic lactams **7a**,**b** and **6a**,**b** derived from **3e**,**k** and **4e**,**k**,[7] respectively: irradiation of the methyl group in **7a** and **7b** provided a 2.5 and 3.4% increment in H-9a/H-10a, respectively, while no increment was observed when the same experiment was carried out with **6a** and **6b**. The relative stereochemistry of the major isomers **4d**,**f** and **4j**,**l**[8] was determined to be the same as that for **4e** and **4k** after chemical correlation as described above for **3b**,**c** and **3h**,**i**. The olefinic hydrogens in the butenolide ring proved to be diagnostic of the relative configuration of the adducts, as previously mentioned by Martin[4a] for the H-2 signal: in the *erythro* series the olefinic hydrogens are deshielded as compared to the same ones in the minor *threo* isomers. Additionally, the hitherto not observed regioisomers **5d**, **5e** and **5j** (relative configuration not determined) were formed due to increased steric hindrance at C-5 in silyloxyfuran **1b**.



6a, n=1
6b, n=2



7a, n=1
7b, n=2

Although the observed diastereoselectivity in the addition of silyloxyfuran **1a** to cyclic *N*-acyliminium ions is consistent with it's acid-catalyzed additions to cyclic electrophiles, which give preferentially *threo* adducts,[4] the formation of the major isomers **4d**–**f** and **4j**–**l** in the reactions of **1b** with **2a**–**f** is rather unexpected.

Table 1. Addition of silyloxyfurans **1a**,**b** to carbamates **2a**–**i**

Entry	*n*	Reagent	R_1	R_3	Products	dr (**3**:**4**:**5**)[a]	Yield (%)[b]
1	3	**2a**	Boc	H	**3a**:**4a**	12.6:1:0	83
2	3	**2b**	CBz	H	**3b**:**4b**	6:1:0	46
3	3	**2c**	CO_2Me	H	**3c**:**4c**	4:1:0	49
4	3	**2a**	Boc	Me	**3d**:**4d**:**5d**	1:3.8:3.5	80
5	3	**2b**	CBz	Me	**3e**:**4e**:**5e**	1:9.1:7.4	75
6	3	**2c**	CO_2Me	Me	**3f**:**4f**	1:2.3:0	70
7	2	**2d**	Boc	H	**3g**:**4g**	7.5:1:0	58
8	2	**2e**	CBz	H	**3h**:**4h**	2:1:0	63
9	2	**2f**	CO_2Me	H	**3i**:**4i**	3:1:0	74
10	2	**2d**	Boc	Me	**3j**:**4j**:**5j**	1:18.5:11	67
11	2	**2e**	CBz	Me	**3k**:**4k**	1:2:0	75
12	2	**2f**	CO_2Me	Me	**3l**:**4l**	1:5.2:0	70
13	1	**2g**	Boc	H	**3m**:**4m**	19:1:0	82
14	1	**2h**	CBz	H	**3n**:**4n**	4:1:0	76
15	1	**2i**	CO_2Me	H	**3o**:**4o**	5:1:0	70

[a] Diastereoselectivity determined by GC and confirmed by ^1H NMR analysis.
[b] Yields determined after column chromatography on silica gel of the crude mixture.

In conclusion, the data described herein clearly show the role of the ring size of the *N*-acyliminium ion controlling the diastereoselection, particularly for *N*-Boc derivatives, to afford *threo* adducts as the major isomers from silyloxyfuran **1a**. Additionally, the formation of *threo* isomer **3** was enhanced by more sterically hindered carbamates (Boc>Cbz>CO_2Me). For silyloxyfuran **1b**, the picture was not as clear due to the competitive formation of regioisomers **5d**,**e** and **5j**, but for both six- and seven-membered *N*-acyliminium ions *erythro* isomer **4** predominated over *threo*-**3**.

An application of the results above in the total synthesis of (±)-homopumiliotoxin 223G is described in the following communication.

Acknowledgements

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4. For examples of addition of silyloxyfurans to cyclic *N*-acyliminium ions, see inter alia: (a) Martin, S. F.; Corbett, J. W. *Synthesis* **1992**, *1*, 55; (b) Morimoto, Y.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Tetrahedron Lett.* **1993**, *34*, 5773; (c) Pichon, M.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1996**, *37*, 7963; (d) Morimoto, Y.; Iwahashi, M. *Synlett* **1995**, 1221; (e) Zanardi, F.; Battistini, L.; Rassu, G.; Pinna, L.; Mor, M.; Culeddu, N.; Casiraghi, G. *J. Org. Chem.* **1998**, *63*, 1368; (f) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990; (g) Pilli, R. A.; D'Oca, M. G. M.; Vencato, I. *Tetrahedron Lett.* **2000**, *41*, 9709.
5. Pilli, R. A.; Russowsky, D. *J. Chem. Soc., Chem. Commun.* **1987**, *14*, 1053.
6. We are indebted to Professor Ivo Vencato, Departamento de Química, UFSC, Brazil, for kindly carrying out the X-ray analyses. Crystallographic data (excluding structure factors) for the structures **3m**, **3g** and **3a** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-158008, -158009 and -158010, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
7. Compounds **3e** and **4e** were hydrogenated (H_2, Pd–C, ethyl acetate), followed by cyclization (MeONa, MeOH, rt) to afford lactams **6b** and **7b**, respectively (92 and 76% yield, respectively).
8. Analytical data. Compound **3g**: IR (film): 3097, 2979, 1743, 1685, 1597, 1454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K): δ 1.41 (s, 9H), 1.64 (m, br, 2H), 1.82 (m, br, 4H), 2.83 (d, br, $J=13.1$ Hz, 1H), 4.00 (s, br, 1H), 4.41 (s, br, 1H), 5.19 (s, br, 1H), 6.07 (s, br, 1H), 7.54 (d, br, $J=4.9$ Hz, 1H); ^{13}C NMR (75.54 MHz, $CDCl_3$, 293 K): δ 19.8, 24.5, 27.0 (br), 28.2, 41.2 (br), 51.1 (br), 80.0, 87.1 (br), 121.1 (br), 154.9 (br), 172.8; HRMS (EI, 40 eV): 211.08752; calcd for $C_{10}H_{13}NO_4$ ($M^+-C_4H_8$): 211.08446. Compound **4j**: IR (film): 3086, 2976, 2937, 2871, 1768, 1689, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K): δ 1.41 (s, 3H), 1.46 and 1.42 (2×s, 9H), 1.54–1.70 (m, br, 4H), 1.98 (d, br, $J=6.9$ Hz, 1H), 3.12 (t, br, $J=12.8$, 1H), {[3.82 (d, br, $J=12.8$ Hz), 4.0 (d, br, $J=12.8$ Hz), 4.05–4.20 (m, br), 4.30 (m, br) and 4.50 (s, br)], 3H}, {[5.90 (s, br) and 6.07 (d, $J=5.5$ Hz)], 1H}, {[7.39 (d, $J=5.5$ Hz) and 7.55 (s, br)], 1H}; ^{13}C NMR (75.4 MHz, $CDCl_3$, 293 K): 18.9 (br) and 20.4; 21.4 and 22.0 (br), 23.4, 24.0, 24.8, 28.2 and 28.3, 39.5 (br) and 40.8, 52.7 and 54.0 (br), 79.9, 118.4 (br) and 120.9, 156.4 (br), 159.5 (br) and 160.4, 172.2 (br); HRMS (IE, 40 eV): 224.0924; calcd for $C_{11}H_{14}NO_4$ ($M^+-C_4H_9$): 224.0923.