Tetrahedron Letters 50 (2009) 5395–5398

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective synthesis of *N,N*-acetals by cyclization of an *N*-acyliminium ion through interaction with an *N*-sulfonyl group

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ARTICLE INFO

Article history:
Received 14 June 2009
Revised 7 July 2009
Accepted 9 July 2009
Available online 12 July 2009

ABSTRACT

A new method for the stereoselective synthesis of five- and six-membered bicyclic *N,N*-acetals with trans configuration was developed using *N*-acyliminium ion cyclization. The *N*-sulfonyl substituted compounds were effectively cyclized to give the corresponding acetals in high yields and stereoselectivities, suggesting that the intramolecular interaction between the iminium and the sulfonyl group plays a key role in the cyclization.

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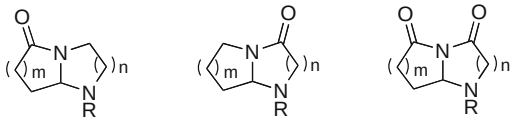
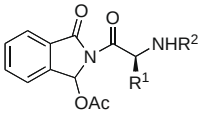
Bicyclic *N,N*-acetal ring systems I and II are observed in a number of natural products[1] and biologically active compounds,[2] and, therefore, various methods for the construction of these ring systems have been extensively explored. We, however, were interested in the synthesis of the *N,N*-acetal ring system III with a bislactam framework as no method for the stereoselective synthesis of this group of compounds has been established despite their potential bioactivities.[3]



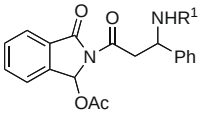
I II III

The *N*-acyliminium ion[4]-mediated cyclization reaction is a useful method for the construction of various ring systems. Although the application of this cyclization method toward *N,N*-acetal formation seems to be promising, there have been few examples of its use apart from the tandem cyclization of certain peptides.[2a,2b] We speculated that this methodology would be applicable to the construction of ring system III compounds as outlined in Scheme 1. In this Letter, we report a new method for diastereoselective cyclic *N,N*-acetal synthesis via the *N*-acyliminium ion, where the *N*-sulfonyl substituent plays a key role in determining the yields and stereoselectivities.

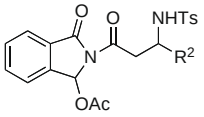
Substrates **1a–c** and **2a–i** were synthesized by the coupling of 3-(1-ethoxyethoxy)isoindolin-1-one[5] and the corresponding *p*-nitrophenylesters using *n*-BuLi followed by the deprotection of the ethoxyethyl group and acetylation.[6] Various acids were employed for the generation of the *N*-acyliminium ions from compound **1a**.[7] The results are summarized in Table 1. In the presence of a catalytic amount of TfOH, the cyclization of **1a** was undertaken in CH_2Cl_2 at 0 °C to rt to give *N,N*-acetal **3a** in 47% yield along with a recovery of 31% of the substrate (entry 1); however, trifluoroacetic acid was found to be ineffective (entry 2). Lewis acids, such as BF_3OEt_2, $SnCl_4$ and TMSOTf, served as effective catalysts to afford *N,N*-acetal **3a** (entries 3–5). The reaction with 1.1 equiv of TMSOTf for 5 h gave **3a** without any reduction in the yield or selectivity from those obtained under the conditions shown in entry 5 (entry 6).



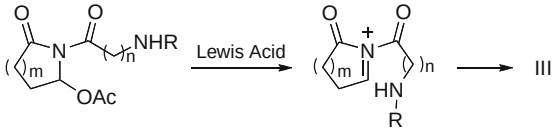
1a: R^1 = Ts, R^2 = Ph
1b: R^1 = Ts, R^2 = Bn
1c: R^1 = Ms, R^2 = Ph



2a: R^1 = Ts
2b: R^1 = Ms
2c: R^1 = Ns
2d: R^1 = Cbz
2e: R^1 = Boc
2f: R^1 = Ac



2g: R^2 = Me
2h: R^2 = Et
2i: R^2 = *p*-ClC_6H_4



Scheme 1.

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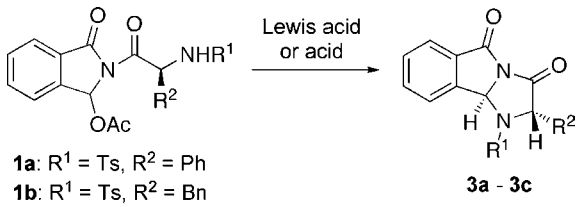
doi:10.1016/j.tetlet.2009.07.042

Table 1
Face-selective cyclization of **1a–c**

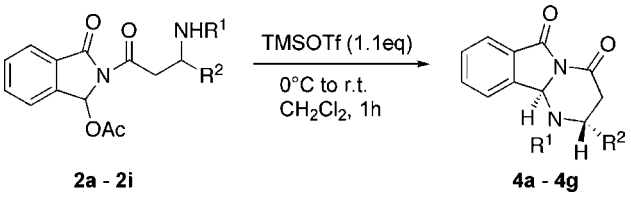


1a: R^1 = Ts, R^2 = Ph
1b: R^1 = Ts, R^2 = Bn
1c: R^1 = Ms, R^2 = Bn

Entry	Compd	Time (h)	LA or acid (equiv)	Yield of **3**[a] (%)	dr[b]
1	**1a**	15	TfOH (cat)	47	89:11
2	**1a**	15	CF_3CO_2H (cat)	0	—
3	**1a**	15	BF_3OEt_2 (2.0)	69	81:19
4	**1a**	15	$SnCl_4$ (2.0)	79	91:9
5	**1a**	15	TMSOTf (2.0)	78	83:17
6	**1a**	5	TMSOTf (1.1)	78	90:10
7	**1b**	5	TMSOTf (1.1)	92	87:13
8	**1c**	5	TMSOTf (1.1)	64	99:1

[a] Isolated yield.
[b] Determined ^{1}H NMR spectra.

Table 2
Face-selective cyclization of **2a–i**



Entry	Compd	Yield of **4**[a] (%)	de[b]
1	**2a**	92	>99
2	**2b**	79	>99
3	**2c**	85	>99
4	**2d**	24	78
5	**2e**	0	—
6	**2f**	0	—
7	**2g**	86	>99
8	**2h**	84	>99
9	**2i**	73	>99

[a] Isolated yield.
[b] Determined by ^{1}HNMR spectra.

The cyclization of compound **1b** having a benzyl group also gave **3b** in high yield under the same conditions (entry 7). The replacement of the Ts group at the *N*-atom with the Ms group afforded excellent stereoselectivity (entry 8). The structure of the major product **3a** was determined by X-ray crystallographic analysis.[8] The relationship between the two methine hydrogens adjacent to the nitrogen atom was trans as shown in Figure 1. A comparison of the ^{1}H NMR spectra of **3b** and **3c** with that of **3a** indicated that they also had trans stereochemistry. It is interesting to note that no cyclization with the aromatic ring was detected.[9]

Next, the intramolecular cyclizations of **2a–i,** having a longer chain, were conducted under the same reaction conditions as those described above and the results are listed in Table 2. The cyclization of **2a** and **2b** having a Ts and Ms group, respectively, gave the corresponding six-membered *N,N*-acetals with excellent diastereoselectivities (entries 1 and 2).[10] The X-ray structural analysis of the product **4a**[11,12] confirmed a trans stereochemistry similar to that of **3a**. The Ns group is also available in this reaction, which provides a synthetic merit due to the easy deprotection of the Ns group (entry 3).[13] However, when the N-protective group was a Cbz group, the product yield was significantly decreased (entry 4). Moreover, no cyclized products were obtained from the reactions of **2e** and **2f** possessing a Boc and acetyl group, respectively.

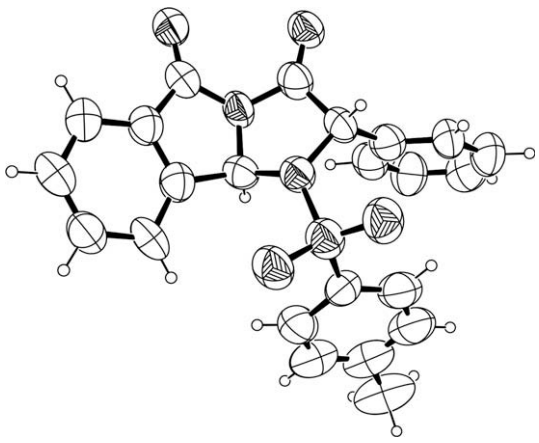


Figure 1. X-ray structure of **3a**.

The cyclization of the other substrates **2g–i** with various alkyl substituents afforded **4g–i** in good yields and high stereoselectivities.

The significant differences in the product yields and stereoselectivities according to whether or not the N-substituent is a sulfonyl group can be explained by differences in the optimized geometries of the intermediate iminium ions. Figure 2 shows the optimized geometries of **A** and **B** produced from **2b** and **2f**, respectively, which were predicted by DFT calculations at the B3LYP/6-31G* level after the conformation search and the AM1 optimization.[14] The S=O group of **A** is on the plane of the iminium moiety with an O···C1 distance of 2.759 Å, whereas the *N*-acetyl moiety of the iminium ion **B** is on the side of the iminium plane with an O···C1 distance of 3.320 Å. Both distances are much shorter than the sum of the atomic radii of C and O atoms, suggesting the existence of intramolecular interactions between them.

The N2···C1 distance of 3.712 Å for the intermediate **A** is much shorter than that for **B** (5.149 Å). The lone pair of the *N*-Ms moiety is antiperiplanar to the S–C bond due to the hyperconjugation of the σ^*s–c and the lone pair orbital,[15] which enables the attack of the lone pair on the iminium. On the other hand, the nitrogen lone pair of **B** is perpendicular to the iminium plane. These geometrical differences are thought to cause the significant differences in yields and stereoselectivities between the *N*-sufonyl and *N*-acyl derivatives described above. It has been reported that various types of double bonds, such as C=C, C=O and C=S bonds, serve as π-components for cation-π interactions.[16,17] Although the origin of the interactions observed in **A** is still not clear, the interaction between the S=O and the iminium ion may also be a cation-π interaction as no intramolecular HOMO–LUMO interaction was observed in the intermediate **A**.

The all conformers for **2b** obtained by the conformation search and the AM1 optimization showed that the all *N*-Ms moieties are located on the same side of the iminium plane as that shown in Scheme 2. This enables intramolecular cyclization at the same side of the iminium plane to give trans products, which can explain the high diastereoselectivity described in Table 2.

Table 3 lists the energies of **3a**, **3c**, **4a** and **4b** predicted by DFT calculations at the B3LYP/6-31G* level together with their differences ΔE.[14] As can be seen from Table 3, the cis isomers are much more stable than the trans isomers, suggesting that the cyclization reaction is controlled under a non-thermodynamic process.

In summary, we described a new method for the synthesis of *N,N*-acetals with a bislactam framework via the intramolecular

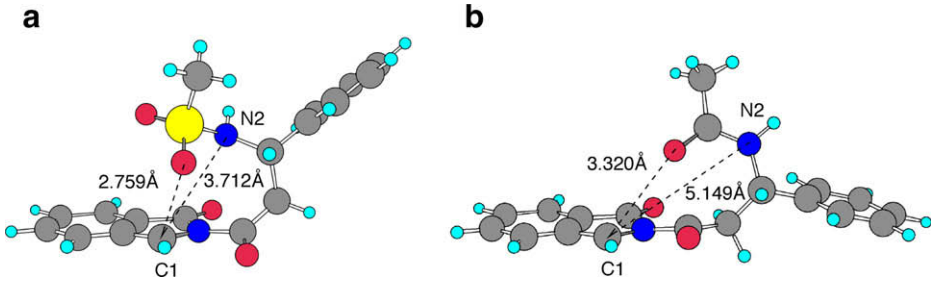
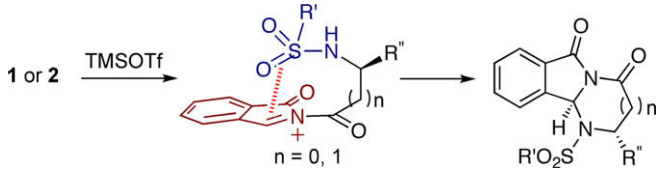
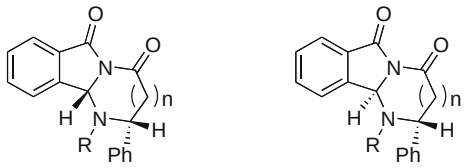


Figure 2. Most stable conformers **A** and **B** for the iminium ions of (a) **2b** and (b) **2f**, respectively.



Scheme 2.

Table 3
Energies for cis and trans isomers for **3a**, **3c**, **4a** and **4b**, and their differences[a]



Compd	E_{cis}	E_{trans}	ΔE
3a	−1064149.82	−1064146.91	2.91
3c	−919163.26	−919157.97	5.29
4a	−1088818.29	−1088815.75	2.54
4b	−943831.49	−943830.53	0.96

[a] Energy in kcal/mol.

cyclization of *N*-acyliminium ion intermediates. The key feature in this reaction is that the product yields and stereoselectivities were significantly dependent on the N-protective groups. DFT calculations for the intermediate iminium ion suggest that an intramolecular interaction between the S=O and the iminium ion plays a key role in determining the yields and stereoselectivities. Taking the related interaction systems into consideration, a cation-π interaction may make a major contribution to this interaction.

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6. *A typical procedure for the synthesis of substrates*: to a solution 3-(1-ethoxyethoxy)isoindolin-1-one (474.7 mg, 2.15 mmol) in dry THF (10 ml) at −78 °C under nitrogen atmosphere were added *n*-BuLi (1.6 M in hexane, 1.61 ml) and 4-nitrophenyl 2-*N*-tosylamino-2-phenylethanoate (1.189 g, 2.79 mmol) in dry THF (5.6 ml), and the solution was stirred at −78 °C for 2 h. The reaction mixture was warmed to room temperature and was quenched by satd NH_4Cl solution. After removal of the solvent, the residue was extracted with CH_2Cl_2 three times, and the combined extracts were dried over anhydrous $MgSO_4$. The evaporation of the solvent gave a crude product, which was subjected to column chromatography (Florisil, hexane/ethyl acetate = 3/1–1/1) to afford a pure product (899.7 mg, 82.4%).To a solution of produced amide (899.7 mg, 1.77 mmol) in a 3:1 mixture of THF and H_2O (18 ml) was added PPTS (89 mg), and the solution was stirred for overnight at 50 °C. The reaction mixture was neutralized with 5% $NaHCO_3$ solution, and the solvent was removed. The residue was extracted with $CHCl_3$ three times, and the combined extracts were dried over anhydrous $MgSO_4$. The solvent was removed to give a yellow solid, which was purified by column chromatography (hexane/ethyl acetate = 2/1–1/2) to afford a pure hemiaminal (581 mg, 75.3%). Acetylation of this product was carried out by using acetic anhydride in the presence of triethylamine (2 equiv) and DMAP (0.1 equiv) in dry THF (13.5 ml). A usual work-up and purification gave pure **1a** (630.9 mg, 95.4%).
7. Compound **1a**: a 7:3 mixture of diastereomers; mp 174.5–176.0 °C; IR (KBr) 3235, 3019, 1748, 1708, 1599, 1355, 1214, 1164, 1091, 1023, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85–7.13 (m, 13H), 6.48 and 4.67 (each d, J = 10.0 Hz, 1H), 5.92 and 5.90 (each d, J = 9.6 Hz, 1H), 2.34 and 2.25 (each s, 3H), 2.09 and 2.04 (each s, 3H); MS *m/z* 478 (M^+, 0.08 %), 418 (3.2), 368 (3.2), 323 (3.4), 263 (24), 260 (88), 233 (2.2), 213 (1.9), 177 (10), 155 (73), 132 (51), 104 (49), 91 (100), 77 (23), 69 (17), 57 (12), 43 (42); HRMS calcd for $C_{23}H_{18}O_4N_2S$ ($[M-C_2H_3O_2]^+$) 418.0987, found 418.0961.
8. *X-ray crystal data for* **3a**: $C_{23}H_{18}N_2O_4S$, M = 418.47, monoclinic, $P2_1/c$, μ = 1.730 mm^{-1}, a = 8.1593(4) Å, b = 26.3275(12) Å, c = 9.8578(4) Å, β = 109.8433(19)°, V = 1991.86(16) $Å^3$, T = 298 K, Z = 4, D_c = 1.395 g cm^{-1}. A total of 31,242 reflections were collected and 3601 are unique (R_{int} = 0.1539). R_1 and wR_2 are 0.0974 [$I > 2\sigma(I)$] and 0.3474(all data), respectively. See CCDC 735494.
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10. *A typical procedure for the cyclization of hemiaminals*: to a solution of hemiaminal **2a** (50.0 mg, 0.1 mmol) in dry CH_2Cl_2 (1 ml) was added TMSOTf (25.5 mg, 0.11 mmol) at 0 °C, and the solution was stirred for 1 h at rt. A saturated $NaHCO_3$ solution was added to the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layer was dried over $MgSO_4$ and was evaporated. The resulting crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 2/1–1/2) to afford **4a** (39.7 mg) in 92% yield. The diastereomeric excess of **4a** was determined by ^1H NMR analysis.
11. *X-ray crystal data for* **4a**: $C_{24}H_{20}N_2O_4S$, M = 432.49, triclinic, $P1$, μ = 1.651 mm^{-1}, a = 7.98275(14) Å, b = 16.7357(3) Å, c = 16.7367(3) Å, α = 86.7370(8)°, β = 76.2000(8)°, γ = 76.2080(8)°, V = 2108.81(7) $Å^3$, T = 298 K, Z = 4, D_c = 1.362 g cm^{-1}. A total of 33,976 reflections were collected and 13346 are unique (R_{int} = 0.043). R_1 and wR_2 are 0.0587 [$I > 2\sigma(I)$] and 0.1674 (all data), respectively. See CCDC 735495.
12. Compound **4a**: mp 225.0–225.5 °C; IR (KBr) 3031, 1761, 1697, 1599, 1391, 1344, 1295, 1169, 1050, 769, 691, 565 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.2 Hz, 1H), 7.77–7.56 (m, 5H), 7.48 (t, J = 8.4 Hz, 2H), 7.40 (t, J = 7.6 Hz, 1H), 7.17 (br s, 4H), 6.01 (s, 1H), 5.82 (t, J = 8.0 Hz,1H), 3.13 (dd, J = 17.2, 6.8 Hz, 2H), 2.41 (s, 3H); MS *m/z* 432 (M^+, 9.7 %), 368 (5.4), 300 (9.8), 277 (43), 236 (7.2), 199 (5.9), 155 (14), 131 (100), 103 (50), 91 (55), 77 (29), 69 (34), 57 (29), 43 (26); HRMS calcd for $C_{24}H_{20}O_4N_2S$ 432.1144, found 432.1172.

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