Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 47 (2006) 4477–4480

Tetrahedron Letters

Eco-friendly *N*-acyliminium ion chemistry: solvent-free $HNTf_2$ and TIPSOTf-catalyzed α-amidoalkylation of silicon-based π-nucleophiles

Marie-José Tranchant, Charlotte Moine, Raja Ben Othman, Till Bousquet, Mohamed Othman and Vincent Dalla*

URCOM, Faculté des Sciences et Techniques de l'Université du Havre, BP 540, 25 rue Philippe Lebon, 76058 Le Havre Cedex, France

Received 13 March 2006; revised 5 April 2006; accepted 7 April 2006
Available online 11 May 2006

Abstract—The α-amidoalkylation of silicon-based π-nucleophiles is efficiently catalyzed by $HNTf_2$ or TIPSOTf at very low levels of loading in neat conditions.

C–C bond forming reactions between weak carbon nucleophiles and *N*-acyliminium ions generated from cyclic *N*,*O*-acetals represent an important field of research in organic chemistry to provide useful α-functionalized amino compounds.[1] While these α-amidoalkylation reactions have been routinely promoted by highly reactive, but also often toxic Lewis acids such as $TiCl_4$, BF_3–OEt_2, $SnCl_4$, etc., the development of safe procedures for their production has recently become a subject of intensive investigation.[2–6]

Our group has recently contributed to the development of improved conditions for *N*-acyliminium ion chemistry by documenting the use of TIPSOTf[5] and $HNTf_2$[6] as practical and highly efficient substitutes for the conventional, but quite instable, TMSOTf[7] to catalyze the amidoalkylation of silicon-based nucleophiles by five-membered ring *N*-acyliminium ion precursors. Typically, these reactions were achieved in presence of catalyst in the range of 2–10 mol % in dichloromethane or acetonitrile as a solvent. In an international context where 'green chemistry' is paramount,[8] we report in this note the success of such reactions under solvent-free conditions as a key improvement. These new conditions now provide a totally eco-friendly, yet powerful C–C-bond forming process that work under very mild conditions. Overall, this modification renders the catalytic amidoalkylation process highly efficient,[5,6] with the more favorable cases now successful at the remarkable level of 0.3 mol %.

The two generic *N*-acyliminium ion precursors **1a** (Table 1) and **1b** (Table 2) were initially used as representative *N*,*O*-acetals. The feasibility studies were undertaken using the highly reactive carbamate **1a**[9] and common silicon-based π-nucleophiles (1.4 equiv). The results are summarized in Table 1. The initial experiments using $HNTf_2$ as a catalyst immediately revealed that a solvent-free approach was possible with this reagent. According to previous literature[10] and control experiments,[6] $HNTf_2$ is assumed to be the pre-catalyst which generates Me_3SiNTf_2 as an active species by protodesilylation.

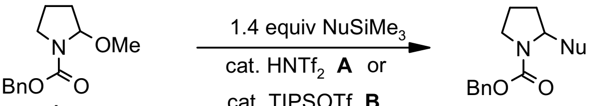
$HNTf_2$ gave a prompt allylation reaction at a remarkable level of 0.3 mol % (run 1, **A**).[11] In terms of catalyst loading, this example represents by far the most efficient C–C bond forming process between a *N*,*O*-acetal and a carbon nucleophile. We were surprised to observe that the amount of catalyst should be slightly increased when using the much more nucleophilic trimethylsilyl enol ethers[12] (runs 2–4 **A**). Interestingly, the catalyst loading varies with the Lewis base properties of the accordant carbonyl moiety. Indeed, 1 mol % of $HNTf_2$ was necessary to catalyze the amidoalkylation of the silyl enol ether of acetophenone (run 2, **A**), while a level of 5 mol % was necessary for the amidoalkylation of the silyl enol ether of cyclohexanone and that of the silyl

---

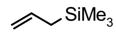
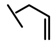
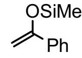
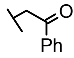
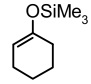
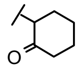
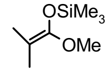
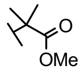
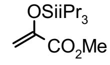
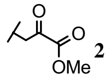
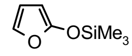
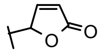
* Corresponding author. Tel.: +33 02 32 74 44 01; fax: +33 02 32 74 43 91; e-mail: vincent.dalla@univ-lehavre.fr

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.04.090

Table 1. Reactions of *N*,*O*-acetal **1a** and generic silicon-based π-nucleophiles catalyzed by $HNTf_2$ and TIPSOTf under solvent-free conditions



1a **2a-g**

Entry	$NuSiMe_3$	**A**, time (yield %)[a]	Nu adduct	**B**, time (yield %)[a]
1		0.3 mol %, 3 h 30 min (92)	 **2a**	Not attempted
2		1 mol %,[b] 30 min (97)	 **2b**	0.3 mol %, 4 h 30 min[c] (98)
3		5 mol %,[d] 1 h (100)	 **2c**	1 mol %, 2 h 30 min (100)
4		5 mol %,[d] 30 min (90)	 **2d**	1 mol %, 24 h[e]
5		5 mol %, 1 h 30 min[c] (75)	 **2e**	5 mol %, 1 h 30 min[c] (47)
6		5 mol %, 5 min (99)[f] 2 mol %, 24 h (70% conv)[g]	 **2f**	Not attempted

[a] Isolated yields.

[b] Less than 10% conversion was achieved when 0.3 mol % $HNTf_2$ was used.

[c] Time not optimized.

[d] Less than 10% conversion was achieved when 1 mol % $HNTf_2$ was used.

[e] Less than 10% conversion was achieved.

[f] Ratio threo/erythro = 8.5/1.

[g] Determined by ^1H NMR spectroscopy.

ketene acetal derived from 2-methyl propionic acid methyl ester to proceed efficiently (runs 3–4, **A**). These results may be explained by assuming a product inhibition mode upon a ditopic binding of Me_3SiNTf_2 by the keto and the urethane groups of the Mannich adducts **2b–c**. This phenomenon is likely to partially alter the catalytic turnover (Fig. 1).[13] We anticipated by replacing Me_3SiNTf_2 with the more hindered and less oxophilic TIPSOTf[13] the (limited) adverse effect should be overridden and thus restore a fully efficient catalytic amidoalkylation process. This was confirmed when the Mannich reactions of the silyl enol ethers of acetophenone and cyclohexanone were efficiently catalyzed by only 0.3 mol % and 1 mol % of TIPSOTf, respectively (runs 2–3, **B**).

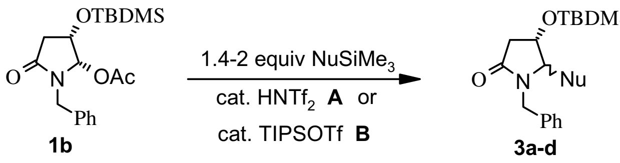
On the other hand, no improvement was observed for the formation of the ester **2d**, the two oxygen atoms wherein may themselves coordinate the catalyst (run 4, **B**). Using $HNTf_2$ as catalyst, the more challenging TIPS enol ether derived from methyl pyruvate was amidoalkylated in good yield within short reaction time. In contrast, a less selective reaction took place when TIPSOTf was employed, with several unidentified side-products being formed (run 5, **A** vs **B**). This solvent-free approach proved to be also successful for the vinylogous *N*-acyliminium ion trapping by 2-trimethysilyloxyfuran[14] with a catalytic activity very similar to that of the acyclic silyl ketene acetal analog (run 6 **A**–**B** versus run 4 **A**–**B**).

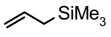
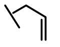
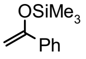
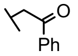
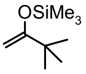
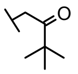
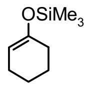
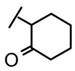
In order to expand the scope of our process, we then shifted toward examining the 4-*tert*-butyldimethylsilyloxy-5-acetoxy *N*-acyliminium cation precursor **1b** (Table 2).

In our precedent study, the reaction of **1b** with the trimethylsilyl enol ether of acetophenone catalyzed by $HNTf_2$ either in dichloromethane or acetonitrile as solvents performed poorly.[15] Similarly, the amidoalkylation involving the trimethylsilyl enol ethers of cyclohexanone and pivalone completed at a relatively high level of catalyst loading, that is, 10 mol %.[6] These three reactions thus served as an excellent measure for further confirmation regarding the benefits of this solvent-free approach. The results obtained herein clearly demonstrate the advantage of the present method (runs 2–4). Remarkably, the amidoalkylation of the trimethylsilyl enol ethers of acetophenone and pivalone proceeded efficiently at a level of 0.5 mol % of catalyst loading. It should be noticed that the reaction presented in run 2 (method **A**) succeeded on a one gram scale.

However, it is worth mentioning that, in stark contrast to the results obtained with **1a**, the amidoalkylation of allyltrimethylsilane (run 1) proceeded with moderate efficiency. Obviously, the procedure carried out in solvent is more adapted for this specific case.[5,6] This is one of the rare cases we have identified to date that works less favorably than its variant in solution. The *N*-acyliminium ions derived from 2-oxy pyrrolidines *N*-carbamate are considered to be more reactive than those originating from hydroxylactam derivatives.[9] Hence, the need for less loading of $HNTf_2$ in the amidoalkylation of the trimethylsilyl enol ether of aceto-

Table 2. Reactions of *N*,*O*-acetal **1b** and generic silicon-based π-nucleophiles catalyzed by $HNTf_2$ and TIPSOTf under solvent-free conditions



Entry	$NuSiMe_3$	**A**, time (yield %)[a]	Nu adduct	**B**, time (yield %)[a]
1	 2 equiv	2 mol %, 3 h 30 min (48)	 **3a**	2 mol %, 3 h (43)
2[b]	 1.4 equiv	0.5 mol %, 4 h[c] (89)[d]	 **3b**	0.5 mol %, 4 h, quantitative[e]
3	 2 equiv	2 mol %, 2 h[c] (86)[f] 0.5 mol %, 3 h (90)[g]	 **3c**	Not attempted
4	 2 equiv	5 mol %, 4 h[c] (77)[h]	 **3d**	Not attempted

[a] Isolated yields.

[b] The reaction catalyzed by $HNTf_2$ was performed on a one gram scale.

[c] Time not optimized.

[d] Two separable diastereomers obtained (cis adduct, 19%, trans adduct, 70%).

[e] Estimated by ^1H NMR spectroscopy (trans/cis ratio ∼ 5/1).

[f] Two separable diastereomers obtained (cis adduct, 24%, trans adduct, 62%).

[g] Based on conversion, measured by ^1H NMR spectroscopy, with a trans/cis ratio ∼ 5/1.

[h] Two separable diastereomers obtained (cis adduct, 13%, trans adduct, 64%).

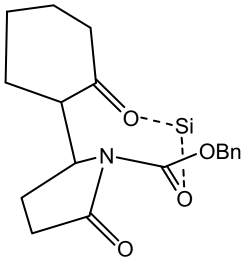
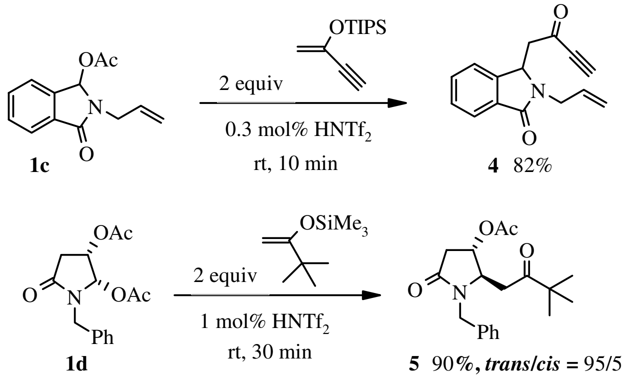


Figure 1. Product inhibition mode by Me_3SiNTf_2 (the substituents on silicon have been omitted for clarity).

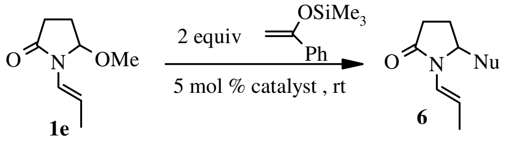
phenone by **1b** (Table 2, run 2) than in that involving **1a** (Table 1, run 2) seems astonishing and is actually in line with the product inhibition event discussed above (Fig. 1).

The practicality of our solvent-free amidoalkylation is further exemplified with the Mannich reactions of the crystalline acetoxy lactams **1c** and **1d** (Scheme 1). The two attempted reactions produced the desired adducts **4** and **5** at very low catalyst loadings within short reaction times and good yields. It is worth noting that the Mannich reaction of **1c** with *a sterically demanding TIPS enol ether required only 0.3 mol %* of $HNTf_2$. These results emphasize the synthetic usefulness of this solvent-free conversion.



Scheme 1.

Finally, the challenging (due to the dienic nature of the related *N*-acyliminium ion) *N*-propenyl-5-methoxy lactam **1e** was subjected to a set of reactions in the presence of 5 mol % of $HNTf_2$ or TIPSOTf under neat conditions. Of the nucleophiles tested [$H_2C{=}C(Ph)(OSiMe_3)$, $H_2C{=}C(t\text{Bu})(OSiMe_3)$, $H_2C{=}CH{-}CH_2SiMe_3$], only the former gave the expected adduct **6** after a sluggish reaction (Scheme 2), bracketing the weak reactivity expected for **1e** and the threshold nucleophilicity required for an addition.[12] Thus, it seems that silyl enol ethers whose nucleophilicity is at the same order of magnitude to that of the trimethylsilyl enol ether of acetophenone have set



catalyst	time	yield %
$HNTf_2$	7 h	76
TIPSOTf	7 h	76

Scheme 2.

a critical limit for reactivity toward the iminium cation of **1e**.[12,16] In our previous work, we observed a significant accelerating effect in the amidoalkylation reactions involving weakly reactive *N*-acyliminium ion precursors by changing TIPSOTf with the outstanding oxophilic R_3SiNTf_2 species as catalysts.[6] Obviously, this clear-cut effect can be rationalized by assuming that the *N*-acyliminium ion formation, which is generally accepted as the rate-determining step in these reactions, is greatly accelerated by R_3SiNTf_2 species. In the transformations of **1e**, we have clearly shown that the reaction rate is insensitive to the nature of the catalyst, suggesting that in the present case the rate-limiting step is the trapping of the accordant stabilized iminium cation.

In summary, a key improvement in the α-amidoalkylation of generic π-nucleophiles by cyclic *N*,*O*-acetals catalyzed by $HNTf_2$ and TIPSOTf has been realized upon achieving these reactions under solvent-free conditions.[17] This refinement has led to a simple and totally eco-friendly procedure, now enabling the use of very low levels of catalyst loading, in the range of 0.3–5 mol %. We believe that this method improves considerably the usability of amidoalkylation, and trust it will find use in the scientific community. We are currently applying this solvent-free approach to the synthesis of complex aza-bicyclo compounds and our first results in this area will be published shortly.

References and notes

1. Reviews: (a) Speckamp, W. N.; Molenaar, M. J. *Tetrahedron* **2000**, *56*, 3817; (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.
2. Recently, Kobayashi and co-workers reported efficient nucleophilic substitution reactions of 2-methoxy and 2-acetoxy *N*-carbonyl piperidine derivatives by trialkylsilyl nucleophiles catalyzed by 10 mol % of various metal triflates: (a) Okitsu, O.; Suzuki, R.; Kobayashi, S. *Synlett* **2000**, 989; (b) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809.
3. Recently, Pilli and co-workers reported some Mannich reactions catalyzed by HCl and carried out in water in the presence of SDS as a surfactant. Unfortunately, the reaction was restricted to β-substituted enol ethers: Pilli, R. A.; Camilo, N. S. *Tetrahedron Lett.* **2004**, *45*, 2821.
4. Recently, Pilli and co-workers implemented allylation and Mannich reactions performed in the organoindate(III) ionic liquid BMI–$InCl_4$: Pilli, R. A.; Robello, L. G.; Camilo, N. S.; Dupont, J.; Lapis, A. A. M.; da Silveiro Neto, B. A. *Tetrahedron Lett.* **2006**, *47*, 1669.
5. Ben Othman, R.; Fousse, A.; Bousquet, T.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 2825.
6. Ben Othman, R.; Bousquet, T.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 5335.
7. For recent examples of truly catalytic (catalyst loading <10 mol %) nucleophilic substitution reactions of *N*-acyliminium ion precursors using TMSOTf: (a) Barrett, A. G. M.; Quayle, P. *J. Chem. Soc., Chem. Commun.* **1981**, 1076; (b) Bernardi, A.; Micheli, F.; Potenza, D.; Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 4949; (c) Pilli, R. A.; Dias, L. C. *Synth. Commun.* **1991**, *21*, 2213; (d) Ahman, J.; Somfai, P. *Tetrahedron* **1992**, *48*, 9537; (e) Arndt, H. D.; Polborn, K.; Koert, U. *Tetrahedron Lett.* **1997**, *38*, 3879; (f) D'Oca, M. G. M.; Pilli, R. A.; Vencato, I. *Tetrahedron Lett.* **2000**, *41*, 9709; (g) Sugiura, M.; Kobayashi, S. *Org. Lett.* **2001**, *3*, 477.
8. (a) Anastas, P. T.; Warner, J. C. *Green Chemistry, Theory and Practice*; Oxford University Press: Oxford, 1998; (b) *Green Chemistry, Frontiers in Benign Chemical Synthesis and Processes*; Anastas, P. T., Williamson, T. C., Eds.; Oxford University Press: Oxford, 1998; (c) Clark, J.; Macquarrie, D. *Handbook of Green Chemistry and Technology*; Blackwell Science, 2002; (d) Eissen, M.; Metzger, J. O.; Schmidt, E.; Schneidewind, U. *Angew. Chem. Int. Ed.* **2002**, *41*, 414.
9. D'Oca, M. G. M.; Moraes, L. A. B.; Pilli, R. A.; Eberlin, M. N. *J. Org. Chem.* **2001**, *66*, 3854, and references cited therein.
10. See Ref. 6 and Refs. 1–6 cited therein.
11. Typical procedure: To a mixture of carbamate **1a** (235 mg, 1 mmol) and allyltrimethylsilane (0.22 mL, 1.4 mmol) was added under an argon atmosphere 0.3 mol % of $HNTf_2$ (0.5 M solution in dichloromethane, 6 μL). After 3 h 30 min of vigorous stirring, the mixture was purified on a short column of silica gel, eluting with cyclohexane/EtOAc 7/3, to give the known allylated adduct **2a** in 92% yield.
12. Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.
13. For a contribution describing the outstanding oxophilic properties of R_3SiNTf_2, see: (a) Mathieu, B.; Ghosez, L. *Tetrahedron Lett.* **1997**, *38*, 5497; (b) Mathieu, B.; Ghosez, L. *Tetrahedron* **2002**, *58*, 8219.
14. For an ealier report describing the vinyloguous amidoalkylation of TMSF catalyzed by 10 mol % of TMSOTf in dichloromethane, see Ref. 7f.
15. Unpublished results from our group.
16. In the reaction of the trimethylsilyl enol ether of pivalone $H_2C{=}C(tBu)(OSiMe_3)$ using either $HNTf_2$ or TIPSOTf, a white precipitate rapidly appeared and no reaction occurred. However, the corresponding Mannich product could be obtained in a correct yield of 64% by performing the reaction in dichloromethane under forced conditions, that is, by using 20 mol % of TIPSOTf and 4 equiv of the silyl enol ether within a long reaction period of 20 h. The nucleophilicity of this enol ether is not reported in the Mayr's scale, but can be compared to that of the trimethylsilyl enol ether of acetone, which is slightly inferior to that of the trimethylsilyl enol ether of acetophenone. Allyltrimethylsilane, however, considerably lacks nucleophilicity for addition to the iminium cation.
17. As this work was in progress, Matsumara and co-workers reported that the Mannich reaction between *N*,*O*-acetals and methylene actives catalyzed by 10 mol % of various Brønsted- and Lewis acids under solvent-free conditions proceeded with more efficiency than those carried out in dichloromethane Matsumara, Y.; Ikeda, T.; Onomura, O. *Heterocycles* **2006**, *67*, 113.