Tetrahedron Letters 53 (2012) 2414–2416

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Water-promoted one-pot vinylogous Mannich-type reaction of trimethylsilyloxyfuran

Grégory Landelle, Aurélie Claraz, Sylvain Oudeyer *, Vincent Levacher

Université de Rouen, Laboratory COBRA UMR 6014 & FR 3038, IRCOF, 1 Rue Tesnière, 76821 Mont St. Aignan Cedex, France
INSA de Rouen, Avenue de l'Université, 76800 St. Etienne du Rouvray, France
CNRS Délégation Normandie, 14 Rue Alfred Kastler, 14052 Caen Cedex, France

ARTICLE INFO

Article history:
Received 13 February 2012
Revised 22 February 2012
Accepted 29 February 2012
Available online 8 March 2012

Keywords:
Vinylogous Mannich-type reaction
One-pot reaction
Solvent-free
Imines
Trimethylsilyloxyfuran

ABSTRACT

Water, produced in situ during the formation of imines from aldehydes **1** and amines **2**, is employed to promote the one-pot Mannich reaction of trimethylsilyloxyfuran **3a** without addition of extra solvent or catalyst. This clean and quick reaction allows the obtention of a series of 5-substituted γ-butenolides **4** with good yields and modest diastereomeric ratio. A large panel of substituents is tolerated ranging from aliphatic chains to aromatic or heteroaromatic rings.

The 5-substituted γ-butenolide motif is part of several natural products[1] or serves as a versatile building block.[2] As such, a lot of efforts have therefore been devoted to its synthesis in the past years.[1b,3] The most convenient approach to access to 5-substituted furanone involves the vinylogous addition of silyloxyfurans[1b,4] or direct addition of γ-crotonolactone to preformed imines.[5] The reactions involving the in situ generation of imines from aldehydes and amines (i.e., three-component reaction) remain rare in the literature.[4b,6] In the actual economical context, the development of efficient processes which (1) use cheap and nontoxic catalysts or promoters (2) avoid the use of organic solvent and (3) limit the generation of by-products (atom economy) has became a challenging area for synthetic chemists.

In 2005, Yus and co-workers reported a catalyst free multicomponent Strecker reaction in acetonitrile in which a molecule of water generated during the in situ generation of imine acts as an activator of both TMSCN via a hypervalent silicate species and the imine via the formation of an iminium.[7] However, in 2007, Najera and co-workers mentioned that commercial TMSCN is polluted by HCN (detected by NMR) which could also play an important role in the three-component Strecker reaction.[8] Thus, we postulated that water could act as an efficient activator of other silyl nucleophiles for the three-component Mannich-type reaction by extrapolating the general principle of using a by-product generated during a first reaction (i.e., water generated during the formation of imines) to promote an addition reaction. Silyloxyfuran could be a good candidate for such reactions as it is commercially available or easy to prepare. In addition, its hydrolysis product is less acidic than HCN and thus would not interfere with the outcome of the reaction if pollution occurred (Fig. 1).

A first set of experiments was aimed at confirming this working hypothesis. The one-pot reaction between benzaldehyde **1a**, aniline **2a,** and trimethylsilyloxyfuran **3a** was carried out and we were pleased to observe the formation of the addition product **4a** in 86% isolated yield as a 53:47 *anti/syn* mixture in only 20 min without solvent (Scheme 1).

The importance of water generated during the imine formation was assessed by performing the reaction between the preformed imine **5a** and the trimethylsilyloxyfuran **3a**. Under these conditions no addition product **4a** was detected by ^{1}H NMR. Moreover, the addition of 1 equiv of water to the previous mixture resulted in the formation of the desired product **4a** in almost complete conversion and comparable stereoselectivity as for the one-pot procedure (Scheme 2).[9]

With these promising results in hand several reaction parameters and additives were screened (Table 1).

First, the order of addition of the reagents does not have an impact on both the yield and selectivity (entries 1 and 2). Aware of a possible competitive 1,2-addition of **3a** to the aldehyde, we then chose to maintain a sequential order of addition of the reagents. A reduction of the amount of **3a** did not induce significant changes

---

* Corresponding author. Fax: +33 (0) 235522962.
E-mail address: sylvain.oudeyer@univ-rouen.fr (S. Oudeyer).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.02.115

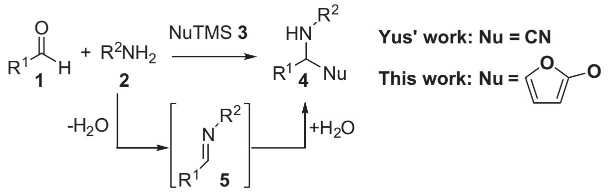
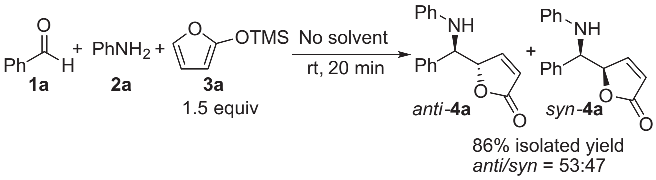
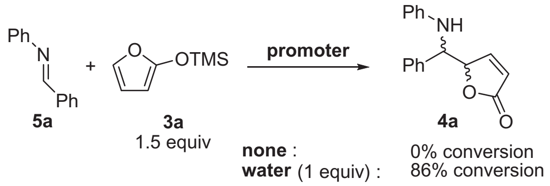


Figure 1. Working hypothesis based on previous work of Yus and co-workers with TMSCN.

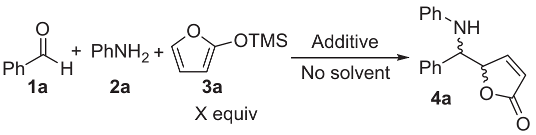


Scheme 1. Preliminary result.



Scheme 2. Demonstration of the crucial role of water.

Table 1
Screening of the reaction parameters

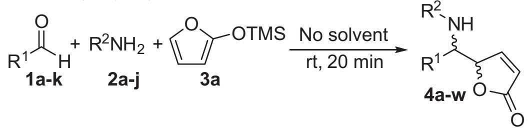


Entry	Additive (mol %)	**3a**:X equiv	Yield[a] (%)	dr[b] (*anti*/*syn*)[c]
1	–	1.5	87[d] (86[e])	53:47
2	–		87[f]	56:44
3	–	1.2	88	51:49
4	AcOH (10)	1.5	72	51:49
5	TsOH (10)		100	37:63
6	TfOH (10)		100	42:58
7	*i*-PrOH (10)		77	48:52
8	H_2O (10)		82	50:50
9	H_2O (1000)		81	48:52

[a] Determined by ^1H NMR with respect to MTBE used as internal standard.
[b] Measured by ^1H NMR.
[c] All attempts to separate both isomers have failed.
[d] **2a** was added to **1a** and the mixture was stirred at rt for 5 min before the introduction of **3a**.
[e] Isolated yield.
[f] **1a**, **2a** and **3a** were added simultaneously.

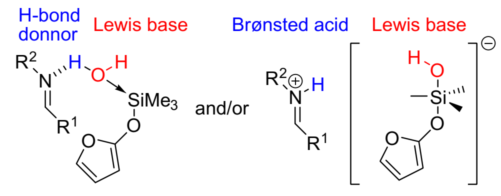
in the yield nor in the diastereomeric ratio (entry 3). In further attempts to improve the low *anti*/*syn* selectivity of the reaction, various acidic additives were tested. Although *p*-toluenesulfonic acid and triflic acid allowed to reach quantitative yields (entries 5 and 6), no significant improvement in the diastereoselectivity could be observed. It is worth noting that whereas, the amount of water formed in situ during imine formation proved to be crucial to promote the vinylogous Mannich reaction, the addition of additional water has no impact on the reaction in terms of both conversion and diastereoselectivity (entries 8 and 9).

Table 2
Scope of aldehydes **1** and amines **2** for the water promoted vinylogous Mannich reaction of trimethylsilyloxyfuran **3a**[a]



Entry	**1**: R^1	**2**: R^2	**4**: Yield[b] (%)	dr[c] (*anti*/*syn*)[d]
1	**1a**: C_6H_5	**2a**: C_6H_5	**4a**: 86	53:47
2	**1b**: 4-Br-C_6H_4		**4b**: 61	57:43
3	**1c**: 3-NC-C_6H_4		**4c**: 73	58:42
4	**1d**: 4-Me-C_6H_4		**4d**: 73	48:58
5	**1e**: 4-MeO-C_6H_4		**4e**: 73	40:60
6	**1f**: 2-(5-Me-furanyl)		**4f**: 68	59:41[e]
7	**1g**: 3-Thiophenyl		**4g**: 81	56:44[e]
8	**1h**: CO_2Et		**4h**: 86	65:35[e]
9	**1i**: Me		**4i**: 11 (71)[f]	65:35[f]
10	**1j**: Et		**4j**: 66	68:32
11	**1k**: Cyclopropyl		**4k**: 69	57:43[e]
12	**1a**: C_6H_5	**2b**: 4-Cl-C_6H_4	**4l**: 87	53:47
13		**2c**: 4-F-C_6H_4	**4m**: 55	50:50
14		**2d**: 3-Br-C_6H_4	**4n**: 68	63:37
15		**2e**: 4-*n*Bu-C_6H_4	**4o**: 65	50:50
16		**2f**: 3-MeO-C_6H_4	**4p**: 89	58:42
17		**2g**: 2-HO-C_6H_4	**4q**: 50	55:45
18		**2h**: (4-MeO)(3-O_2N)-C_6H_3	**4r**: 86	58:42
19		**2i**: 3-NC-C_6H_4	**4s**: 71	53:47
20		**2j**: *n*Pr	**4t**: –	–
21	**1d**: 4-Me-C_6H_4	**2f**: (4-MeO)(3-O_2N)-C_6H_3	**4u**: 90	51:49
22	**1c**: 3-NC-C_6H_4	**2d**: 3-Br-C_6H_4	**4v**: 76	69:31
23	**1e**: 4-MeO-C_6H_4	**2b**: 4-Cl-C_6H_4	**4w**: 81	51:49

[a] 1 mmol of **2** was added to 1 mmol of **1** under vigorous agitation. After 5 min, 1.5 mmol of **3a** was added and the mixture was stirred for 15 min.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis of the crude product and by comparison (or extrapolation) with spectroscopic data of known compounds (see Supplementary data).
[d] All attempts to separate both isomers have failed.
[e] The relative configuration of both isomers has not been determined.
[f] 1 mmol of **1i** was added to 1.5 mmol of **3a** immediately followed by the addition of **2a**. The resulting mixture was then stirred for 20 min.



(a) Neutral intermediate (b) charged intermediate

Figure 2. Postulated reactive intermediates.

Having in hand the optimized conditions, we then focused our attention on the scope and limitations of this method (Table 2).

In all cases, complete conversion was observed in only 20 min. Regarding the substitution pattern at the aldehyde, a large panel of functional groups are tolerated ranging from aromatic (entries 1–5) or heteroaromatic (entries 6 and 7) rings to aliphatic chains (entries 9–11) and ester (entry 8). For substituted aromatic and heteroaromatic rings, good isolated yields were obtained along with modest diastereomeric excesses of about 20–30%. Surprisingly, while the general trend in the stereoselection is in favor of the trans isomer, an inversion of the *anti*/*syn* ratio was observed when the aromatic ring is substituted at the *para*-position by an electron donating group such as methoxy or methyl (entries 4 and 5 vs 1–3). Interestingly, the use of aliphatic aldehydes or ethyl glyoxylate, for which the isolation of the imine remains tricky, furnished good isolated yields albeit with modest 30% de (entries 8–11). In addition, it should be noted that the reaction involving acetaldehyde requires a change in the order of introduction of the reagents to ensure a decent isolated yield (entry 9). The amine part is somewhat less tolerant to substitution as only aniline derivatives provided the addition products (entries 12–19 vs 20) with isolated yields ranging from 50% to 89% and diastereomeric ratio up to 63:37. All attempts to use other amines such as *N*-benzylamine, α-methylbenzylamine, or *n*-propylamine failed giving rise only to formation of the corresponding imines **5a**. All the anilines tested furnished preferentially the trans isomer whatever the electronic nature of the substituents of the aromatic ring. Finally, several substituted benzaldehydes and anilines were tested providing good yields and diastereomeric ratio up to 69:31. It is noteworthy that the use of other silyl nucleophiles ($TMSCH_2CO_2Et$, $TMSCF_3$ or $TMSOC(OMe) = CMe_2$) did not provide the addition product.

In order to gain insights into the mechanism and more specifically into the role of the water in this one-pot reaction, additional control experiments were conducted. We thus controlled that TMSOH which is actually the only by-product of the reaction did not act as a promoter of the vinylogous Mannich reaction by mixing **5a**, **3a,** and 1 equiv of TMSOH. Moreover, no formation of γ-crotonolactone was observed when **3a** was allowed to react with 1 equiv of TMSOH, while only 21% of γ-crotonolactone was detected by ^{1}H NMR after 20 min by adding 1 equiv of water to **3a**. All these experiments along with the mechanisms of activation of silyl pro-nucleophiles by Lewis bases postulated in the literature[7,10] led us to propose two possible intermediates where, water acts as a dual activator of both imine **5a** and trimethylsilyloxyfuran **3a** as depicted in Figure 2. According to this hypothesis, water would activate both imine **5a** either via protonation (Fig. 2b) or hydrogen bond (Fig. 2a) and trimethylsilyloxyfuran **3a** through the presence of oxygen lone pairs of the water acting as Lewis base.

In summary, we have reported a clean and easy to implement one-pot vinylogous Mannich-type reaction of trimethylsilyloxyfuran under solvent-free conditions. This methodology allows the rapid access to a series of 5-substituted γ-butenolides **4** with good yields. The crucial role of the water generated during the imine formation was underlined and a dual activation model was proposed to account for high reactivity.

Acknowledgments

This work was supported by CNRS, University of Rouen and INSA of Rouen, the région Haute-Normandie and the FEDER 'FLUORG' (convention No. 33236). G.L. and A.C. thank, respectively, the région Haute-Normandie and the CRUNCh for a Grant.

Supplementary data

Supplementary data (general informations, general procedure for the synthesis of 5-substituted γ-butenolides **4a–w** and copies of NMR spectra for products **4a–w**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.02.115.

References and notes

1. (a) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G. *Synlett* **2009**, 1525–1542; (b) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076–3154; (c) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895–904.
2. Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625–694.
3. Pansare, S. V.; Paul, E. K. *Chem. Eur. J.* **2011**, *17*, 8770–8779.
4. For review, see Ref. 1b. For selected examples, see: (a) Spanedda, M. V.; Ourévitch, M.; Crousse, B.; Bégué, J-P.; Bonnet-Delpon, D. *Tetrahedron Lett.* **2004**, *45*, 5023–5025; (b) Oudeyer, S.; Dudot, B.; Royer, J. *Heterocycles* **2005**, *65*, 823–841; (c) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7230–7233; (d) Salvador González, A.; Gómez Arrayás, R. N.; Rodríguez Rivero, M.; Carretero, J. C. *Org. Lett.* **2008**, *10*, 4335–4337; (e) Akiyama, T.; Honma, Y.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2008**, *350*, 399–402; (f) Ruan, S-T.; Luo, J-M.; Du, Y.; Huang, P-Q. *Org. Lett.* **2011**, *13*, 4938–4941; (g) Hermange, P.; Dau, M. E. T. H.; Retailleau, P.; Dodd, R. H. *Org. Lett.* **2009**, *11*, 4044–4047; (h) Curti, C.; Battistini, L.; Zanardi, F.; Rassu, G.; Zambrano, V.; Pinna, L.; Casiraghi, G. *J. Org. Chem.* **2010**, *75*, 8681–8684; (i) Deng, H-P.; Wei, Y.; Shi, M. *Adv. Synth. Catal.* **2009**, *351*, 2897–2902.
5. (a) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2319–2322; (b) Zhou, L.; Lin, L.; Ji, J.; Xie, M.; Liu, X.; Feng, X. *Org. Lett.* **2011**, *13*, 3056–3059.
6. Mandai, H.; Mandai, K.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 17961–17969.
7. Martínez, R.; Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **2005**, *46*, 8471–8474.
8. Baeza, A.; Nájera, C.; Sansano, J. M. *Synthesis* **2007**, 1230–1234.
9. During the preparation of the manuscript, Casiraghi et al. published an aqueous and solvent-free uncatalyzed three-component vinylogous Mannich reaction of pyrrole-based silyl dienolates in which the crucial role of the water was underlined: Sartori, A.; Dell'Amico, L.; Curti, C.; Battistini, L.; Pelosi, G.; Rassu, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal.* **2011**, *353*, 3278–3284.
10. For selected examples of activation of silyl pro-nucleophiles with Lewis bases, see: (a) Kawano, Y.; Kaneko, N.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 1508–1509; (b) Gembus, V.; Poisson, T.; Oudeyer, S.; Marsais, F.; Levacher, V. *Synlett* **2009**, 2437–2440; (c) Bernardi, L.; Indrigo, E.; Pollicino, S.; Ricci, A. *Chem. Commun.* **2012**, *48*, 1428–1430; (d) Gawronski, J.; Wascinska, N.; Gajewy, J. *Chem. Rev.* **2008**, *108*, 5227–5252.