Tetrahedron Letters 55 (2014) 6220–6223

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Reactions of silyl nitronates with dimethylformamide dimethyl acetal as a new general procedure for the synthesis of 2-nitroenamines

Alexander S. Shved [a,b], Andrey A. Tabolin [b,*], Yulia A. Khomutova [b], Sema L. Ioffe [b]

[a] Higher Chemical College of the Russian Academy of Sciences, D. I. Mendeleev University of Chemical Technology of Russia, Miusskaya sq. 9, Moscow 125047, Russian Federation
[b] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prosp. 47, Moscow 119991, Russian Federation

ARTICLE INFO

Article history:
Received 26 July 2014
Revised 29 August 2014
Accepted 11 September 2014
Available online 21 September 2014

Keywords:
Aliphatic nitro compounds
Push–pull alkenes
Silyl nitronates
Nitroenamines
Amide acetals

ABSTRACT

Silyl nitronates obtained in situ from the corresponding aliphatic nitro compounds react with dimethylformamide dimethyl acetal giving 2-nitroenamines in moderate to good yields. The reaction pathway is discussed.

© 2014 Elsevier Ltd. All rights reserved.

2-Nitroenamines serve as versatile intermediates in organic synthesis (Scheme 1).[1–3] Some bioactive compounds including the anti-ulcer drugs Nizatidine[4] and Ranitidine,[5] as well as an insecticide family[6] possess a nitroenamine motif. Nucleophilic substitution of dialkylamino groups with activated arenes or aromatic heterocycles,[7] enolates,[8] amines,[9] hydroxide[10] and Grignard reagents[11] gives rise to various nitroalkene derivatives. As such, nitroenamines have been used as convenient precursors for 1,2-aminoalcohols, which have been employed in total syntheses of several natural compounds, such as (−)-detoxinine,[3a] (+)-castanospermine[3b] and (−)-rosmarinecine.[3c] Recently, an asymmetric synthesis of 1,2-diamines based on organocatalytic addition of aldehydes to 2-nitroenamines was reported.[2]

Several types of nitroenamines can be outlined depending on their substitution pattern. β-Substituted species **1** can be readily synthesized by amination of the corresponding α-nitroketones [Scheme 2, (1)].[12] In contrast, the synthesis of β-unsubstituted nitroenamines **1** (R^2 = H) requires other paths, since 2-nitroaldehydes are unstable and cannot be isolated.[9] General methods for the synthesis of 2-nitroenamines **1** (R^2 = H) employ primary aliphatic nitro compounds **2** (ANC) as precursors [Scheme 2, (2)].[13–19] However, for aliphatic substituents R^1 (R^1 = Me, Et, etc.) the yields decrease dramatically and an excess of the ANC is necessary.[13–15] This makes these procedures only applicable to the simplest and commercially available ANCs (nitromethane,[14] nitroethane[15] and so forth), or activated ANCs (α-nitroketones[16] or nitroacetic acid esters[13]). Considering the aforementioned facts, an efficient procedure employing functionalized and inactivated ANCs is needed.

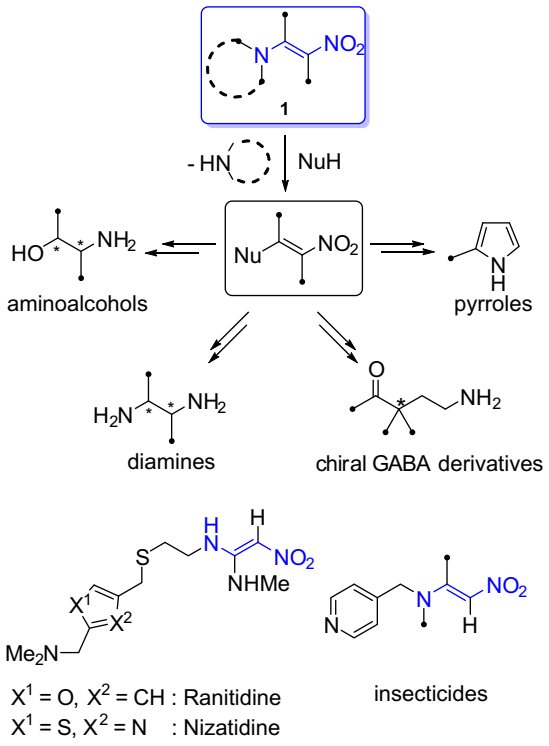
Synthesis of nitroenamines 1

We assumed that higher nitroalkanes could be involved in nitroenamine synthesis by employing silyl nitronates **3**. The latter have proved themselves as useful synthetic equivalents of ANCs **2**, which react with greater selectivity under milder conditions.[20] Employment of a silyl group avoids the occurrence of mobile protons, thus making the crucial C–C bond forming step **3** → **4** irreversible (Table 1).[21] The presented strategy for the synthesis of nitroenamines **1** involves three steps. In the first step (i) ANC **2** is converted into silyl nitronate **3** via a literature procedure,[22] followed by treatment at −78 °C with dimethylformamide dimethyl acetal (DMFDMA) to give intermediate hemiaminal **4** (step ii). Upon warming, the latter undergoes elimination of methanol leading to the target nitroenamine **1** (step iii).[23]

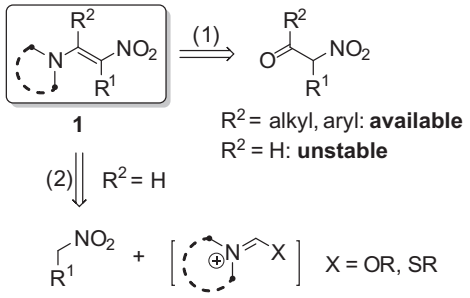
The data presented in Table 1 reveal that high yields can be achieved for a wide variety of nitroenamines **1**. In most cases there was no need to exceed a stoichiometric amount of reagents. Separation of target **1** from the by-product salt $[DBUH]^+Cl^-$ was accomplished by ether extraction (Et_2O or *t*-BuOMe). For large

* Corresponding author. Tel.: +7 499 135 5329; fax: +7 499 135 5328.
E-mail address: tabolin87@mail.ru (A.A. Tabolin).

http://dx.doi.org/10.1016/j.tetlet.2014.09.071
0040-4039/© 2014 Elsevier Ltd. All rights reserved.

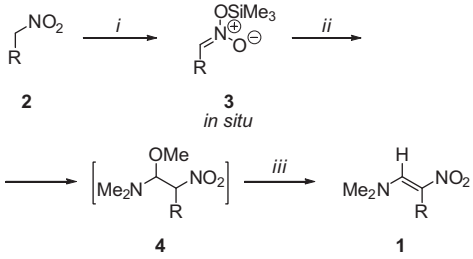


Scheme 1. Nitroenamines as biologically active compounds and useful intermediates in organic syntheses.



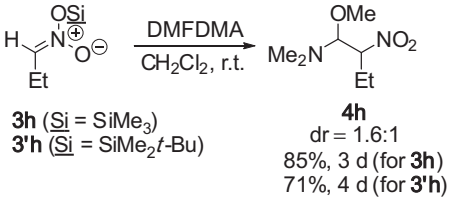
Scheme 2. Existing approaches for the synthesis of β-nitroenamines. Reagents and conditions: X = OR: (a) $Me_2NCH(OMe)_2$, Temp (°C) (Refs. 16,17); (b) amine, $HC(OR)_3$, *p*-TsOH, Temp (°C) (Refs. 14,15,18). X = SR: (c) $[Me_2NCHSMe]^+I^-$, KF, TEBAC, CH_2Cl_2, rt (Ref. 19).

Table 1
Synthesis of nitroenamines **1** via silylation of ANCs **2**



Entry	ANC	R	Yield of **1**[a] (%)	Conversion of **2**[b] (%)
1	**2a**	$CH_2CH_2CO_2Me$	92	100
2[c]	**2a**	$CH_2CH_2CO_2Me$	80	100
3	**2b**	$CH_2CH_2C(O)Me$	85	100
4	**2c**	$CH_2CH(Me)CO_2Me$	85	90
5	**2d**	$CH(Me)CH_2CO_2Me$	68	100
6[d]	**2d**	$CH(Me)CH_2CO_2Me$	n/d [e]	40
7	**2e**	1-Cyclohexenyl	45	65
8	**2f**	H	75	n/d
9	**2g**	Me	95	n/d
10	**2h**	Et	90	100
11	**2i**	Ph	78	100
12	**2j**	CH_2Ph	80 (35[f])	96
13	**2k**	$CH(Ph)CH_2CO_2Et$	41	n/d
14	**2l**	CH_2CH_2Ph	75	100

i: DBU (1.05 equiv), TMSCl (1.1 equiv), −15 °C → rt, 40 min.
ii: DMFDMA (1.1 equiv), −78 °C, 1 h (for **1k**: 2.2 equiv).
iii: −78 °C → rt, overnight [for **1d**: DBU (1 equiv), TMSCl (1 equiv), then −78 °C → rt, overnight].
[a] Isolated yield.
[b] Determined by integration of the ^1H NMR spectra.
[c] TBSCl was used instead of TMSCl.
[d] Without addition of DBU/TMSCl at step iii.
[e] Not determined.
[f] Yield after purification by column chromatography on alumina.



Scheme 3. Reaction of isolated silyl nitronates **3** and DMFDMA.

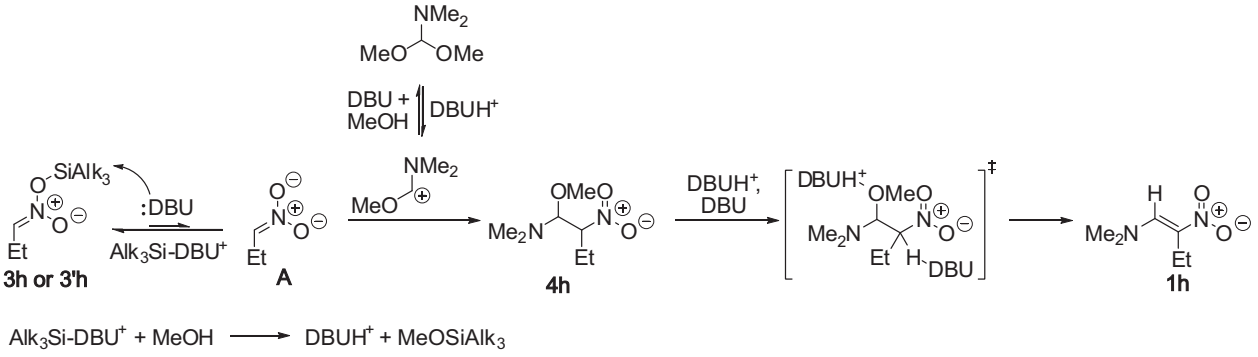
scale preparations (36–50 mmol of ANC **2**), Soxhlet extraction was used. It is worthy of note that purification of products **1** via aqueous extraction or column chromatography was not efficient and led to substantial loss of the target enamines **1** (e.g., see Table 1, entry 12), due to their high polarity and hydrolytic lability.[9] If the nitroenamine possesses a high melting point, the separation of **1** and **2** was easily performed by recrystallization. Otherwise, full conversion of the initial ANC **2** was preferable.

The structures of the obtained enamines **1** were supported by ^1H and ^{13}C NMR data, as well as by elemental analysis or HRMS data. All nitroenamines **1** in chloroform solutions were observed as (*E*)-isomers (NOESY data). This is in accordance with known rules for *E*/*Z*-isomerism in similar substances.[9,24]

For the synthesis of enamines **1** more stable TBS-nitronates can also be used (Table 1; cf. entries 1 and 2). However, branching at the β-position of the carbon skeleton in ANC **2** (substrates **2d**,**e**,**k**) significantly diminished the conversion of ANC **2** and consequently the yield of products **1**; for example, for ANC **2d** (Table 1, entry 6) the conversion was 40%.[25] Fortunately, the addition of DBU (10 mol %) to the reaction mixture increased the conversion of **2d** from 40% to 90%. An even better effect was achieved by the addition of 1 equiv of a mixture of DBU/TMSCl, capable of trapping the methanol. Thus the conversion of ANC **2d** was increased to 100% (Table 1, cf. entries 5 and 6). However, for ANC **2k**, this procedure was not successful. For the transformation of **2k** → **1k** the use of a twofold excess of DMFDMA was the method of choice (see Table 1, entry 13).

Studies on the mechanism

It was interesting to elucidate in more detail the mechanism of nitroenamine **1** formation. To the best of our knowledge, there is only one known example of a similar process [coupling of silyl nitronates with a hemiaminal ($TMSOCH_2NMe_2$)].[26] It turned out that coupling of DMFDMA with isolated silyl nitronates **3h** or **3′h** [simulation of step (ii), see Table 1] did not lead to enamine **1h**, while hemiaminal **4h** was observed as the major product (Scheme 3).

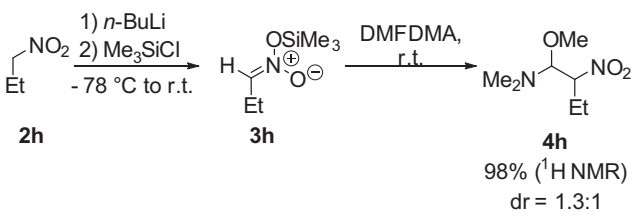


Scheme 4. Proposed mechanism for the formation of **1** from silyl nitronates **3**.

Moreover, while the synthesis of nitroenamine **1h** by the standard procedure was completed within 24 h (Table 1, entry 10), conversion of pure silyl nitronate **3h** via the reaction with DMFDMA over 24 h exposure was only 76%. Several days were needed to reach quantitative conversion. The structure of hemiaminal **4h** was confirmed from ^{1}H, ^{13}C, COSY and HSQC data. Unfortunately, we did not obtain accurate elemental analysis or HRMS data due to the hydrolytic lability of the hemiaminal.

Due to the hydrolytic instability of TMS-nitronate **3h**, further investigations were performed on its TBS-analogue **3′h**. Several substances, including DBU, its salt $[DBUH]^{+}Cl^{-}$ and chlorosilanes *Si*Cl (*Si* = $SiMe_3$, $SiMe_2t$-Bu) were tested as catalysts for the reaction of **3′h** with DMFDMA (see Supplementary data for details). Presumably, activation of both the reaction components was necessary for the successful synthesis of **1** (Scheme 4). The function of hydrogen bond donors ($[DBUH]^{+}Cl^{-}$, MeOH) consists of the activation of DMFDMA by removal of the MeO group.[27,28] Lewis bases (e.g. DBU) activate the silyl nitronate **3** by its equilibrium conversion into nitronate anion **A**. As mentioned before, when silyl nitronate **3h** was prepared in situ, a high yield of **1h** was observed (see Table 1). But in order to reach a similar yield with the isolated nitronate, simultaneous use of both DBU and its salt $[DBUH]^{+}Cl^{-}$ was required. Thus, in the presented one-pot procedure for the synthesis of enamines **1** from ANC **2**, the in situ generation of silyl nitronates **3** is important, since the by-product ($[DBUH]^{+}Cl^{-}$) catalyses step ii (Table 1), i.e., C–C bond formation (**3** → **4**). Obviously, the nitronate anion **A** can be generated by treating ANC **2** with DBU. However, performing the reaction of **2a** and DMFDMA mediated by DBU (10 mol %) and $[DBUH]^{+}Cl^{-}$ (1 equiv) without prior silylation did not give enamine **1a** in a yield higher than 60%. Moreover, in the latter case, the use of a catalytic amount of $[DBUH]^{+}Cl^{-}$ led to prolonged (2 or more days) reaction times.[29]

Similarly, the use of both DBU and $[DBUH]^{+}$ appeared to be necessary for successful elimination of methanol from intermediate hemiaminal **4**. Additionally, in another experiment, silyl nitronate **3h** was obtained in situ from ANC **2h** by treatment with *n*-BuLi and TMSCl.[30] After addition of DMFDMA to the reaction mixture, rapid and quantitative conversion of **3h** into hemiaminal **4h** was observed (according to ^{1}H NMR) (Scheme 5). Presumably, in this case, the activation of DMFDMA is due to the Lewis acidity of LiCl.



Scheme 5. Synthesis of hemiaminal **4h** from **2h**.

In conclusion, a new and efficient procedure for the synthesis of nitroenamines **1** from ANCs **2** through in situ formed silyl nitronates **3** is described. The mechanism of the reaction is elucidated. Detailed investigations revealed the roles and interactions of the reagents, intermediates and by-products.

Acknowledgments

This work was supported by the Russian Foundation for Basic Research (Grant 12-03-00278) and the Program of the Russian Academy of Sciences Presidium (8P).

Supplementary data

Supplementary data (experimental details, compound characterization) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09.071.

References and notes

1. For reviews, see: (a) Rajappa, S. *Tetrahedron* **1981**, *37*, 1453–1480; (b) Rajappa, S. *Tetrahedron* **1999**, *55*, 7065–7114; (c) Maslova, N. B.; Glushkov, R. G. *Pharm. Chem. J.* **1993**, *27*, 263–276 (Khimiko-farmatsevticheskii Zhurnal **1993**, 27, 41–51).
2. (a) Zhu, S.; Yu, S.; Wang, Y.; Ma, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4656–4660; (b) Rehak, J.; Hut'ka, M.; Latika, A.; Brath, H.; Almassy, A.; Hajzer, V.; Durmis, J.; Toma, S.; Sebesta, R. *Synthesis* **2012**, *44*, 2424–2430.
3. (a) Denmark, S. E.; Hurd, A. R.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668–1674; (b) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046–3056; (c) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 8266–8277.
4. Price, A. H.; Brodgen, R. N. *Drugs* **1988**, *36*, 521–539.
5. Grant, S. M.; Langtry, H. D.; Brodgen, R. N. *Drugs* **1989**, *37*, 801–870.
6. Minamida, I.; Iwanaga, K.; Tabuchi, T.; Uneme, H.; Dantsuji, H.; Okaucji, T. *J. Pestic. Sci.* **1993**, *18*, 31–40.
7. Buchi, G.; Mak, C. P. *J. Org. Chem.* **1977**, *42*, 1784–1786.
8. (a) Severin, T.; Bruck, B. *Chem. Ber.* **1965**, *98*, 3847–3853; (b) Fuji, K.; Node, M.; Nagasawa, H.; Naniwa, Y.; Terada, S. *J. Am. Chem. Soc.* **1986**, *108*, 3855–3856.
9. Fettell, A. I.; Feuer, H. *J. Org. Chem.* **1978**, *43*, 1238–1241.
10. Kraus, G. A.; Thurston, J.; Thomas, P. J. *Tetrahedron Lett.* **1988**, *29*, 1879–1882.
11. Kondratyev, N. S.; Zemtsov, A. A.; Levin, V. V.; Dilman, A. D.; Struchkova, M. I. *Synthesis* **2012**, *44*, 2436–2440.
12. Hurd, C. D.; Nilson, M. E. *J. Org. Chem* **1955**, *20*, 927–936.
13. Severin, T.; Boehme, H.-J. *Chem. Ber.* **1968**, *101*, 2925–2930.
14. Falques, M.; Rene, L.; Royer, R. *Synthesis* **1982**, 260–261.
15. Node, M.; Nagasawa, H.; Naniwa, Y.; Fuji, K. *Synthesis* **1987**, 729–732.
16. Agarwal, P. K.; Dathi, M. D.; Saifuddin, M.; Kundu, B. *Beilstein J. Org. Chem.* **2012**, *8*, 1901–1908.
17. Meerwein, H.; Florian, W.; Schoen, N.; Stopp, G. *Liebigs Ann.* **1961**, *641*, 1–39.
18. Krowzcynski, A.; Kozerski, L. *Synthesis* **1983**, 489–491.
19. Harjit, S.; Batra, M. S.; Paramjit, S. *Indian J. Chem., Sect B* **1984**, *23*, 1176–1180.
20. Ioffe, S. L. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis: Novel Strategies in Organic Synthesis*, 2nd ed.; Feuer, H.; Ed.; John Wiley & Sons: Hoboken, New Jersey; 2008, pp 435–748.
21. For details on the reversibility of Henry and related reactions, see: (a) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1–18; (b) Colvin, E. W.;

Seebach, D. *J. Chem. Soc., Chem. Commun.* **1978**, 689–691; (c) Tikhonova, N. A.; Babievskii, K. K.; Belikov, V. V. *Russ. Chem. Bull.* **1967**, 842–844 (*Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, 877–880).

22. (a) Aizpurua, J. M.; Oiarbide, M.; Palomo, C. *Tetrahedron Lett.* **1987**, *28*, 5361–5364; (b) Danilenko, V. M.; Tishkov, A. A.; Ioffe, S. L.; Lyapkalo, I. M.; Strelenko, Yu. A.; Tartakovsky, V. A. *Synthesis* **2002**, 635–647.
23. (a) General procedure for the synthesis of nitroenamines **1**: To a 1 M solution of ANC **2** in CH_2Cl_2 at −15 °C, DBU (1.05 equiv) was added dropwise. The mixture was stirred for 20 min and TMSCl (1.1 equiv) was added. After 10 min, the cooling bath was removed, the mixture was stirred for 40 min, cooled to −78 °C and DMFDMA (1.1 equiv) was added dropwise. The mixture was stirred at the same temperature for 1 h, slowly warmed to room temperature and left overnight. As a rule, the resulting solution attained a dark red color. The solvent was removed in vacuo. Et_2O (20 ml/1 mmol of **2**) was added to the residue and the mixture was vigorously stirred (as a rule, insoluble $[DBUH]^+Cl^-$ solidified). The ether layer was decanted, and extraction was repeated several times. The combined ether extracts were filtered through cotton wool and evaporated to give the target enamine **1**. Representative example: *Methyl (4E)-5-(dimethylamino)-4-nitropent-4-enoate (**1a**)*. Obtained from **2a** (1.47 g, 10 mmol). Yield: 1.85 g (92%), orange crystalline solid, mp 74–78 °C. When the reaction was scaled to 36 mmol of **2a**, Soxhlet extraction with Et_2O was used to separate **1a** and $[DBUH]^+Cl^-$. Yield: 6.45 g (89%). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.24 (s, 1H, =CH), 3.59 (s, 3H, CO_2Me), 3.15 (s, 6H, NMe_2), 2.96 (t, J = 7.4 Hz, 2H, CH_2-2), 2.54 (t, J = 7.4 Hz, 2H, CH_2-1). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2 (CO_2Me), 149.5 (=CH), 122.3 (CNO_2), 51.5 ($CO_2\underline{Me}$), 43.9 (NMe_2), 32.7 (CH_2-2), 21.7 (CH_2-1). Anal. Calcd for $C_8H_{14}N_2O_4$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.53; H, 7.17; N, 13.79.; (b) Performing steps (ii) and (iii) simultaneously at rt resulted in a lower yield of **1a**, since the significant amount of methanol eliminated in step (iii) led to desilylation of nitronate **3** to give ANC **2** before the latter could undergo step (ii) completely.
24. (a) Ostercamp, D. L.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1021–1028; (b) Chiara, J. L.; Gomez-Sanchez, A.; Bellanato, J. *J. Chem. Soc., Perkin Trans. 2* **1992**, 787–798.
25. Increasing the reaction time during any of the steps i–iii (Table 1) did not increase the yield of **1d** nor the conversion of **2d**.
26. Kalinin, A. V.; Apasov, E. T.; Ioffe, S. L.; Kozyukov, V. P.; Kozyukov, Vik. P. *Russ. Chem. Bull.* **1985**, *34*, 2442–2443 (*Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 2635–2636). However, the authors of this work did not perform any mechanistic investigations.
27. Evidence for the formation of hydrogen bonds with protonated DBU species was previously reported in (a) Miran, S. M.; Kinoshita, H.; Tomohiro, Y.; Susan, Md. A. B. H.; Watanabe, M. *Chem. Commun.* **2011**, 12676–12678; (b) Coady, D. J.; Fukushima, K.; Horn, H. W.; Rice, J. E.; Hedrick, J. L. *Chem. Commun.* **2011**, 3105–3107.
28. DMF itself failed to react with silyl nitronates under the reported conditions.
29. We did not consider the use of catalytic amounts of DBU and TMSCl, since the reaction of nitro compound **2** will result in the formation of a DBU/$[DBUH]^+Cl^-$ mixture, the action of which is discussed.
30. MacDonald, F. K.; Carneiro, K. M. M.; Pottie, I. R. *Tetrahedron Lett.* **2011**, *52*, 891–893.