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

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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.

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

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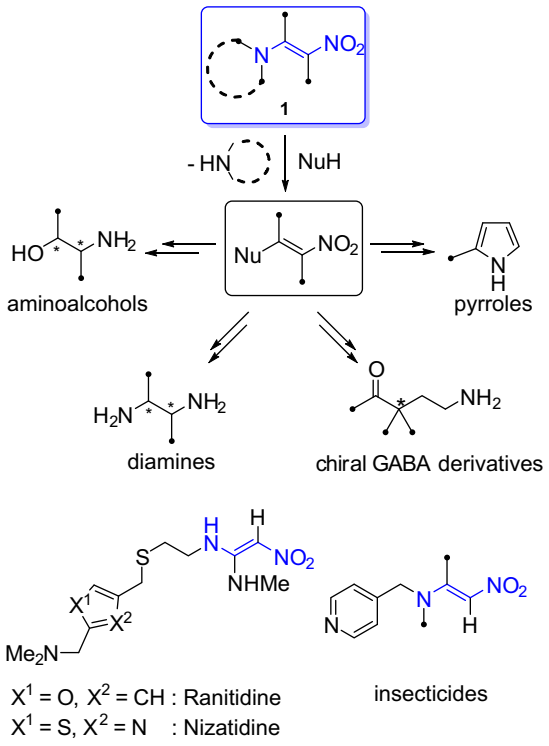
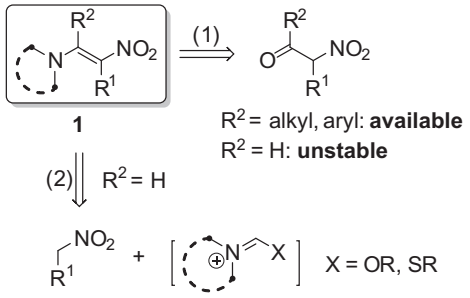
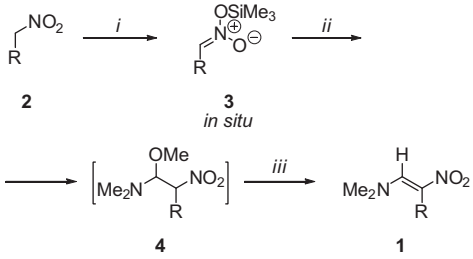


Scheme 1. Nitroenamines as biologically active compounds and useful intermediates in organic syntheses.



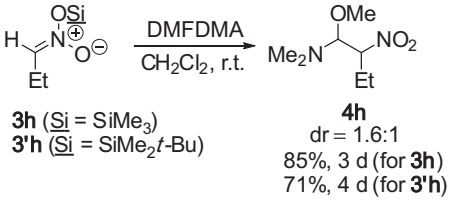
Scheme 2. Existing approaches for the synthesis of β-nitroenamines. Reagents and conditions: X = OR: (a) $Me_2NCH(OMe)_2$, Temp (°C) (Refs. 16,17); (b) amine, $HC(OR)_3$, *p*-TsOH, Temp (°C) (Refs. 14,15,18). X = SR: (c) $[Me_2NCHSMe]^+I^-$, KF, TEBAC, CH_2Cl_2, rt (Ref. 19).

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).