N-Methylidene[bis(trimethylsilyl)methyl]amine: the first isolable and stable monomeric methanimine allowing thermal [2 + 2] cycloadditions with ketenes

Claudio Palomo,* Jesus M. Aizpurua, Marta Legido and Regina Galarza

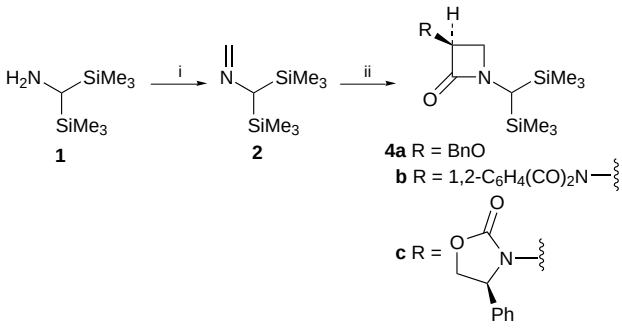
Departamento de Química Orgánica, Facultad de Química, Universidad del Pais Vasco, Aptdo 1072, 20080 San Sebastián, Spain

***N*-Methylidene[bis(trimethylsilyl)methyl]amine acts as a stable methanimine synthon [CH_2=NH] equivalent in [2 + 2] cycloadditions to ketenes, generated from acid chlorides and triethylamine, to provide 4-unsubstituted β-lactams in a single step.**

Although the chemistry of the C=N double bond has been extensively exploited over the years, reactions with formaldehyde imines have been virtually ignored.[1] Two main reasons have contributed to this fact: on the one hand the inaccessibility of monomeric methanimine in the condensed state[2] and, on the other hand, their great instability caused by spontaneous tri- or oligo-merization.[3] A very limited number of investigations have been conducted to address this problem. For example, Barluenga's group[4] has demonstrated that both *N*-methylenearyl- and *N*-methylenealkyl-amines are stable at −60 °C and can be generated *in situ* by the reaction of organometallic reagents with *N*-(alkoxymethyl)arylamines and *N*-alkyl-*N*-(alkylthiomethyl)ammonium chlorides, respectively. Independently to this group, Overman *et al.*[5] has also revealed that formaldehyde imines can be produced in solution, generally at −70 °C, from the reaction of *N*-(cyanomethyl)amines with strong bases. Although these authors also noticed the low temperature trapping of such methyleneamine species with carbon nucleophiles, no report on the reactivity of a methanimine species withstanding higher temperature reaction conditions has been published to date.

Here we report the chemical behaviour of some ketenes of interest in the context of β-lactam antibiotic chemistry,[6] (Scheme 1) towards the first isolable and stable methanimine,[7] easily prepared by the simple mixing of 33% formaldehyde aqueous solution and the readily available *C,C*-bis(trimethylsilyl)methylamine **1**.[8,†] To establish the correct reaction conditions for the expected [2 + 2] cycloaddition reaction, Table 1, we investigated the behaviour of imine **2** towards benzyloxyketene generated *in situ* from the carboxylic acid chloride **3a** and triethylamine. As entries 1 and 2 show, only poor yields of the expected β-lactam were obtained when the reactions were performed either at low temperature or under reflux of CH_2Cl_2 but, interestingly, the chromatographic analysis (GC–MS) of the reaction mixtures after 16 h revealed the presence of important quantities of unreacted imine **2** (typically 30–35%) surviving these reaction conditions. After several runs increasing the temperature by changing the solvent and using two- and four-fold excesses of the acid chloride **3a** (entries 3 and 4) a reasonable 62% yield of the isolated β-lactam **4a** was obtained after column chromatography. In view of this result, we next examined the suitability of this approach to the construction of the 3-amino 4-unsubstituted azetidin-2-one ring owing to its importance as a key structural element for the development of β-lactam antibiotics.[6] Actually, comparatively good yields of **4b** (65%, mp 207–209 °C) and **4c** {75%, mp 150–151 °C, $[\alpha]_D^{25}$ +89.6 (*c* 1.0, Cl_2CH_2)} could be reached, without the need for an excess acid chloride, by simply performing the reaction in refluxing benzene or chloroform as solvents (entries 5 and 6). This result contrasts with the fact that the cycloaddition between the Evans–Sjögren acid chloride **3c** and methanimine trimers, derived from benzylamine and trimethylsilylmethylamine, under the reported conditions[9] only affords traces of the expected β-lactams (< 15%) together with major amounts of 3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]-acetic acid. In addition, the total asymmetric induction observed during the single step convergent formation of the β-lactam **4c**‡ was unaffected by the reaction temperature (entries 6 and 7), and it was particularly noteworthy when compared with the limited diastereomeric excesses achieved in comparable approaches reported to date.[10]

On the other hand, because the easy cleavage of the bis(trimethylsilyl)methyl moiety was fundamental in β-lactams **4** finding synthetic applications, we tried several deprotection methods using compound **5** {mp 124–126 °C, $[\alpha]_D^{25}$ +13.6 (*c* 1.0, Cl_2CH_2)} as a model, Scheme 2. This compound was easily obtained in 70% yield through the oxazolidinone moiety cleavage[11] and further *N*-Boc protection of the resulting free amino derivative. After screening our previously reported method[12] we found that exposure of **5** to the action of

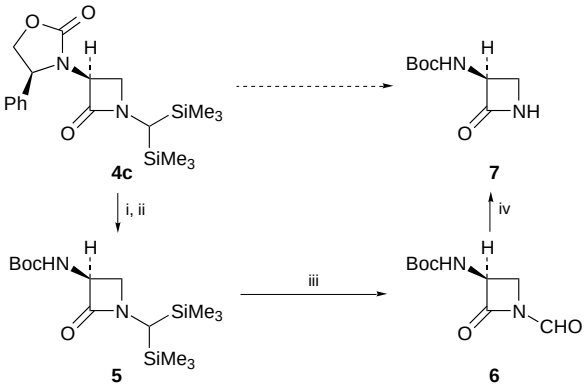


Scheme 1 *Reagents and conditions*: i, 30% HCHO (1.2 equiv.), H_2O, room temp., 20 h, 75%; ii, RCH_2COCl **3a**–**c**, NEt_3, for conditions, see Table 1

Table 1 Cycloaddition reaction of methanimine **2** with alkoxy- and amido-ketenes derived from acyl chlorides **3**

Entry	Product **4**	Conditions[a] Solvent; *T*/°C; *t*/h	Yield (%)[b]
1	**a**	CH_2Cl_2; −78 → 20; 16	28
2	**a**	CH_2Cl_2; 0 → 40; 16	30
3	**a**	$CHCl_3$; 0 → 80[c]; 2	39
4	**a**	$CHCl_3$; 80[d]; 1	62
5	**b**	C_6H_6; 0 → 80; 16	65
6	**c**	C_6H_6; 0 → 80; 16	75[e]
7	**c**	CH_2Cl_2; −78 → 20; 16	33[e]

[a] Unless otherwise stated, the acid chloride (1.2 equiv.) was added to the imine **2** (1 equiv.) and triethylamine (2.4 equiv.) at the first temperature, and the reaction mixture was then stirred at the second temperature for the indicated time. [b] Yields of pure isolated products after column chromatography (silica gel, hexanes). [c] A twofold excess of the acid chloride and triethylamine was used. [d] The acid chloride (4.0 equiv.) was dropwise added to the imine **2** (1 equiv.) and triethylamine (8.0 equiv.) at reflux temperature. [e] Product obtained as single stereoisomer.



Scheme 2 *Reagents and conditions*: i, Li (6 equiv.), THF, Bu^{t}OH, NH_3 (10 : 1 : 33), −78 °C, 10 min, then 1 m HCl, 5 min, 70%; ii, $(Boc)_2O$, room temp., 3 h; iii $(NH_4)_2Ce(NO_3)_6$, MeCN, H_2O, room temp., 3 h, 84%; iv, $NaHCO_3$, Na_2CO_3, Me_2CO, H_2O, room temp., 2 h, 78%

cerium(iv) ammonium nitrate in acetonitrile–water furnished the intermediate formyl derivative **6** [mp 134–136 °C, $[\alpha]_D^{25}$ −17.7 (*c* 1.0, Cl_2CH_2)] in a clean and high-yielding (90%) reaction. Further exposure of **6** to *N*-deformylation under usual conditions[12,13] afforded **7** [mp 172–174 °C, $[\alpha]_D$ −18.4 (*c* 1.0, MeOH), lit.,[14] mp 171–172 °C], which was identical in all respects to that previously described. Therefore, the bis-(trimethylsilyl)methyl group must be considered as a new protecting group for β-lactam synthesis.[15]

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Footnotes

† In sharp contrast to this result, analogous condensation of *C*-trimethylsilylmethylamine and formaldehyde afforded only the corresponding 1,3,5-tris(trimethylsilylmethyl)-1,3,5-triazine, see: T. Morimoto, Y. Nezu and K. Achiwa, *Chem. Pharm. Bull.*, 1985, **33**, 4596.

‡ For **4c** the 3*S* stereochemistry, relative to the known 4′*S* configuration of the oxazolidinone ring, was unambiguously established by X-ray analysis. *Crystal data* for **4c**. $C_{19}H_{30}N_2O_3Si_2$, M = 390.63; crystal dimension 0.20 × 0.15 × 0.30 mm, orthorhombic, $P2_12_12_1$, a = 6.444(1), b = 22.025(2), c = 32.083(3) Å, V = 4553.5(3) Å^3, T = 293 K, Z = 8, D_c = 1.140 g cm^{-3}, μ (Cu-Kα) = 1.527 mm^{-1}, λ = 1.54178 Å, 3608 total reflections, 1962 observed [$I > 2\sigma(I)$], 709 refined parameters, final conventinal R = 0.047, wR = 0.067, residual electron density 0.25 eÅ^3. The asymmetric unit was formed by two independent molecules with different conformation around the $(SiMe_3)_2CH$–N bond. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/329.

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