Pergamon

Tetrahedron Letters 40 (1999) 3017–3020

TETRAHEDRON
LETTERS

Reaction of Nitrones with Trimethylsilylketene

Kiyo Takaoka, Toyohiko Aoyama,* and Takayuki Shioiri*

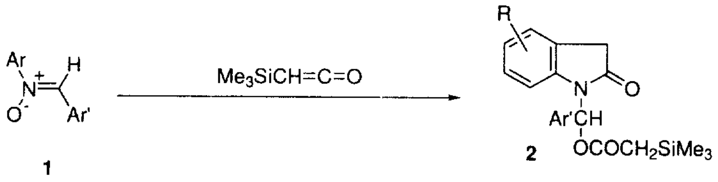
Faculty of Pharmaceutical Sciences, Nagoya City University
Tanabe-dori, Mizuho-ku Nagoya 467-8603, Japan

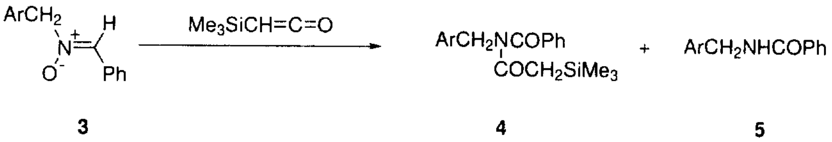
Received 16 January 1999; revised 18 February 1999; accepted 19 February 1999

Abstract: Trimethylsilylketene smoothly reacts with α,*N*-diarylnitrones to give oxindoles in good yields. On the other hand, the reaction of trimethylsilylketene with *N*-arylmethylnitrones gives a mixture of *N*,*N*-diacylamines and *N*-acylamines. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: silylketene, nitrone, oxindole, *N*,*N*-diacyl(or *N*-acyl)amine

Recent publications from our laboratories have disclosed the first example of the [4+2] cycloaddition reaction of silylketenes[1] with electron-rich 1,3-dienes and *o*-quinodimethanes,[2] the novel type of cycloaddition reaction of silylketenes with enamines,[3] and a simple one-pot preparation of 2-pyridones from acyl isocyanates using trimethylsilylketene.[4] Our continued interest in the reactivities of silylketenes has led us to investigate the reaction of trimethylsilylketene with nitrones. We have found that trimethylsilylketene (TMSCH=C=O) smoothly reacts with α,*N*-diarylnitrones **1**[5a,b] to give *N*-alkyloxindoles **2** in good yields, while the reaction of TMSCH=C=O with *N*-arylmethylnitrones **3**[5a,c] gives a mixture of *N*,*N*-diacylamines **4** and *N*-acylamines **5**.

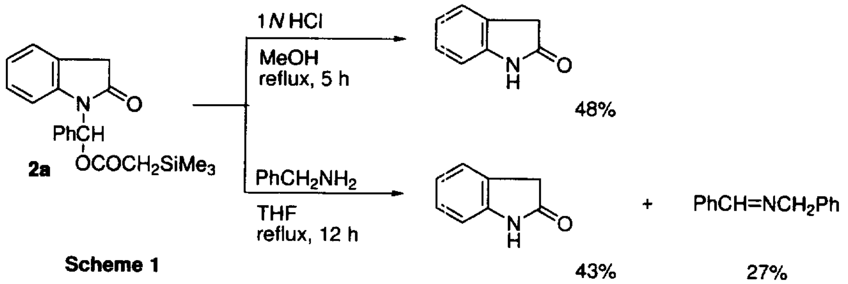




First, 1.2 equivalents of TMSCH=C=O reacted with α,*N*-diphenylnitrone (**1a**)[6] in ethyl acetate at reflux for 4 h to give the *N*-alkyloxindole **2a** in 31% yield, and the corresponding [3+2] cycloadducts could not be detected. Acidic treatment of the adduct (**2a**) gave oxindole in 48% yield. The reaction of **2a** with benzylamine afforded oxindole in 43% yield and *N*-benzylidenebenzylamine in 27% yield, although *N*-benzyltrimethylsilylacetamide was not detected (Scheme 1). Using 2.2 equivalents of TMSCH=C=O in ethyl acetate at reflux or in toluene at 80°C for 4 h, **2a** was obtained in 77% or 79% yield, respectively (Table, entries 1 and 2). Changing the reaction solvent to hexane, THF or MeCN led to a significant decrease in the yield (Table, entries 3, 4, and 5).

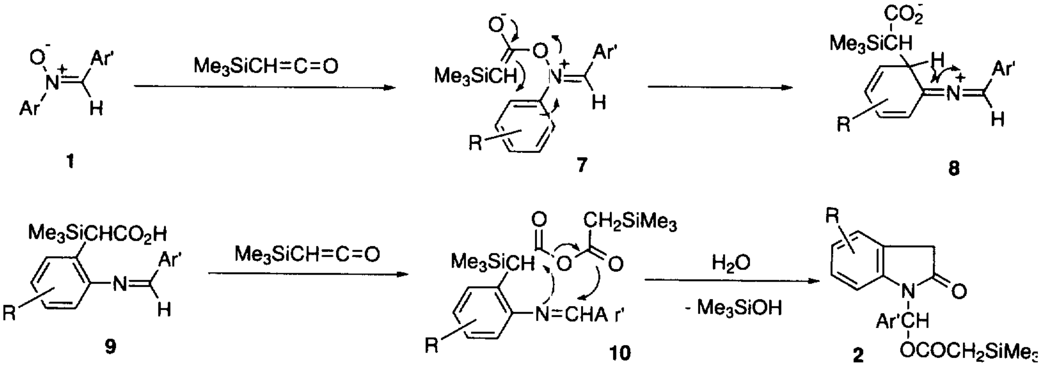
PII: S0040-4039(99)00407-4

A typical experimental procedure is as follows: A mixture of **1** (0.5 mmol) and TMSCH=C=O (2.2 eq.) in a solvent (3 ml) was stirred at reflux (in ethyl acetate) or 80°C (in toluene) for 3~19 h under argon. After concentration *in vacuo*, the residue was purified by flash column chromatography (silica gel, hexane:AcOEt=5:1) to give **2**.[7]



Scheme 1

The formation of **2** may be explained by the reaction in Scheme 2. First, one molecule of TMSCH=C=O reacts with **1** to give the betaine **7**, which undergoes a sigmatropic rearrangement to give the *o*-imino substituted arylacetic acid **9** *via* the carboxylate intermediate **8**. Subsequently, **9** reacts with a second molecule of TMSCH=C=O gives the anhydride **10**, which undergoes a rearrangement to furnish **2**.



Scheme 2

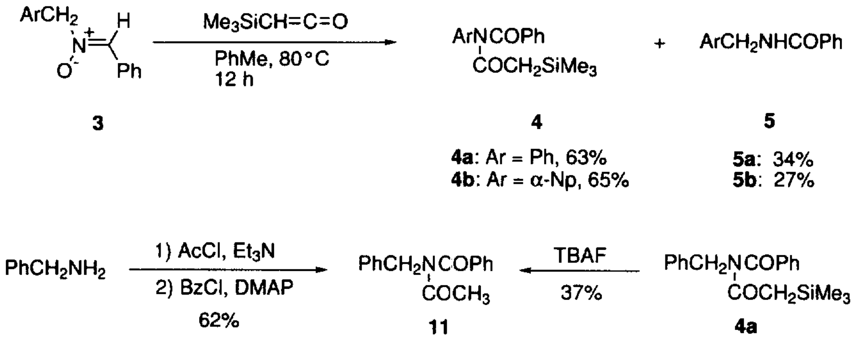
Various aromatic α,N-diarylnitrones were smoothly converted to the corresponding oxindoles **2** in satisfactory yields. While the reaction of dimethylketene with the nitrone **1b** has been reported to give the corresponding oxindole in 7% yield,[6b] the use of TMSCH=C=O gave **2b** in 77% yield (Table, entry 6). The reaction of **1f** with TMSCH=C=O was very slow, because of the effect of electron-withdrawing group. Unfortunately, α-phenylethyl-*N*-phenylnitrone was found to be completely inert.

Table.[a] Preparation of *N*-alkyloxindoles (**2**)

Entry	**1**	Ar	Ar'	Solvent	Reaction Time(h)	Yield **2**(%)
1	**a**	Ph	Ph	AcOEt	4	77
2	**a**	Ph	Ph	PhMe	4	79
3	**a**	Ph	Ph	Hexane	4	60
4	**a**	Ph	Ph	THF	4	58
5	**a**	Ph	Ph	MeCN	4	38
6	**b**	o-MeC_6H_4	Ph	AcOEt	3	77
7	**c**	p-$MeOC_6H_4$	Ph	AcOEt	3	62
8	**d**	Ph	p-$MeOC_6H_4$	PhMe	3	58
9	**e**	Ph	p-ClC_6H_4	PhMe	4	75
10	**f**	Ph	p-$NO_2C_6H_4$	PhMe	19	58[b)]

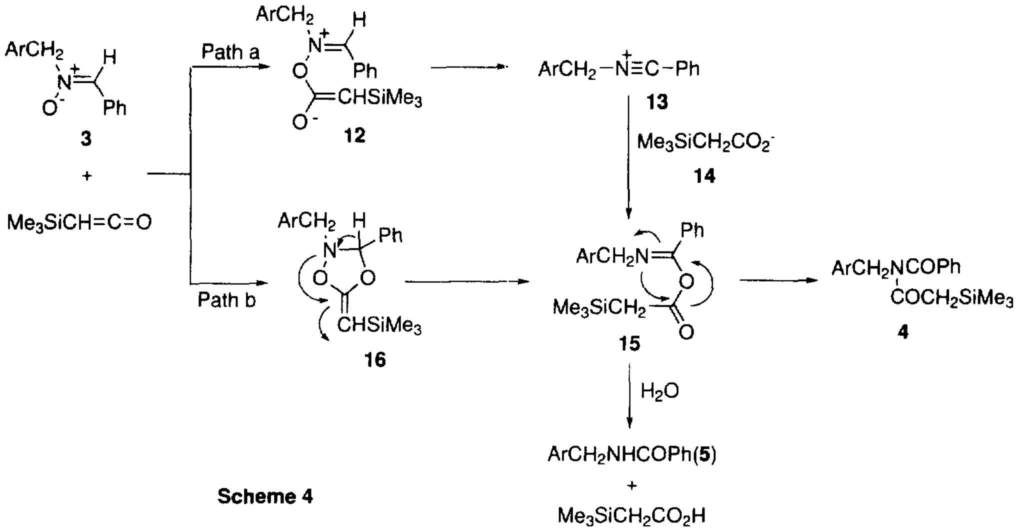
a) All new compounds gave satisfactory spectral data and HRMS spectra. b) TMSCH=C=O(3 eq.) was used.

The reaction of 1.2 equivalents of TMSCH=C=O with *N*-benzylidenebenzylamine *N*-oxide (**3a**) in toluene at 80°C for 12 h under argon gave *N*-benzoyl-*N*-trimethylacetybenzylamine (**4a**) and *N*-benzylbenzamide (**5a**)(Scheme 3). All the spectral data support the structure of **4a**,[8] which was further confirmed by desilylation with tetra-*n*-butylammonium fluoride (TBAF). The resulting *N*-benzoyl-*N*-acetybenzylamine (**11**) was identified with the sample prepared from benzylamine. Also, *N*-benzylidene-α-naphtylamine *N*-oxide (**3b**) gave a mixture of **4b** and **5b**.



Scheme 3

The formation of **4** and **5** may be explained as shown in Scheme 4. TMSCH=C=O reacts with **3** to give the betaine **12**. The resulting **12** unlike **7** can not undergo a sigmatropic rearrangement. Therefore elimination of trimethylsilylacetoxylate ion **14** from **12** occurs to yield the nitrilium ion **13**, which reacts again with **14** to give the acetoxyimine **15** (path a). Alternatively, the [3+2] cycloaddition reaction of TMSCH=C=O with **3** gives **16**, which undergoes ring cleavage to furnish **15** (path b). The Mumm rearrangement[9] of **15** affords **4**, while **5** is obtained by the hydrolysis of **15**.



Scheme 4

In conclusion, TMSCH=C=O smoothly reacts with α,N-diarylnitrones to give N-alkyloxindoles in good yields. On the other hand, the reaction of TMSCH=C=O with N-arylmethylnitrones gives a mixture of N,N-diacylamines and N-acylamines. The synthetic reaction developed here will open a new possibility for the use of TMSCH=C=O as a synthetic reagent.

References and Notes

1. For a review, see Pommel, A.; Kocienski, P.; Pons, J-M. *J. Chem. Soc. Perkin. Trans.1* **1998**, 2105-2118.
2. Ito, T.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 6583-6586.
3. Takaoka, K.; Aoyama, T.; Shioiri, T. *Synlett*, **1994**, 1005-1006.
4. Takaoka, K.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1996**, *37*, 4973-4976. Takaoka, K.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1996**, *37*, 4977-4978. Matsumoto, T.; Takaoka, K.; Aoyama, T.; Shioiri, T. *Tetrahedron* **1997**, *53*, 225-236.
5. (a) Murahashi, S-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736-1744. (b) Hilton, R. D.; Janzen, E. G. *J. Org. Chem.* **1992**, *57*, 2646-2651. (c) Dondoni, A. *Synth. Comm.* **1994**, *24*, 2537-2550.
6. The reaction of ketenes with **1a** has been reported to give the iminio acid[6a] and oxindoles.[6b,c] (a) Hassal, G. H.; Lippman., A. E. *J. Chem. Soc.*, **1953**, 1059-1063. (b) Pratt, R. N.; Stokes, D. P.; Taylor, G. A.; Brookes, P. C. *J. Chem. Soc. (C)* .**1968**, 2086-2089. Evans, A. R.; Hafig, M.; Taylor, G. A. *J. Chem. Soc. Perkin. Trans.1* **1984**, 1241-1245. (c) Barker, A.; D. Wong, D.; Lo, S.; Bloch, M.; Horozoglu, G.; Goldman, N. L.; Engle, R. *Tetrahedron Lett.* **1978**, *19*, 215-218. (d) The reaction of α,α,N-triphenylnitrone with ketenes gives the corresponding oxindoles. Hafiz, M.; Taylor, G. A. *J. Chem. Soc. Perkin. Trans.1* **1980**, 1700-1705.
7. **2a**: ^{1}H NMR (CDCl$_3$, 270MHz) δ: 0.07 (s, 9H), 2.04 (s, 2H), 3.65 (s, 2H), 6.71-6.74 (m, 1H), 6.98-7.38 (m, 8H), 7.98 (s, 1H). IR (neat): 1732, 1615. High-resolution MS Cacld for $C_{20}H_{23}NO_3Si$: 353.1448. Found 353.1448.
8. **4a**: ^{1}H NMR (CDCl$_3$, 270MHz) δ: 0.02 (s, 9H), 2.14 (s, 2H), 4.98 (s, 2H), 7.26-7.56 (m, 10H). IR (neat): 1694, 1651, 1252, 853. High-resolution MS Cacld for $C_{19}H_{23}NO_2Si$: 325.1498. Found 325.1491.
9. Heine, H. W.; Zibuck, R.; VandenHauvel, W. J. A. *J. Am. Chem. Soc.* **1982**, *104*, 3691-3694.