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Unexpectedly cyclized products by reaction of *N*-tosyliminoisoquinolinium ylides with trimethylsilylketene

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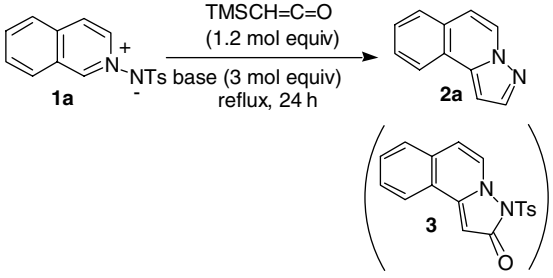
Abstract—The reaction of *N*-tosyliminoisoquinolinium ylides with trimethylsilylketene as a C2 unit introducing reagent, giving unexpected [3+2] cycloadducts, pyrazolo[5,1-*a*]isoquinolines, is described.

Trimethylsilylketene (TMS ketene) occupies an important position, most notably in its service as a masked ketene (CH_2=C=O).[1] TMS ketene exhibits milder reactivity than labile ketene and is more convenient in view of its easy handling and long-term storable stability. We have already demonstrated that TMS ketene, as a C2 unit introducing reagent, is quite useful for the construction of various heterocycles.[2] For instance, TMS ketene smoothly reacts with isoquinolinium methylides to give [3+2] cycloadducts, pyrroloisoquinolines.[2i] As extension of this work, we planned to investigate the reaction of tosyliminoisoquinolinium ylides **1**, aza-analogs of isoquinolinium methylides, with TMS ketene.

The reaction of tosyliminoisoquinolinium ylide **1a** with 1.2 mol equiv of TMS ketene[3] was examined under various reaction conditions. The selected results are shown in Table 1. As can be seen, some trends are apparent. First, non-base, and the use of pyridine exhibiting weak basicity and K_2CO_3 were not particularly effective at all. Second, the use of Et_3N and *i*-Pr_2NEt allowed ylide **1a** and TMS ketene to react. After completion of the reaction, usual work-up and purification afforded the unexpectedly cyclized product **2a**, pyrazolo[5,1-*a*]isoquinoline: our expected product **3** was not produced in detectable amounts. The structure of **2a** was unambiguously determined by comparison of sample **2a**, which was prepared independently by Hosomi and Tominaga's method.[4] The physical data of **2a** were as follows. Yellow powders of mp 61 °C (EtOAc): lit.[5] 62 °C. IR ($CHCl_3$): $\nu = 1484$, 1435, 1371 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): $\delta = 6.92$ (d, $J = 8.2$ Hz, 1H), 6.93 (s, 1H), 7.45–7.54 (m, 2H), 7.65 (br d, $J = 7.7$ Hz, 1H), 7.95 (d, $J = 1.6$ Hz, 1H), 8.03 (br d, $J = 8.2$ Hz, 1H), 8.21 (d, $J = 7.4$ Hz, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 97.3$, 111.9, 123.5, 124.4, 126.2, 126.9, 127.4, 127.6, 128.5, 138.1, 140.9. EIMS: m/z (%) = 168 (100, M^+). Anal. Calcd for $C_{11}H_8N_2$: C, 78.55; H, 4.79; 16.66. Found: C, 78.72; H, 5.00; 16.44. Thus, Et_3N as a base and aromatic solvent were found to be the most effective combination for obtaining unexpected [3+2] cycloadduct **2a** (entry 5).

Table 1. Optimization of reaction conditions



Entry	Solvent	Base	Yield (%) of **2a**
1	THF	None	No reaction
2	Toluene	None	Complex mixture
3	Toluene	Pyridine	Complex mixture
4	Toluene	K_2CO_3	Complex mixture
5	Toluene	Et_3N	63
6	Toluene	*i*-Pr_2NEt	50
7[a]	DMF	Et_3N	47

[a] The reaction was performed at 110 °C.

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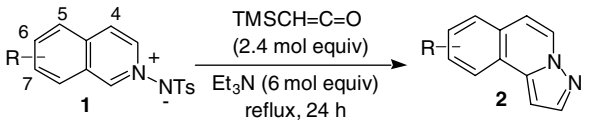
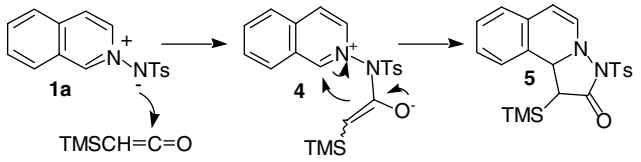
Table 2. Substrate generality



Entry	R	Solvent	Time (h)	Yield (%)
1[a]	4-Br (**1b**)	Toluene	48	75 (**2b**)
2[a]	5-NO_2 (**1c**)	Toluene	48	79 (**2c**)
3	6-F (**1d**)	Toluene	24	71 (**2d**)
4	6-Me (**1e**)	Toluene	24	62 (**2e**)
5	6-MeO (**1f**)	Xylene	72	71 (**2f**)
6	6,7-di-MeO (**1g**)	Xylene	72	14 (**2g**)

[a] The reaction temperature was 80 °C.



Scheme 1.

The substrate generality of this unexpected reaction is shown in Table 2. The reactions were performed with 2.4 mol equiv of TMS ketene and 6 mol equiv of Et_3N, because the yields of the reactions in Table 2 with 1.2 mol equiv of TMS ketene and 3 mol equiv of Et_3N were moderate or low.[6] Tosyliminoisoquinolinium ylides **1b–f** bearing electron-withdrawing substituents such as fluoro and nitro groups, and electron-donating substituents such as mono-methoxy and methyl groups on the isoquinoline ring were found to be employable, giving the corresponding pyrazolo[5,1-*a*]isoquinolines **2b–f** in 62–79% yield.[7] Unfortunately, ylide **1g** bearing strong electron-donating substituents such as di-methoxy groups gave **2g** in 14% yield. The reaction mechanism[8] for the formation of unexpected [3+2] cycloadduct **2** including the deoxygenation and detosylation steps[9] (from **5** to **2**) is not clear at the present time. But we are tempted to assume that the initial step is a stepwise process as follows: nucleophilic attack of ylide **1** to TMS ketene followed by cyclization of the resulting betaine **4** produces **5** (Scheme 1), because we previously demonstrated that the [4+2] cycloaddition of TMS ketene and a 1,3-diene proceeded by a stepwise process.[2a]

In summary, the reaction of *N*-tosyliminoisoquinolinium ylides with TMS ketene as a C2 unit introducing reagent has been found to give unexpected [3+2] cycloadducts, pyrazolo[5,1-*a*]isoquinolines.[10–12]

Acknowledgement

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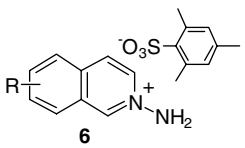
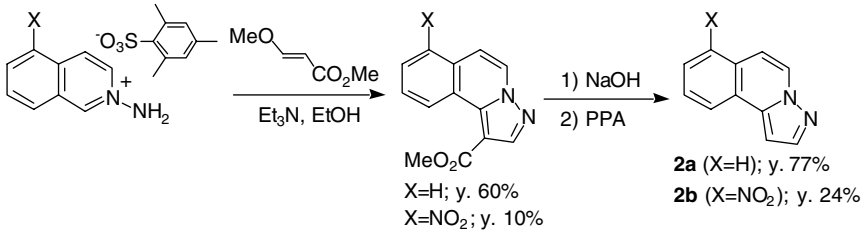
6. The results for the reactions with 1.2 mol equiv of TMS ketene and 3 mol equiv of Et_3N were as follows: **2b** (y. 40%), **2c** (52%), **2d** (55%), **2f** (23%).
7. The synthesis of **2b** bearing a nitro group using Hosomi and Tominaga's method[4] was not efficient, although the efficiency for the synthesis of **2a** was similar to our method (Scheme 2).
8. For a recent example of the 1,3-dipolar cyclization of *N*-ylides, see: Fang, X.; Wu, Y.-M.; Deng, J.; Wang, S.-W. *Tetrahedron* **2004**, *60*, 5487–5493, and references cited therein.
9. A fragment of *p*-acetoxytoluene in the reaction mixture, which was quenched with Ac_2O, was observed by LC–MS.
10. The *N*-*p*-tosyliminoisoquinolinium ylides **1a–g** were easily prepared by the standard tosylation of **6**.



11. *Representative procedure for cyclization:* a mixture of *N*-*p*-tosyliminoisoquinolinium ylide (**1a**) (50.0 mg, 0.168 mmol) and Et_3N (0.07 mL, 0.50 mmol) and trimethylsilylketene (0.45 mL, 0.20 mmol, 0.45 M in toluene solution) in toluene (2.0 mL) was refluxed for 24 h, allowed to cool, and directly concentrated. The residue was purified

by silica gel column chromatography (hexanes–EtOAc, 7:1) to afford pyrazolo[5,1-*a*]isoquinoline (**2a**) (17.9 mg, 63%).

12. Selected spectral data are as follows. For **2c**: Orange powders of mp 180–182 °C (EtOAc–hexane). IR ($CHCl_3$): $\nu = 1371, 1339, 1211\ cm^{-1}$. ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.09$ (br d, $J = 2.2$ Hz, 1H), 7.67 (dd, $J = 8.1$, 8.1 Hz, 1H), 7.77 (d, $J = 8.1$ Hz, 1H), 8.05 (d, $J = 2.2$ Hz, 1H), 8.24 (br d, $J = 8.1$ Hz, 1H), 8.38 (br d, $J = 8.1$ Hz, 1H), 8.42 (d, $J = 8.1$ Hz, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 98.84, 105.97, 121.83, 124.54, 126.22, 126.70, 129.03, 129.26, 136.91, 141.96$. EIMS: m/z (%) = 213 (100, M^+). For **2f**: Orange powders of mp 104–105 °C (EtOAc–hexane). IR ($CHCl_3$): $\nu = 1485, 1472, 1437\ cm^{-1}$. ^1H NMR (270 MHz, $CDCl_3$): $\delta = 3.93$ (s, 3H), 6.85–6.87 (m, 1H), 6.92 (d, $J = 7.4$ Hz, 1H), 7.11 (d, $J = 2.5$ Hz, 1H), 7.18 (dd, $J = 8.7$, 2.5 Hz, 1H), 7.93 (d, $J = 2.0$ Hz, 1H), 8.00 (d, $J = 8.7$ Hz, 1H), 8.23 (d, $J = 7.4$ Hz, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 55.47, 96.24, 108.23, 111.61, 117.21, 118.63, 125.16, 126.70, 130.27, 138.38, 141.16, 159.13$. EIMS: m/z (%) = 198 (100, M^+).



Scheme 2.