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Reaction of isoquinolinium methylide derivatives with trimethylsilylketene

Mayumi Kobayashi, Mika Tanabe, Kazuhiro Kondo and Toyohiko Aoyama*

Graduate School of Pharmaceutical Sciences, Nagoya City University, 3-1 Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan

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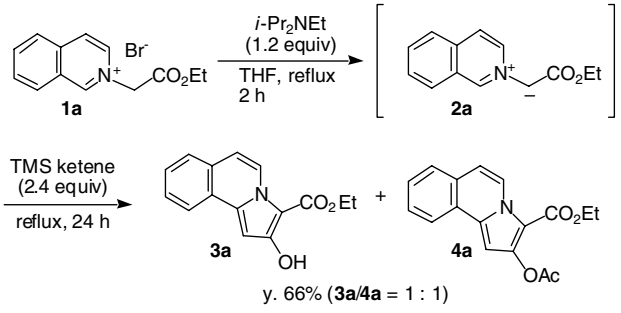
Abstract—Our investigation on the reaction of isoquinolinium methylide derivatives with trimethylsilylketene (TMS ketene), giving [3+2] cycloadducts, pyrroloisoquinolines, is described. TMS ketene is found to function as the C2 unit introducing reagent in the reaction of isoquinolinium methylide derivatives. Furthermore, the advantage of TMS ketene in comparison with ketene (CH_2=C=O) is shown.

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 considered to be more convenient in view of its easy handling and long-term storable stability. As part of our program[2] directed toward development of new reactions using TMS ketene, we herein report our investigation on the reaction of isoquinolinium methylide derivatives with TMS ketene.

We first investigated the reaction with isoquinolinium salt **1a** as shown in Scheme 1. After intensive screening of reaction conditions,[4] the use of 2.4 equiv of TMS ketene,[3] 1.2 equiv of *i*-Pr_2NEt as a base and THF as a solvent was found to be the most effective combination for obtaining the desired [3+2] cycloadducts, pyrroloisoquinolines, **3a** and **4a**.[5]



Scheme 1.

Having the best conditions, we examined the reaction of several isoquinolinium salts **1b–d**, **5** and **8** as shown in Scheme 2. Isoquinolinium salts **1b–d** with electron-donating and -withdrawing groups on the isoquinoline ring were found to be employable, giving the corresponding pyrroloisoquinolines in 63–71% yield. Furthermore, isoquinolinium salts **5** and **8** bearing a sterically hindered *tert*-butyl ester group and a methyl group in the α position of the ester gave the corresponding pyrroloisoquinolines **6/7** and **9** in good yields.

In order to demonstrate the advantage of TMS ketene, we compared the reactivity of ketene (CH_2=C=O) with that of TMS ketene in reaction with **10**. The results are shown in Scheme 3. The use of ketene with **10** has been reported by Kato,[6] giving product **12**, which was formed by the reaction of two molecules of ketene with one molecule of **10**. On the other hand, as expected, the use of TMS ketene gave the desired pyrroloisoquinoline **11** in 63% yield. In this case, Li_2CO_3 as a base in place of *i*-Pr_2NEt was the best.[7] Taking the experimental results independently reached by Kato's group and ours into consideration, we could conclude TMS ketene was an effective reagent.

The reaction mechanism[8] for the formation of hydroxy-pyrroloisoquinoline **3a** and/or acetoxy-pyrroloisoquinoline **4a** may be considered to be as shown in Scheme 4.

* Corresponding author. Tel./fax: +81 52 836 3439; e-mail: aoyama@phar.nagoya-cu.ac.jp

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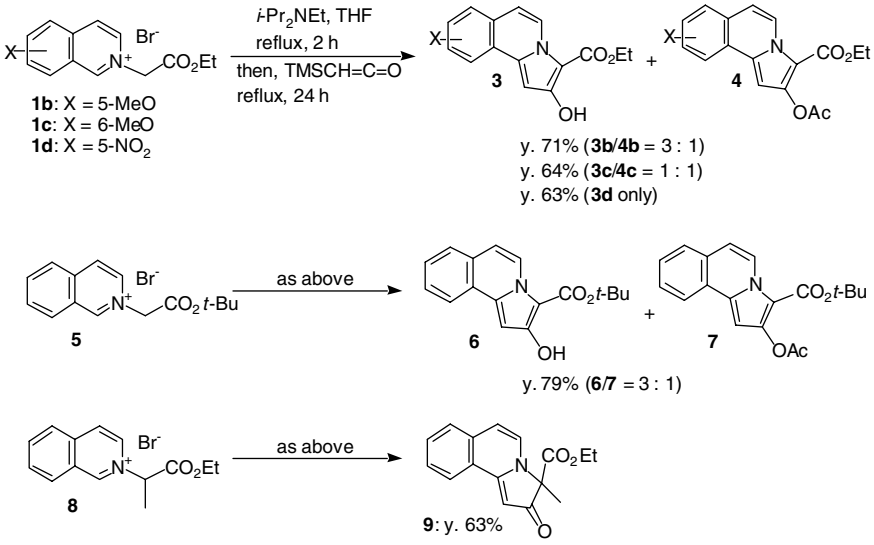
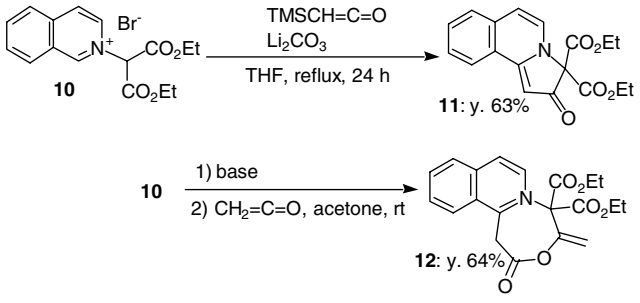


Scheme 2. Substrate generality.



Scheme 3. Comparison with $CH_2{=}C{=}O$.

Nucleophilic attack of carbanion in ylide **2a** to TMS ketene followed by cyclization of the resulting betain **13** produces **14**. Desilylation and aromatization and of **14** afford hydroxy-pyrroloisoquinoline **3a**. Subsequent nucleophilic attack of the OH group in **3a** to TMS ketene and then desilylation afford acetoxy-pyrroloisoquinoline **4a**.

In summary, TMS ketene has been found to function as the C2 unit introducing reagent in the reaction of isoquinolinium methylide derivatives.[9] Work on other synthetic reactions using TMS ketene is now in progress.

Acknowledgements

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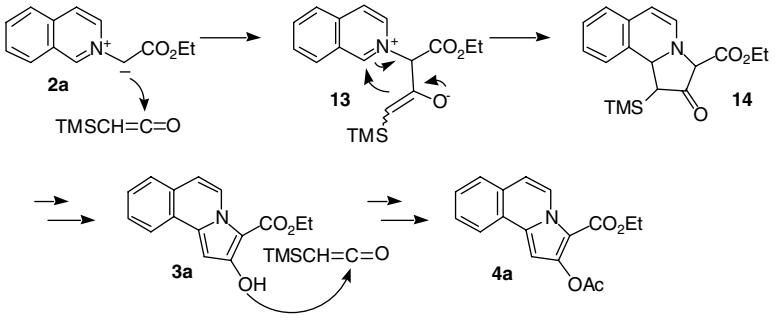
References and notes

1. (a) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworths: London, 1985, Chapter 14, pp 174–177; (b) Leobach, J. L.; Danheiser, R. L. In *Encyclopedia of Reagents for Organic Synthesis*; Paquett, L. A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 7, pp 5266–5268; (c) Pommier, A.; Kocienski, P.; Pons, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2105–2118; (d) Shioiri, T.; Takaoka, K.; Aoyama, T. *J. Heterocycl. Chem.* **1999**, *36*, 1555–1563; For recent selected examples, see: (e) Evans, D. A.; Janey, J. M. *Org. Lett.* **2001**, *3*, 2125–2128; (f) Rossé, G.; Gerber, F.; Specklin, J.-L.; Hubschwerlen, C. *Synlett* **2001**, 538–540; (g) Ponomarev, S. V.; Zolotareva, A. S.; Ezhov, R. N.; Kuznetsov, Yu. V.; Petrosyan, V. S. *Russ. Chem. Bull., Int. Ed.* **2001**, *50*, 1093–1096; (h) Holland, A. W.; Bergman, R. G. *Inorg. Chem.* **2002**, *341*, 99–106; (i) Fournier, L.; Gaudel-Siri, A.; Kocienski, P. J.; Pons, J.-M. *Synlett* **2003**, 107–111; (j) Ungvári, N.; Kégl, T.; Ungváry, F. *J. Mol. Catal. A: Chem.* **2004**, *219*, 7–11.
2. (a) Ito, T.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 6583–6586; (b) Takaoka, K.; Aoyama, T.; Shioiri, T.



Scheme 4. Possible reaction mechanism.

Synlett **1994**, 1005–1006; (c) Takaoka, K.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1996**, *37*, 4973–4976; (d) Takaoka, K.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1996**, *37*, 4977–4978; (e) Matsumoto, T.; Takaoka, K.; Aoyama, T.; Shioiri, T. *Tetrahedron* **1997**, *53*, 225–236; (f) Takaoka, K.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1999**, *40*, 3017–3020; (g) Takaoka, K.; Aoyama, T.; Shioiri, T. *Heterocycles* **2001**, *54*, 209–215; (h) Arai, S.; Sakurai, T.; Asakura, H.; Fuma, S. *Heterocycles* **2001**, *55*, 2283–2287.

3. For preparation of TMS ketene: Valentí, E.; Pericàs, M. A.; Sarratosa, F. *J. Org. Chem.* **1990**, *55*, 395–397.
4. The use of Et_3N as a base resulted in no reaction. The results of solvent effects were as follows: toluene (62% yield), DMF (complex mixtures).
5. Representative procedure: A mixture of 2-ethoxycarbonylmethylisoquinolinium bromide (**1a**) (118 mg, 0.40 mmol) and *i*-Pr_2NEt (0.0840 mL, 0.480 mmol) in THF (10 mL) was refluxed for 2 h under argon and then to this mixture trimethylsilylketene (2.91 mL, 0.960 mmol, 0.330 M in toluene solution) was added. The reaction mixture was refluxed for 24 h, diluted with water, and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes/EtOAc, 30:1 to 10:1) to afford 2-hydroxy-pyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid ethyl ester (**3a**) (35.1 mg, 34%) as brown powders and 2-acetoxy-pyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid ethyl ester (**4a**) (38.4 mg, 32%) as white powders. The spectral data of **3a** were as follows. Mp 77–78 °C (EtOAc–hexanes). IR (nujol): 3356, 1638 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): $\delta = 1.46$ (t, $J = 7.1$ Hz, 3H), 4.47 (q, $J = 7.1$ Hz, 2H), 6.50 (s, 1H), 6.79 (d, $J = 7.6$ Hz,1H), 7.39–7.46 (m, 2H), 7.51–7.56 (m, 1H), 7.90–7.94 (m, 1H), 8.59 (br s, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 14.6$, 60.2, 88.5, 101.5, 110.5, 123.3, 123.6, 124.4, 126.5, 127.0, 127.5, 128.3, 134.0. EIMS: m/z (%) = 255 (87, M^+), 209 (100). HRMS (M^+): m/z calcd for $C_{15}H_{13}NO_3$: 255.0896; found: 255.0929. The spectral data of **4a** were comparable to those reported.[10]
The spectral data of selected pyrrolo[2,1-*a*]isoquinoline derivatives were as follows.
2-Hydroxy-8-methoxy-pyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid ethyl ester (**3c**): Yellow plates of mp 173–175 °C (EtOAc–hexanes). IR (nujol): 3271, 1636 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): $\delta = 1.48$ (t, $J = 7.1$ Hz, 3H), 3.92 (s, 3H), 4.49 (q, $J = 7.1$ Hz, 2H), 6.46 (s, 1H), 6.85 (d, $J = 7.3$ Hz, 1H), 7.02 (d, $J = 2.3$ Hz, 1H), 7.14 (dd, $J = 8.9$, 2.3 Hz, 1H), 7.93 (d, $J = 8.9$ Hz, 1H), 8.50 (br s, 0.5H), 9.30 (br s, 0.5H). ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 14.8$, 55.4, 60.2, 87.6, 107.5, 110.4, 117.4, 118.1, 125.2, 130.2, 159.3. EIMS (EI): m/z (%) = 285 (48, M^+), 239 (100). HRMS (M^+): m/z calcd for $C_{16}H_{15}NO_4$: 285.1001; found: 285.1003.
2-Acetoxy-8-methoxy-pyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid ethyl ester (**4c**): Yellow needles of mp 138–141 °C (EtOAc–hexanes). IR (nujol): 1767, 1670 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): $\delta = 1.40$ (t, $J = 7.1$ Hz, 3H), 2.37 (s, 3H), 3.92 (s, 3H), 4.36 (q, $J = 7.1$ Hz, 2H), 6.73 (s, 1H), 6.98 (d, $J = 7.6$ Hz, 1H), 7.06 (d, $J = 2.4$ Hz, 1H), 7.16 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.95 (d, $J = 8.8$ Hz, 1H), 9.19 (d, $J = 7.6$ Hz, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 14.9$, 21.4, 55.8, 60.3, 94.3, 106.6, 107.9, 112.7, 118.0, 118.8, 125.1, 125.4, 129.9, 133.3, 145.5, 159.5, 160.7, 169.2. EIMS: m/z (%) = 327 (70, M^+), 239 (100). HRMS (M^+): m/z calcd for $C_{18}H_{17}NO_5$: 327.1107; found: 327.1101.
2-Hydroxy-7-nitro-pyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid ethyl ester (**3d**): Orange powders of mp 193–194 °C (EtOAc–hexanes). IR (nujol): 3471, 1682 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): $\delta = 1.49$ (t, $J = 7.1$ Hz, 3H), 4.53 (q, $J = 7.1$ Hz, 2H), 6.67 (s, 1H), 7.58 (dd, $J = 8.0$, 8.0 Hz, 1H), 7.66 (d, $J = 8.0$ Hz, 1H), 8.19 (d, $J = 8.0$ Hz, 1H), 8.29 (d, $J = 8.0$, 1H), 8.86 (br s, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 14.7$, 60.9, 90.3, 102.4, 104.8, 121.6, 124.5, 125.5, 126.1, 127.7, 129.0, 132.2, 145.5. EIMS: m/z (%) = 300 (38, M^+), 254 (100). Anal. Calcd for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.03; N, 9.33. Found: C, 59.76; H, 4.14; N, 9.11.
2-Oxo-2*H*-pyrrolo[2,1-*a*]isoquinoline-3,3-dicarboxylic acid diethyl ester (**11**): A yellow oil. IR (neat): 1732, 1683, 1634 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): $\delta = 1.33$ (t, $J = 7.1$ Hz, 6H), 4.35 (q, $J = 7.1$ Hz, 2H), 4.36 (q, $J = 7.1$ Hz, 2H), 5.59 (s, 1H), 6.57 (d, $J = 7.3$ Hz, 1H), 7.28 (d, $J = 7.3$ Hz, 1H), 7.45–7.53 (m, 2H), 7.63–7.69 (m, 1H), 7.83 (d, $J = 8.1$ Hz, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 14.0$, 63.6, 78.6, 88.7, 108.0, 121.8, 126.7, 127.4, 127.5, 128.6, 133.3, 134.9, 162.7, 166.8, 183.1. EIMS: m/z (%) = 327 (59, M^+), 209 (100). HRMS (M^+): m/z calcd for $C_{18}H_{17}NO_5$: 327.1107; found: 327.1083.

6. Kato, T.; Chiba, T.; Tanaka, S.; Sasaki, T. *Heterocycles* **1978**, *11*, 227–230.
7. Other bases such as pyridine, NaOAc, and $NaHCO_3$ gave less satisfactory results.
8. We previously demonstrated that the [4+2] cycloaddition of TMS ketene and a 1,3-diene proceeded by a stepwise process.[2a] However, in the case of Scheme 1, a concerted mechanism might be considered.
9. 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.
10. Kato, T.; Chiba, T.; Sasaki, T. *Heterocycles* **1979**, *12*, 925–928.