STUDIES ON PYRIDINIUM *N*-YLIDES: ONE STEP SYNTHESIS OF HETEROPOLYCYCLES, INDOLIZINOQUINOLIZINES

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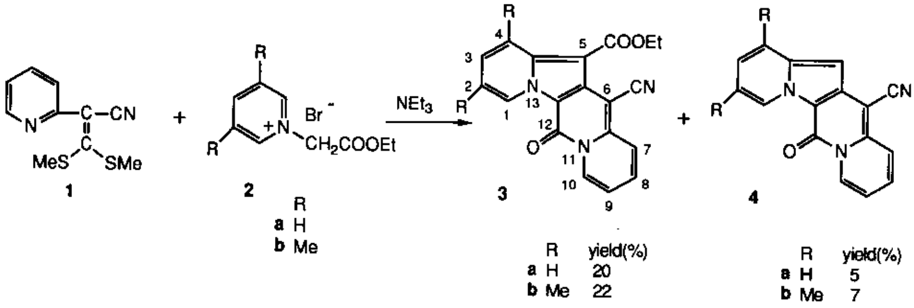
Abstract - The heteropolycycles, indolizinoquinolizines (**3**,**4**) were obtained by the reaction of pyridylketene dithioacetal (**1**) with two molar equivalents of pyridinium salts (**2a**,**b**).

Pyridinium *N*-allylides and *N*-vinylimino ylides which are prepared by the reaction of pyridinium salt with polarized olefins (ketene dithioacetals and ethoxymethylene compounds) in the presence of an appropriate base are well known to undergo thermal 1,5-dipolar cyclization and aromatization giving the corresponding indolizines and azaindolizines.[1-8] On the other hand, ketene dithioacetals appropriately functionalized (cyano, methoxycarbonyl, nitro, sulfonyl, pyridyl, etc.) are versatile reagents which have been extensively utilized in the synthesis of heterocycles.[9,10] As a part of our continuing interest in ketene dithioacetals, we carried out the extensive studies on the reaction of heteroaromatic compounds with various ketene dithioacetals and their analogues.[11-13] In this communication we wish to report the reaction of the pyridylketene dithioacetal, 3,3-bis(methylthio)-2-pyridylacrylonitrile (**1**)[14] with pyridinium salt (**2**) to give the heteropolycycles, indolizinoquinolizines (**3**,**4**) resulted on the interesting one step synthesis.

The starting pyridylketene dithioacetal (**1**) used in the present work was prepared by the condensation of pyridylacetonitrile (**5**) with carbon disulfide in THF in the presence of sodium hydride, followed by methylation with dimethyl sulfate.[14] The reaction of **1** with two molar equivalents of pyridinium salt (**2a**) in the presence of triethylamine in EtOH at room temperature for a week afforded indolizinoquinolizines (**3a**,[15a] **4a**[16a]) together

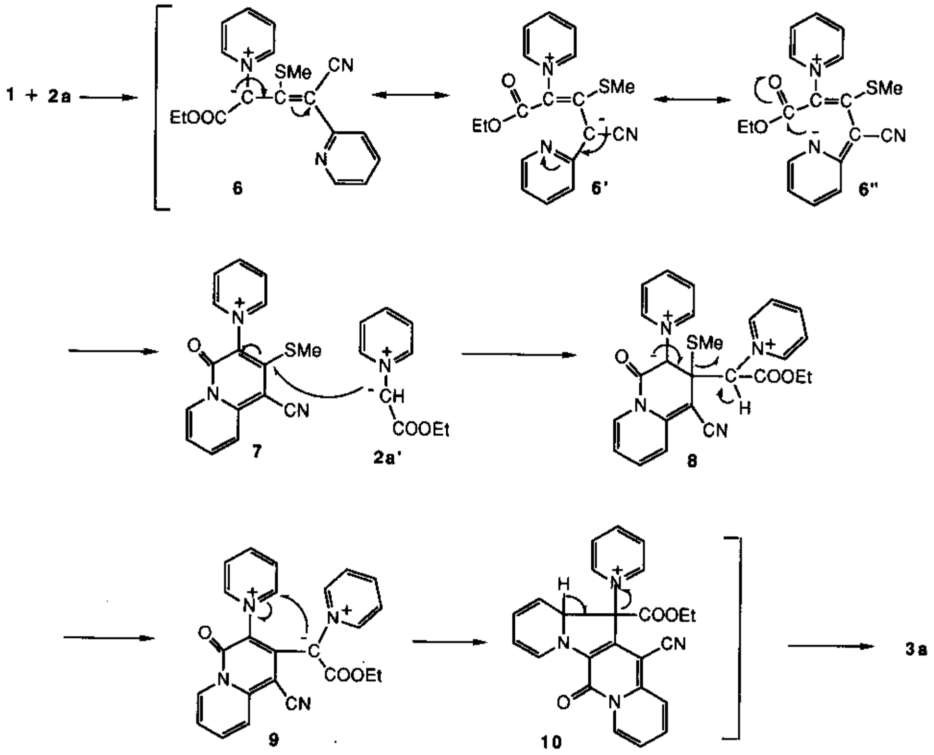
Scheme 1



	R	yield(%)
a	H	20
b	Me	22

	R	yield(%)
a	H	5
b	Me	7

Scheme 2



with unknown decomposed materials. The structure of **3a**, for example, was supported by a satisfactory elemental analysis, the presence of one cyano and two carbonyl absorptions in the ir spectrum, and the signals of four doublets ($C_{1,4,7,10}$-H) in the ^{1}H-nmr spectrum. In addition, 2,4-dimethylindolizinoquinolizines (**3b**,[15b] **4b**[16b]) were obtained by the reaction of **1** with **2b**. (Scheme 1)

The formation of compound (**3a**) may be rationalized as outlined in Scheme 2. Thus, *N*-allylide (**6**) does not undergo 1,5-dipolar cyclization due to the resonance structure (**6'**) to give an indolizine derivative but **6** may cyclize due to **6"** to give pyridinium oxoquinolizine (**7**), followed by the substitution of the methylthio group of **7** with pyridinium *N*-ylide (**2a'**) to give the betaine (**9**) which may lead to **3a** *via* the intermediate (**10**).

The synthesis of indolizines from pyridinium *N*-allylides involving 1,5-dipolar cyclization has been reported.[1-13] However, the present result provides the first example of the one step synthesis of the heteropolycycle, indolizinoquinolizine from pyridinium *N*-allylide.

REFERENCES AND NOTE

1. K. Matsumoto, *J. Syn. Org. Chem. Japan*, 1974, **32** 731.
2. T. Uchida and K. Matsumoto, *Synthesis*, **1976**, 209.
3. F. J. Swinbourne, J. H. Hunt, and G. Klinkert, "Advances in Heterocyclic Chemistry", Vol. **23**, ed. by A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1978, p. 103.
4. R. M. Acheson and N. F. Elmore, *ibid.*, Vol. **23**, 1978, p. 263.
5. Y. Tamura and M. Ikeda, *ibid.*, Vol. **29**, 1981, p. 71.
6. E. C. Taylor and I. J. Turchi, *Chem. Rev.*, 1979, **79**, 181.
7. A. Kakehi, S. Ito, T. Funahashi, and Y. Ota, *J. Org. Chem.*, 1976, **41**, 1570.
8. A. Kakehi, S. Ito, K. Uchiyama, Y. Konno, and K. Kondo, *ibid.*, 1977, **42**, 443.
9. Y. Tominaga and Y. Matsuda, *J. Heterocycl. Chem.*, 1985, **22**, 937.
10. M. Kolb, *Synthesis*, **1990**, 171.
11. Y. Matsuda, H. Gotou, K. Katou, H. Matsumoto, M. Yamashita, K. Takahashi, and S. Ide, *Heterocycles*, 1990, **31**, 997.
12. Y. Tominaga and Y. Matsuda, *J. Syn. Org. Chem. Japan*, 1985, **43**, 669.
13. Y. Matsuda and H. Gotou, *Heterocycles*, 1987, **26**, 2757.
14. G. Kobayashi, S. Furukawa, Y. Matsuda, R. Natsuki, and S. Matsunaga,*Yakugaku Zasshi*, 1970, **90**, 127.

15. a) For **3a:** mp 245°C (20%); ms *m/z* 331(M+); ir(KBr) νmax 2210 (CN), 1700 (CO), 1680 (CO) cm^{-1}; uv(EtOH) λmax(log ε) 224(4.40), 248(4.51), 260(4.49), 292(4.41), 320(4.31), 400(3.81), 424(3.91), 448(3.76) nm; ^{1}H-nmr ($CDCl_3$) δ 1.52(3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 4.59(2H, q, *J*=7 Hz, $C\underline{H}_2CH_3$), 6.97-7.29(2H, m, Ar-H), 7.48-7.71(2H, m, Ar-H), 8.24(1H, d, *J*=9 Hz, C_7-H), 8.56(1H, d, *J*=9 Hz, C_4-H), 9.22(1H, d, *J*=7 Hz, C_{10}-H), 9.98(1H, d, *J*=7 Hz, C_1-H). *Anal.* Calcd for $C_{19}H_{13}N_3O_3$: H, 3.95; C, 68.88; N, 12.68. Found: H, 4.07; C, 69.01; N, 12.78.

    b) For **3b:** mp 243-245°C (22%); ms *m/z* 359(M+); ir(KBr) νmax 2200 (CN), 1710 (CO), 1680 (CO) cm^{-1}; uv(EtOH) λmax(log ε) 230(4.42), 263(4.55), 296(4.36), 319(4.34), 354(4.28), 372(4.21)sh, 408(3.79), 430(3.82), 455(3.63) nm; ^{1}H-nmr ($CDCl_3$) δ 1.48(3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 2.42(3H, s, CH_3), 2.63(3H, s, CH_3), 4.56(2H, q, *J*=7 Hz, $C\underline{H}_2CH_3$), 6.96(1H, dd, *J*=6, 7 Hz, C_9-H), 7.15(1H, s, C_3-H), 7.50(1H, dd, *J*=6, 9 Hz, C_8-H), 8.04(1H, d, *J*=9 Hz, C_7-H), 9.15(1H, d, *J*=7 Hz, C_{10}-H), 9.64(1H, s, C_1-H). *Anal.* Calcd for $C_{21}H_{17}N_3O_3$: H, 4.77; C, 70.18; N, 11.69. Found: H, 4.92; C, 70.21; N, 11.60.

16. a) For **4a**: mp 271-273°C (5%); ms *m/z* 259(M+); ir(KBr) νmax 2200 (CN), 1680 (CO) cm^{-1}; uv(EtOH) λmax(log ε) 227(4.06), 266(3.95), 321(4.13), 375(3.54), 412(3.01), 438(2.99), 468(2.79) nm; ^{1}H-nmr ($CDCl_3$) δ 6.74(1H, s, C_5-H), 6.81-6.98(2H m, Ar-H), 7.23-7.52(2H, m, Ar-H), 7.64(1H, d, *J*=9 Hz, C_7-H), 7.90(1H, d, *J*=9 Hz, C_4-H), 9.14(1H, d, *J*=7 Hz, C_{10}-H), 9.68(1H, d, *J*=6 Hz, C_1-H). *Anal.* Calcd for $C_{16}H_9N_3O$: H, 3.50; C, 74.12; N, 16.21. Found: H, 3.67; C, 73.86; N, 15.97.

    b) For **4b**: mp 305-307°C (7%); ms *m/z* 287(M+); ir(KBr) νmax 2200 (CN), 1680 (CO) cm^{-1}; uv(EtOH); λmax 212, 230, 270, 293, 317, 343, 358, 379, 417, 440, 465 nm; ^{1}H-nmr ($CDCl_3$) δ 2.40(3H, s, CH_3), 2.55(3H, s, CH_3), 6.66(1H, s, C_5-H), 6.87(1H, dd, *J*=6, 7 Hz, C_9-H), 7.01(1H, s, C_3-H), 7.23-7.49(1H, m, C_8-H), 7.87(1H, d, *J*=8 Hz, C_7-H), 9.11(1H, d, *J*=7 Hz, C_{10}-H), 9.37(1H, s, C_1-H). *Anal.* Calcd for $C_{18}H_{13}N_3O$: H, 4.56; C, 75.25; N, 14.63. Found: H, 4.71; C, 74.93; N, 14.33.

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