

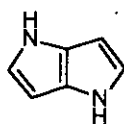
THE REACTION OF ELECTRON EXCESS AROMATIC HETEROCYCLE, 1,4-DIHYDROPYRROLO[3,2-*b*]PYRROLE AND SOME RELATED COMPOUNDS WITH CHLOROSULFONYL ISOCYANATE (CSI)

Kyosuke Satake,\* Kentaro Yano, Makoto Fujiwara, and Masaru Kimura

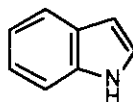
Department of Chemistry, Faculty of Science, Okayama University,  
Tsushima-Naka 3-1-1, Okayama 700, Japan

**Abstract** - The reaction of 3,6-di-*tert*-butyl-1,4-dihydropyrrolo[3,2-*b*]pyrrole and its *N,N'*-dimethoxycarbonyl derivative with chlorosulfonyl isocyanate (CSI) was investigated. The higher reactivity for the electrophilic reaction and a remarkable electron excessiveness of the system were demonstrated by comparing with those of indole and pyrrole derivatives.

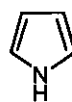
The 1,4-dihydropyrrolo[3,2-*b*]pyrrole (**1**) is a recently occurred bicyclic hetero-aromatic compound<sup>1,2</sup> and its chemical behaviors may be analogized by indole (**2**) or pyrrole (**3**). Despite the intrinsic capability of **1** for electrophilic reaction on the ground of its highly electron excess character expected,<sup>3</sup> little is yet known concerned with the reactivity of this molecule. For instance, Vilsmeier formylation is the only reported electrophilic substitution reaction for **1**, to our knowledge.<sup>4</sup> We report here the reaction of 3,6-di-*tert*-butyl-1,4-dihydropyrrolo[3,2-*b*]pyrrole (**4**),<sup>2</sup> and dimethyl 3,6-di-*tert*-butyl-1,4-dihydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylate (**6**)<sup>2</sup> with chlorosulfonyl isocyanate (CSI). Additionally, the reaction of *N*-methoxycarbonyl derivatives of indole (**12**, **13**) and pyrrole (**15**) was also examined with the intention of comparing the reactivities.



**1**

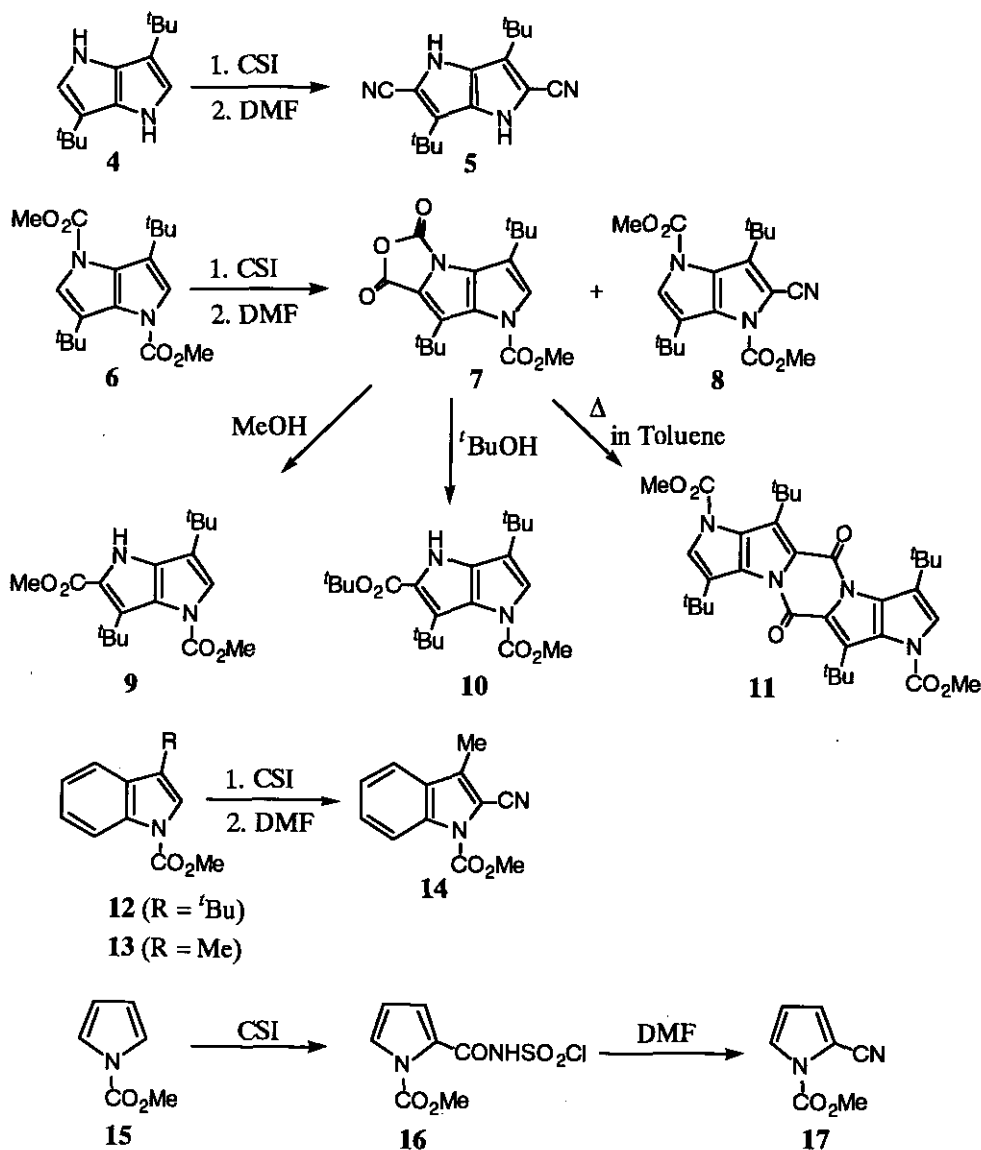


**2**



**3**

The CSI has been widely used as one of the most reactive isocyanate reagent on the ground of having a strongly electron withdrawing chlorosulfonyl group in the molecule.<sup>5</sup> Generally, an electrophilic addition reaction of CSI with hetero-aromatic compound (*e.g.* pyrrole,<sup>6</sup> indole<sup>7a-c</sup> *etc.*) occurred effectively to give carboxamide or cyano compound by a subsequent hydrolysis or reaction with *N,N*-dimethylformamide (DMF), respectively.



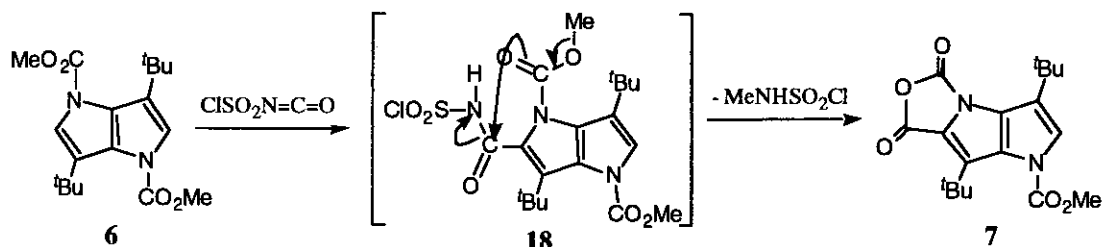
When an equiv. of CSI was added gradually to the dichloromethane solution of **4** at 0°C under dry nitrogen flow, slightly exothermic reaction occurred to give 3,6-di-*tert*-butyl-1,4-dihydropyrrolo[3,2-*b*]pyrrole-2,5-dicarbonitrile (**5**)<sup>8</sup> in 30% yield by a subsequent treatment of the reaction mixture with 2 equiv. of DMF. An

improved yield of 50% for **5** was accomplished when 2 equiv. of CSI were used in the reaction. On the other hand, the reaction of *N,N'*-dimethoxycarbonyl derivative (**6**) with an equiv. of CSI under the similar conditions gave 3,6-di-*tert*-butyl-4-methoxycarbonyl-1,4-dihydropyrrolo[3,2-*b*]pyrrole-1,2-carboxylic anhydride (**7**)<sup>9</sup> along with a trace of expected dimethyl 2-cyano-3,6-di-*tert*-butyl-1,4-dihydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylate (**8**). The anhydride (**7**) was also obtained in a better yield (59%) by the reaction without treatment with DMF. The characteristic ir absorptions observed at 1848 and 1800 cm<sup>-1</sup> were attributed to the C=O stretching mode of the acid anhydride moiety. The structure of **7** was confirmed also by the solvolysis reaction using methyl alcohol or *tert*-butyl alcohol giving respective methyl ester (**9**)<sup>10</sup> or *tert*-butyl ester (**10**) in quantitative yields. On heating **7** in toluene for 1 h, evolution of carbon dioxide occurred to give a bimolecular condensation product, dimethyl 3,6,9,12-tetra-*tert*-butyl-5,11-dioxodipyrrolo[2',3':4,5]pyrrolo[1,2-*a*,1,2-*d*]piperazine-1,7-dicarboxylate (**11**)<sup>11</sup> in 97% yield.

The chemical behaviors of pyrrolo[3,2-*b*]pyrrole derivatives for CSI were compared with those of *N*-methoxycarbonylindole. It has been reported that the reaction of CSI with 2-substituted and 2,3-disubstituted indoles occurred at 3-position and 1-position to give indole-3-carbonitrile and indole-1-carboxamide derivatives, respectively.<sup>7a</sup> For the purpose of reproducing a similar steric conditions and limitation of the reaction site, 3-*tert*-butyl- and 3-methylindole derivatives (**12**) and (**13**) were prepared.<sup>13</sup> Although, methyl 3-*tert*-butylindole-1-carboxylate (**12**) did not give any products even under at higher temperature nor a longer reaction period compared to in the case of **6**, 3-methylindole derivative (**13**) gave methyl 2-cyano-3-methylindole-1-carboxylate (**14**) in 61% yield. Steric hindrance of 3-*tert*-butyl group may contribute to deactivate the 2-position of **12**. When the reaction was applied to *N*-methoxycarbonylpyrrole (**15**), the CSI adduct, methyl 2-chlorosulfonylcarbamoylpyrrole-1-carboxylate (**16**),<sup>7c</sup> which was converted to methyl 2-cyanopyrrole-1-carboxylate (**17**) in 81% yield by treating with DMF, could be isolated quantitatively as a brown solid (mp 90°C (decomp.)). Thus the formation of the anhydride (**7**) would be considered as the innate capability of pyrrolo[3,2-*b*]pyrrole, because an analogous anhydride could not be obtained from the CSI adduct (**16**) nor in the case of indole (**13**), at present.

A proposed mechanism from **6** to the anhydride (**7**) via speculated CSI adduct (**18**) is illustrated. In spite of steric hindrance of neighboring 3-*tert*-butyl group, an addition of CSI to the ring occurs at 2-position of **6** to form intermediary 2-chlorosulfonylcarbamoyl derivative (**18**) and a subsequent intramolecular elimination of MeNHSO<sub>2</sub>Cl gives a tricyclic heterocycle (**7**). The intensive nucleophilicity of the carbonyl oxygen atom of *N*-methoxycarbonyl group of **6** compared to that of indole (**13**) and pyrrole (**15**) would be interpreted by

AM1<sup>14</sup> calculated ionization potentials, these being 7.84 eV for **1**, 8.40 eV for **2** and 8.65 eV for **3**. The intensive electron excessiveness makes the nucleophilicity of the carbonyl oxygen atom increase.



## ACKNOWLEDGEMENTS

We thank the SC-NMR Laboratory of Okayama University for the <sup>1</sup>H and <sup>13</sup>C nmr measurements. Also we are indebted to Dr. Akira Nakamura (KURARAY Co. Ltd., Kurashiki Japan) for providing us a highly purified CSI.

## REFERENCES AND NOTES

1. H. Printzbach, R. Schwesinger, M. Breuninger, B. Gallenkamp, and D. Hunkler, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 347; T. Kumagai, S. Tanaka, and T. Mukai, *Tetrahedron Lett.*, 1984, **25**, 5669; H. Tom Dieck, U. Verfuert, K. Diblitz, J. Ehlers, and G. Fendesak, *Chem. Ber.*, 1989, **122**, 129.
2. K. Satake, T. Kumagai, and T. Mukai, *Chem. Lett.*, 1983, 743.
3. S. Tanaka, T. Kumagai, T. Mukai, and T. Kobayashi, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 1981; Z. Zhou and R.G. Parr, *J. Am. Chem. Soc.*, 1989, **111**, 7371.
4. T. Mukai, T. Kumagai, and S. Tanaka, *Jpn. Kokai Tokkyo Koho*, JP 62,207,275 [87,207,275] (*Chem. Abstr.*, 1988, **108**, 186728v).
5. Reviews: R. Graf, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 172; J.K. Rasmussen and A. Hassner, *Chem. Rev.*, 1976, **76**, 389; A. Kamal and P.B. Sattur, *Heterocycles*, 1987, **26**, 1051.
6. G.H. Barnett, H.J. Anderson, and C.E. Loader, *Can. J. Chem.*, 1980, **58**, 409; C.E. Loader and H.J. Anderson, *ibid.*, 1981, **59**, 2673.
7. a) G. Meath, D.N. Dhar, and S.C. Suri, *Synthesis*, 1978, 374; b) A.L. Borrer, E. Chinoporos, M.P. Filosa, S.R. Herchen, C.P. Petersen, C.A. Stern, and K.D. Onan, *J. Org. Chem.*, 1988, **53**, 2047; c) J.P. Praly, R. Faure, B. Joseph, L. Kiss, and P. Rollin, *Tetrahedron*, 1994, **50**, 6559, a formation of 3-chlorosulfonylcarbamoylindole was reported.

8. **5** : Colorless prisms (mp >300°C);  $^1\text{H}$  nmr (200 MHz, DMSO- $d_6$ )  $\delta$  1.30 (s, 18H), 11.43 (s, 2H);  $^{13}\text{C}$  nmr (50 MHz, DMSO- $d_6$ )  $\delta$  30.5 (q), 31.3 (s), 54.6 (q), 103.2 (s), 116.3 (s), 125.5 (s), 127.8 (s); ir (KBr) 3332, 2972, 2212, 1479, 1381, 1299  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{16}\text{H}_{20}\text{N}_4$ , C 71.62, H 7.51, N 20.87. Found C 71.69, H 7.57, N 20.87.
9. **7** : Colorless prisms (mp 110°C (decomp.));  $^1\text{H}$  nmr (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.41 (s, 9H), 1.57 (s, 9H), 4.01 (s, 3H), 7.35 (s, 1H);  $^{13}\text{C}$  nmr (50 MHz,  $\text{CDCl}_3$ )  $\delta$  30.0 (q), 31.0 (q), 33.6 (s, 2C), 54.6 (q), 119.6 (s), 125.4 (s), 128.5 (d), 129.3(s), 132.0 (s), 137.2 (s), 144.4 (s), 150.7 (s), 153.4 (s); ir (KBr) 2926, 1848, 1800, 1774, 1423, 1327, 1261  $\text{cm}^{-1}$ ; uv-vis. (EtOH) 256 (log  $\epsilon$  = 3.75), 306 (4.34), 344 (4.45) nm; ms (FAB, m/z) 347 (M+1, 93%); Anal. Calcd for  $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_5$ , C 62.42, H 6.40, N 8.09. Found C 62.45, H 6.45, N 7.85.
10. **9** : Colorless needles (mp 161-162.5°C);  $^1\text{H}$  nmr (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.21 (s, 9H), 1.52 (s, 9H), 3.87 (s, 3H), 3.92 (s, 3H), 7.04 (s, 1H), 8.58 (br s, 1H);  $^{13}\text{C}$  nmr (50 MHz,  $\text{CDCl}_3$ )  $\delta$  30.0 (q), 30.4 (q), 30.7 (s), 32.9 (s), 51.5 (q), 53.7 (q), 120.9 (s), 124.3 (s), 125.9 (d), 128.0 (s), 129.3 (s), 130.5 (s), 153.2 (s), 162.4 (s); ir (KBr) 3346, 2962, 1750, 1719, 1665, 1441, 1334, 1215  $\text{cm}^{-1}$ ; uv-vis. (EtOH) 224 (log  $\epsilon$  = 3.92), 304 (4.30) nm; ms (FAB, m/z) 335 (M+1, 13%); Anal. Calcd for  $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_4$ , C 64.65, H 7.84, N 8.38. Found C 64.89, H 8.04, N 8.23.
11. **11** : Yellow needles (mp 275-276°C);  $^1\text{H}$  nmr (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.48 (s, 18H), 1.59 (s, 18H), 3.97 (s, 6H), 7.23 (s, 2H);  $^{13}\text{C}$  nmr (50 MHz,  $\text{CDCl}_3$ )  $\delta$  29.3 (q), 31.2 (q), 32.4 (s), 34.5 (s), 54.3 (q), 122.3 (s), 127.7 (s), 130.0 (d), 131.1 (s), 131.7 (s), 138.0 (s), 144.4 (s), 152.0 (s); ir (KBr) 2964, 2924, 1756, 1698  $\text{cm}^{-1}$ ; ms (FAB, m/z) 605 (M+1, 5%); Anal. Calcd for  $\text{C}_{34}\text{H}_{44}\text{N}_4\text{O}_6$ , C 67.53, H 7.33, N 9.27. Found C 67.51, H 7.39, N 9.12.
12. **16** could not be purified further for preparation of an analytical sample:  $^1\text{H}$ Nmr (200 MHz,  $\text{CDCl}_3$ )  $\delta$  4.11 (s, 3H), 6.39 (t, 1H, J = 3.5 Hz), 7.54-7.60 (m, 2H), 13.22 (br, 1H);  $^{13}\text{C}$  nmr (50 MHz,  $\text{CDCl}_3$ )  $\delta$  56.3 (q), 112.9 (d), 126.7 (s), 129.3 (d), 129.6 (d), 153.1 (s), 154.5 (s); ir (KBr) 3142, 1770, 1727, 1691, 1441, 1354, 1305, 1106, 1065, 1013, 880  $\text{cm}^{-1}$ .
13. B. Cardillo, G. Casnati, A. Pochini, and A. Ricca, *Tetrahedron*, 1967, **23**, 3771.
14. M.J.S. Dewar, E.G. Zoebisch, E.F. Healy, and J.J.P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.