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

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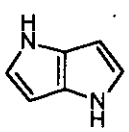
Abstract - The reaction of 3,6-di-*tert*-butyl-1,4-dihydropyrrolo[3,2-*b*]pyrrole and its *N,N'*-dimethoxycarbonyl derivative with chlorosulfonyl isocyanate (CSI) was investigated. The higher reactivity for the electrophilic reaction and a remarkable electron excessiveness of the system were demonstrated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



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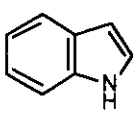

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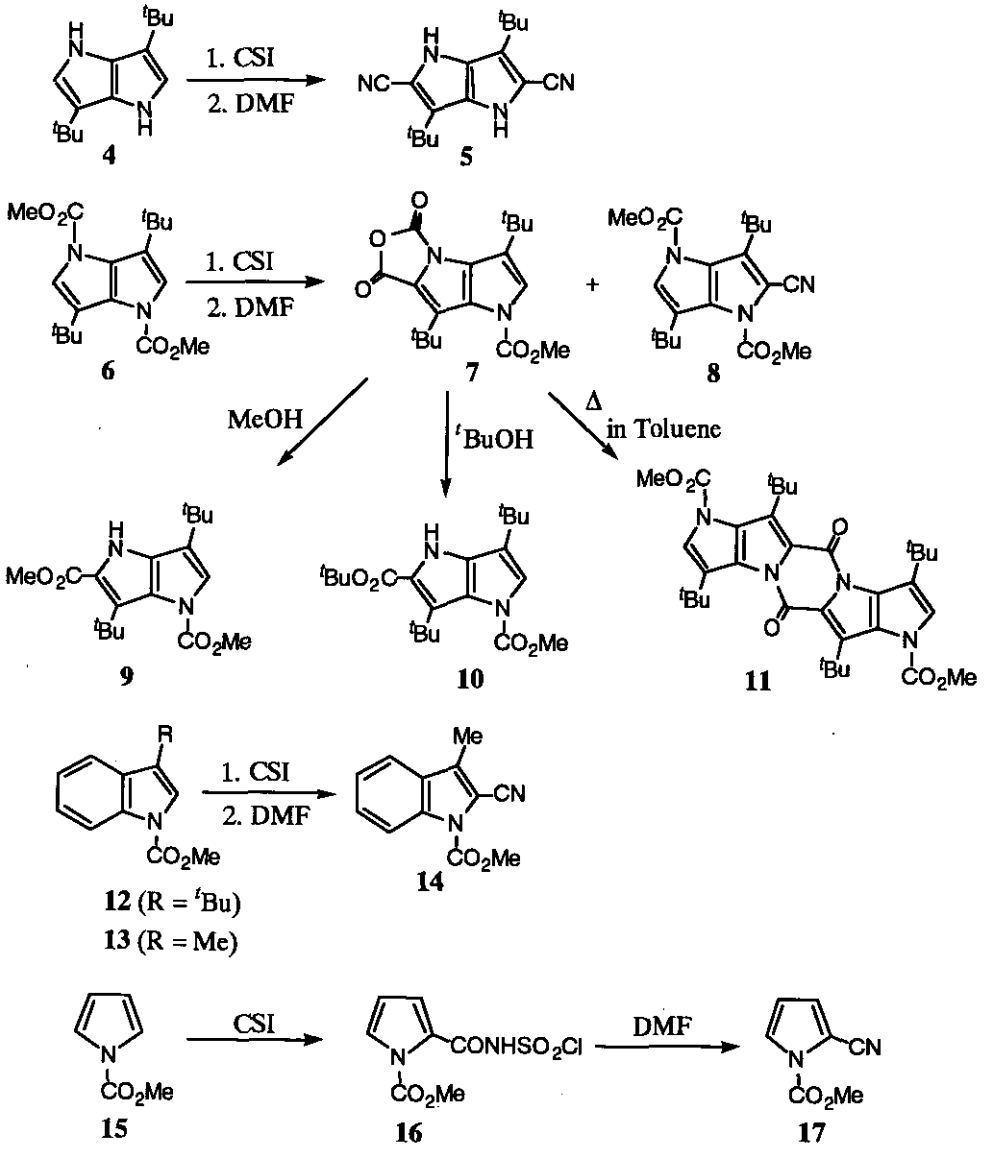
The CSI has been widely used as one of the most reactive isocyanate reagent on the ground of having a strongly electron withdrawing chlorosulfonyl group in the molecule.[5] Generally, an electrophilic addition reaction of CSI with hetero-aromatic compound (*e.g.* pyrrole,[6] indole[7a-c] *etc.*) occurred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



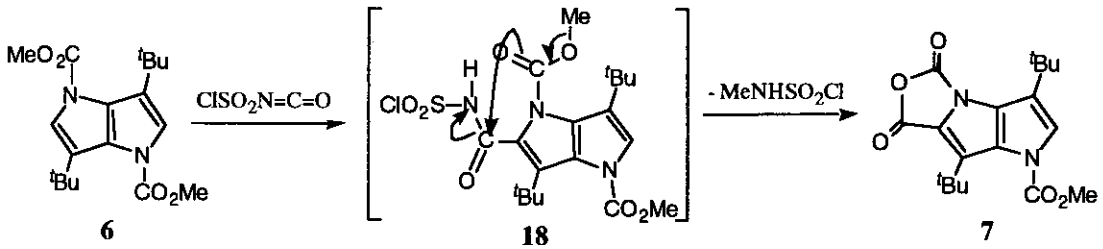
When an equiv. of CSI was added gradually to the dichloromethane solution of **4** at 0°C under dry nitrogen flow, slightly exothermic reaction occurred to give 3,6-di-*tert*-butyl-1,4-dihydropyrrolo[3,2-*b*]pyrrole-2,5-dicarbonitrile (**5**)[8] in 30% yield by a subsequent treatment of the reaction 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**)[9] 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^{-1} 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**)[10] 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-dioxodi-pyrrolo[2',3':4,5]pyrrolo[1,2-*a*,1,2-*d*]piperazine-1,7-dicarboxylate (**11**)[11] 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-disubsti-tuted indoles occurred at 3-position and 1-position to give indole-3-carbonitrile and indole-1-carboxamide derivatives, respectively.[7a] 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.[13] 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-methyl-indole-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**),[7c] 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 $MeNHSO_2Cl$ 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[14] 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.



6 **18** **7**

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8. **5** : Colorless prisms (mp >300°C); ^{1}H nmr (200 MHz, DMSO-d_6) δ 1.30 (s, 18H), 11.43 (s, 2H); ^{13}C nmr (50 MHz, DMSO-d_6) δ 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 cm^{-1}; Anal. Calcd for $C_{16}H_{20}N_4$, 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}H nmr (200 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.57 (s, 9H), 4.01 (s, 3H), 7.35 (s, 1H); ^{13}C nmr (50 MHz, $CDCl_3$) δ 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 cm^{-1}; uv-vis. (EtOH) 256 (log ε = 3.75), 306 (4.34), 344 (4.45) nm; ms (FAB, m/z) 347 (M+1, 93%); Anal. Calcd for $C_{18}H_{22}N_2O_5$, 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}H nmr (200 MHz, $CDCl_3$) δ 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}C nmr (50 MHz, $CDCl_3$) δ 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 cm^{-1}; uv-vis. (EtOH) 224 (log ε = 3.92), 304 (4.30) nm; ms (FAB, m/z) 335 (M+1, 13%); Anal. Calcd for $C_{18}H_{26}N_2O_4$, 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}H nmr (200 MHz, $CDCl_3$) δ 1.48 (s, 18H), 1.59 (s, 18H), 3.97 (s, 6H), 7.23 (s, 2H); ^{13}C nmr (50 MHz, $CDCl_3$) δ 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 cm^{-1}; ms (FAB, m/z) 605 (M+1, 5%); Anal. Calcd for $C_{34}H_{44}N_4O_6$, 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}HNmr (200 MHz, $CDCl_3$) δ 4.11 (s, 3H), 6.39 (t, 1H, J = 3.5 Hz), 7.54-7.60 (m, 2H), 13.22 (br, 1H); ^{13}C nmr (50 MHz, $CDCl_3$) δ 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 cm^{-1}.
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