Synthesis, Structure, Tautomerism, and 1,4-Dipolar Cycloaddition of Thermally Stable, Crystalline 1,4-Dipoles

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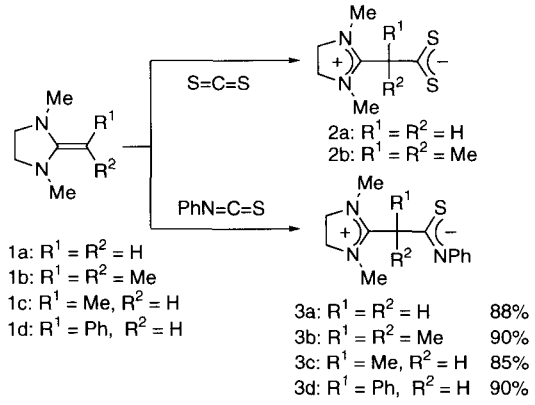
Phenyl isothiocyanate reacted with 2-methylene-1,3-dimethylimidazolidines to give thermally stable, crystalline adducts that possess an inner salt (1,4-dipolar) structure or its tautomeric thioamide structure depending on substituent on the methylene part. Tautomerism between the 1,4-dipolar form and the thioamide form, X-ray diffraction analysis, and 1,4-dipolar cycloaddition with DMAD of these adducts are reported.

Although 1,3-dipolar cycloaddition had gained awareness of many synthetic chemists in the 1960s, seemingly 1,4-dipolar counterpart still has not attained it.[1] In our continuing study on 1,4-dipoles,[2] we have found that carbon disulfide adds to 2-methylene-1,3-dimethylimidazolidines (**1a,b**) to give the thermally stable, crystalline inner salts, 1,3-dimethylimidazolidiniodithioacetates (**2a,b**), which possess a 1,4-dipolar structure where the positive and negative charges are insulated by an sp^3 carbon atom.[3] Here we report that phenyl isothiocyanate adds to imidazolidines **1a-d**[4] to give the thermally stable, crystalline adducts **3a-d** that have a 1,4-dipolar structure or its tautomeric thioamide structure depending on substituent on the methylene part. Chemical properties and X-ray diffraction analysis of these compounds are also reported.



Thus, addition of an equimolar amount of phenyl isothiocyanate to a stirring solution of the imidazolidine **1a**[4] in THF at 0 ° C resulted in the immediate precipitation of the inner salt **3a** as a light yellow solid in 88% yield. In similar ways, **3b**, **3c**, and **3d** were prepared in 90, 85, and 90% yields, respectively.[5,6]

The molecular structure of **3b** is given in Figure 1 along with the relevant bond lengths, bond angles, and torsion angles data.[7] The imidazolidine ring of **3b** is nearly planar as is evident from the torsion angles data. Thus, the carbenium ion center is expected to be fully stabilized by conjugation with the two sp^2-hybridized nitrogen atoms. In harmony with this prediction, the C5-N2 (1.33 Å) and C5-N3 (1.32 Å) bonds are much shorter than the common C(sp^2)–N(sp^3) single bond (1.36 Å).[8] The C1-S bond length (1.71Å) is longer than that (1.67 Å) of **2b**,[3] which is comparable with that of the common C-S double bonds (1.67 Å).[8] Meanwhile, the C1-N1 bond length (1.29 Å) is close to that of the common C-N double bonds (1.28 Å).[8] The non-bonded distance (3.01 Å) of the S-C5 is shorter than the summation of the van der Waals radii of S and C (3.50 Å)[9] because of the existence of coulombic interaction between the negatively charged sulfur atom and the carbenium carbon atom, which reflects an inner salt structure. These data lead to the conclusion that the canonical structure **4b** is the principal contributor of the compound.

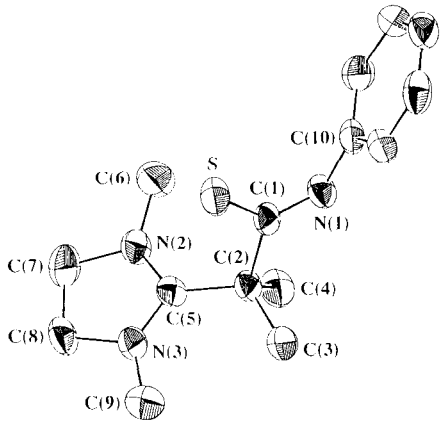
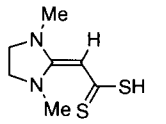


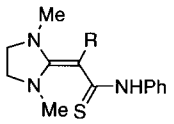
Figure 1. Molecular structure of **4b** by X-ray analysis. Relevant bond lengths (Å), bond angles (°), and torsion angles (°) data (mean values of two molecules). C1-C2 1.556(4), C2-C5 1.524(3), C1-S 1.710(3), C1-N1 1.292(3), C5-N2 1.327(3), C5-N3 1.321(3), C10-N1 1.412(3), C2-C5-N2 121.2(2), C2-C5-N3 127.5(2), C1-C2-C5 109.9(2), C2-C1-S 116.9(2), S-C1-N1 130.0(2), C2-C1-N1 113.1(2), N3-C5-N2-C7 4.8(3), N2-C5-N3-C8 2.7(2), S-C1-C2-C5 38.7(2).

In the case of the inner salt **2a**, no equilibrium between the dithioic acid form **2a'** existed to any appreciable extent detected by ^{1}H NMR, although H/D exchange took place slowly probably via **2a'** by addition of D_2O to its $CDCl_3$ solution.[3] Meanwhile, in the case of **3a**, the 1,4-dipole form **3a** and the thioamide form **3a'** are placed in an equilibrium.[6] Thus, the equilibrium ratios (**3a**:**3a'**) at 27 °C are 1:8, 2:1, 10:1 in $CDCl_3$, CD_3CN, and CD_3OD, respectively, revealing that the more polar form **3a** is more stabilized in polar solvents by solvation. In these solvents, the methylene hydrogens of **3a** is immediately deuterated via **3a'** by addition of D_2O (without addition of D_2O in CD_3OD). The equilibrium goes too far in the case of **3c** and **3d**. Thus, the

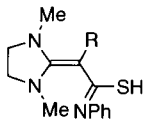
adduct **3c** existed almost exclusively in the 1,4-dipole form **3c** in $CDCl_3$, whereas **3d** almost exclusively existed as the thioamide form **3d'** because of the stabilization due to conjugation between the C=C bond and phenyl group.[6] Incidentally, the presence of another tautomer **3a"** (and also **3d"**) was not detected by ^1H NMR and IR; the SH signal was not observed by these spectroscopies. Methylation of **3b** with MeI took place on the sulfur atom, and not the nitrogen atom, to give the carbenium salt **5b**[5] quantitatively. Reportedly the adduct of the enediamine **1e** with phenyl isothiocyanate exists exclusively as the thioamide form **3e'**.[10]



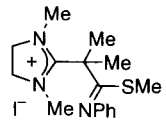
2a'



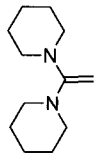
3a': R = H
3c': R = Me
3d': R = Ph



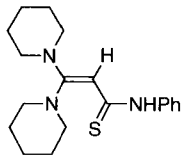
3a"; R = H
3d": R = Ph



5b

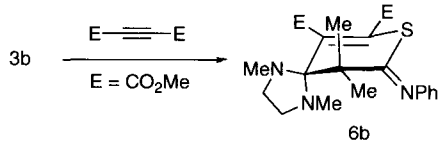


1e



3e'

Noteworthy is that the inner salt **3b** serves as a typical 1,4-dipole, although the inner salt **2b** did not.[3] Thus, **3b** smoothly reacted with dimethyl acetylenedicarboxylate (DMAD) at 0 °C in CH_2Cl_2 to give the thermally unstable, 1,4-dipolar cycloadduct **6b**[5,11] quantitatively.[12] The both ^1H- and ^{13}C-NMR of **6b** showed very broad signals due to the NMe, CMe_2, and CH_2 at 27 °C because of the inversion of the six-membered ring, although they turned to sharp signals at – 20 °C due to fixation to the one conformer.[13]



6b

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References and Notes

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5 Satisfactory elemental analyses were obtained for all new compounds.

6 **3a**: Mp 141-142 °C (dec); yellow crystals; ^1H NMR (400 MHz), in $CDCl_3$, signals due to the 1,4-dipole form **3a**, δ = 3.32 (s, 6H, NMe), 3.87 (s, 4H, ring CH_2), 4.08 (s, 2H, CH_2), signals due to the thioamide form **3a'**, δ = 3.06 (s, 6H, NMe), 3.60 (s, 4H, ring CH_2), 4.93 (s, 1H, vinyl H), 7.42 (broad s, 1H, NH), 7.03-7.30 (phenyl H, **3a** + **3a'**); in CD_3OD, 1,4-dipole form **3a**, δ = 3.21 (s, 6H, NMe), 3.86 (s, 4H, ring CH_2) , 6.87-7.27 (phenyl H); ^{13}C NMR (100.6 MHz), in CD_3OD, 1,4-dipole form **3a**, δ = 34.3, 49.3, 51.0, 123.1, 123.9, 129.5, 153.8, 167.1, 178.5; in $CDCl_3$, thioamide form **3a'**, δ = 37.2, 49.8, 78.5, 122.3, 123.5, 128.9, 140.7, 167.9, 180.6; IR (KBr) 3210 cm^{-1} (NH), ($CHCl_3$) 3394 cm^{-1} (NH). **3b**: Mp 138-139 °C (dec); colorless granules; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.80 (s, 6H, Me), 3.33 (s, 6H, NMe), 3.69 (s, 4H, CH_2), 6.90-6.93 (m, 3H), 7.24-7.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 28.0, 37.1, 51.6, 55.4, 121.4, 121.5, 128.2, 154.0, 173.6, 185.5. **3c**: Mp: 147.5-148.5 °C (dec); colorless crystals; ^1H NMR ($CDCl_3$, 400 MHz), 1,4-dipole form, δ = 1.58 (d, *J* = 7.0 H, 3H, Me), 3.30 (s, 6H, NMe), 3.80 (m, 4H, CH_2), 4.33 (q, *J* = 7.0 Hz, 1H, CH), 6.94-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 14.3, 34.3, 47.4, 50.0, 121.3, 121.4, 128.1, 154.4, 171.0, 177.5. **3d**: Mp 146-148 °C (dec); yellow crystals; ^1H NMR ($CDCl_3$, 400 MHz), thioamide form, δ = 2.96 (broad s, 6H, NMe), 3.73 (broad s, 4H, CH_2), 6.80-7.13 (m, 10H, Ph), 7.17 (broad s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 35.1, 49.1, 91.3, 120.0, 121.3, 123.8, 127.9, 128.1, 128.2, 128.4, 138.5, 141.7, 169.9; IR (KBr) 3152 cm^{-1}, ($CHCl_3$) 3388 cm^{-1} (NH).

7 Crystal data for **3b**: $C_{15}H_{21}N_3S$, *M* = 275.42, triclinic, *P*1, *a* = 7.486(1), *b* = 13.453(2), *c* = 14.732(2) Å, α = 90.004(8), β = 89.993(7), γ = 90.898(7)°, *V* = 1483.5(4) $Å^3$, *Z* = 4, *D* = 1.233 Mg m^{-3}. The structure was solved by a direct method using CRYSTAN. Full matrix least-squares refinement yielded the final R value of 0.046 (R_W = 0.052) for 6275 independent reflections (I>3.00σ(I)) using Mac Science DIP3000 spectrometers. The structure could not be solved as monoclinic.

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11 **6b**: Mp 124-125 °C (dec); ^1H NMR ($CDCl_3$, 400 MHz, 27 °C), δ = 1.44 (broad s, 3H, CMe), 1.53 (broad s, 3H, CMe), 2.52 (broad s, 3H, NMe), 2.71 (broad s, 3H, NMe), 2.90-3.18 (broad m, 4H, CH_2), 3.71 (s, 3H, CO_2Me), 3.77 (s, 3H, CO_2Me), 6.77-7.36 (m, 5H, Ph): at –20 °C, δ = 1.43 (s, 3H), 1.57 (s, 3H), 2.51 (s, 3H), 2.74 (s, 3H), 2.87 (m, 1H), 2.99 (m, 1H), 3.06 (m, 1H), 3.19 (m, 1H), 3.72 (s, 3H), 3.81 (s, 3H), 6.79-7.54 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, –20 °C) δ = 20.1, 24.9, 37.6, 37.7, 51.1, 52.1, 52.3, 53.2, 53.7, 84.9, 118.8, 124.5, 125.6, 129.2, 142.3, 149.2, 162.3, 167.3, 168.8.

12 Reaction of **3a** with DMAD gave a complex mixture from which the 1,4-dipolar cycloadduct could not be isolated.

13 The instability of **6b** in $CDCl_3$ made it impossible to determine the exact coalescence temperature.