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First synthesis of stable 5-alkyl- or 4,5-dialkyl-substituted 1,2-thiazinylium salt

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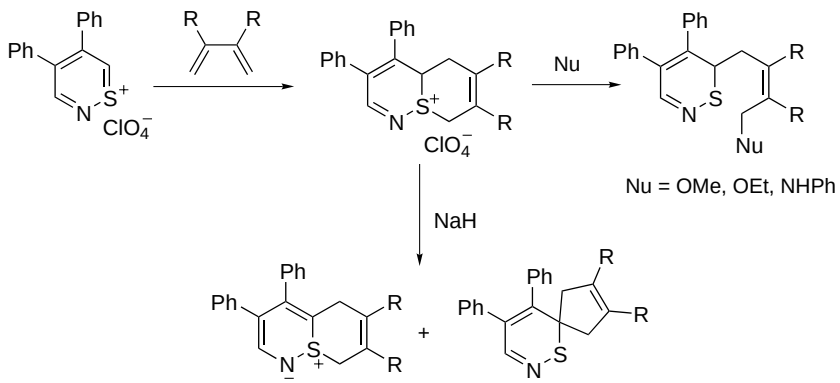
Abstract—5-*t*-Butyl-1,2-thiazinylium **6c** and rigid 5,8-ethano-5,8-dihydrobenzo[*d*]-1,2-thiazinylium salts **17** without conjugated stabilization with the aromatic ring at the 4- or 5-position of the thiazine ring have been successfully obtained as crystals.

Recently, much attention has been paid to hetero Diels–Alder reactions as powerful tools for the construction of heterocyclic compounds.[1] We have reported the unique [2⁺+4]-type polar cycloadditions across the N=S⁺ bond of tricyclic dibenzo[*c*,*e*]-[1,2]thiazinylium salt with 1,3-butadienes.[2] Furthermore, we have also succeeded in the synthesis of monocyclic 4,5-diphenyl-1,2-thiazinylium salt, which provided several 1,2-thiazines having novel biological activities;[3] however, the reactions with 1,3-butadienes underwent the [2⁺+4]cycloaddition across the C=S⁺ bond of the 1,2-thiazinylium salt, not across the N=S⁺ bond, to give 1,6-(2-buteno)-6*H*-1,2-thiazinylium salts, exclusively[4] (Scheme 1). The high regioselectivity of the cycloadditions was explained in terms of LUMO coefficients of the salts obtained from the MOPAC PM3 calculation. These cycloadducts having a sulfonium ion structure have also been reported to be easily converted into other useful 1,2-thiazine derivatives. 4,5-Diphenyl-1,2-thiazinylium salt is very stable and is one of the few examples of monocyclic 1,2-thiazinylium salts synthesized up to now,[5] and it is considered to be stabilized by the resonance interactions with the 4- and/or 5-phenyl group. Our next interest is the synthesis of 5-alkyl- or 4,5-dialkyl-1,2-thiazinylium salts bearing no phenyl substituent on the 1,2-thiazinylium ring to further investigate the substituent effect on the stability and reactivities of 1,2-thiazinylium salts. Here we report the first synthesis of 5-alkyl- or 4,5-dialkyl-1,2-thiazinylium salts.



Scheme 1.

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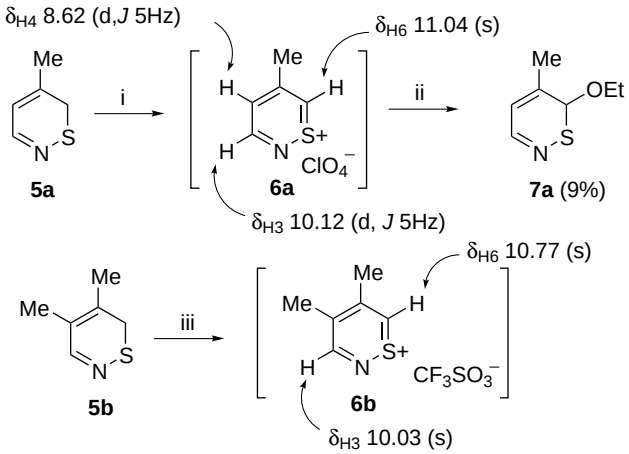
The preparation of 5*H*-1,2-thiazines **5a–c** was achieved as shown in Scheme 2. According to our previous report, 3,6-dihydro-2*H*-1,2-thiazine 1-oxides **4a–c** were obtained in good to high yields from the reactions of *N*-sulfinamide **2** with 1,3-butadienes, followed by reduction with Zn. The Pummerer reactions of **4a–c** with trifluoroacetic anhydride gave only low yields of the desired 5*H*-1,2-thiazines **5a–c**. Therefore, we examined other methods for the conversion of thiazine 1-oxides **4** to the 1,2-thiazines **5**. We found that polyphosphoric acid trimethylsilyl ester (PPSE),[6] which has been usually used for dehydration of alcohols, acts as an effective dehydrating agent. The treatment of **4a–c** with PPSE afforded the 1,2-thiazines **5a–c** in high yields.

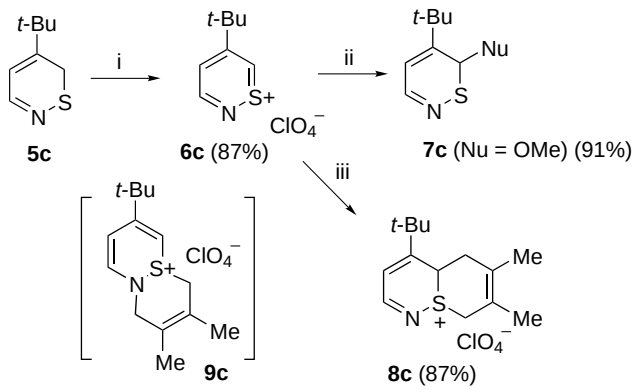
First, we examined the synthesis of 5-methyl-1,2-thiazinylium salt **6a** from **5a** by our original method using SO_2Cl_2/70% $HClO_4$, which was very effective for the preparation of 4,5-diphenyl-1,2-thiazinylium salt; however, the desired **6a** could not be isolated at room temperature because of its high moisture sensitivity. Therefore, we attempted the in situ formation of 1,2-thiazinylium perchlorate **6a**. Treatment of **5a** with SO_2Cl_2 at −30°C and the successive reaction with $HClO_4$ afforded 5-methyl-1,2-thiazinylium perchlorate (**6a**), although it was not a pure salt. The ^{1}H NMR spectrum of the perchlorate **6a** exhibited the characteristic protons of the imine H at δ 10.12 (d, *J* 5 Hz) and the proton α to the sulfur atom at δ 11.04 (s).[7] In order to confirm the formation of **6a**, the in situ formed **6a** at −30°C was treated with NaOEt to give 6-ethoxy-5-methyl-1,2-thiazine (**7a**) in 9% yield[8] (Scheme 3).

Next, we examined the preparation of 4,5-dimethyl-1,2-thiazinylium salt **6b**; however, the attempts provided almost the same result as that of **6a**. The product was a powder, which could not be dissolved in any solvent. These results suggest that 5-methyl- or 4,5-dimethyl-1,2-thiazinylium salts are labile to the moisture and would easily undergo polymerization via the deprotonation of the 4- or 5-methyl group of the 1,2-thiazinylium salts **6a**,**b**. Since 70% $HClO_4$ contains 30% water, we further investigated the in situ formation of **6b** under dry conditions. An addition of SO_2Cl_2 to a CH_2Cl_2 solution of **5b** at −78°C provided a yellow suspension, which was successively treated with anhydrous trifluoromethanesulfonic acid (Scheme 3). The precipitated white powder was immediately collected by filtration and subjected to ^{1}H NMR measurement by which the formation of 4,5-dimethyl-1,2-thiazinylium trifluoromethanesulfonate (**6b**) was observed.[9] The signals of both 3- and 6-H of **6b** appeared at δ 10.03 and 10.77, respectively.

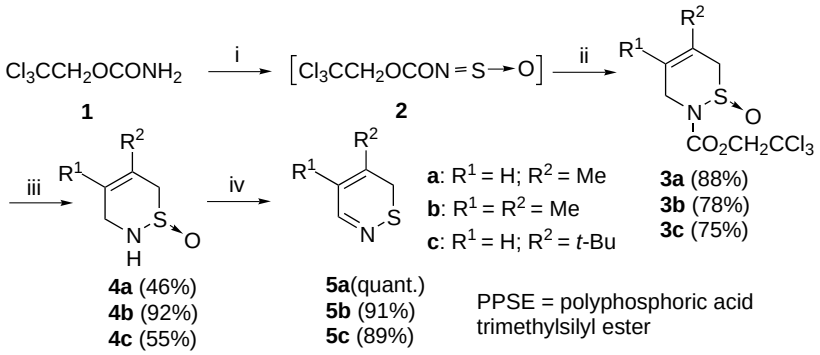
We further investigated the preparation of 5-*t*-butyl-1,2-thiazinylium salt bearing no active hydrogen of the



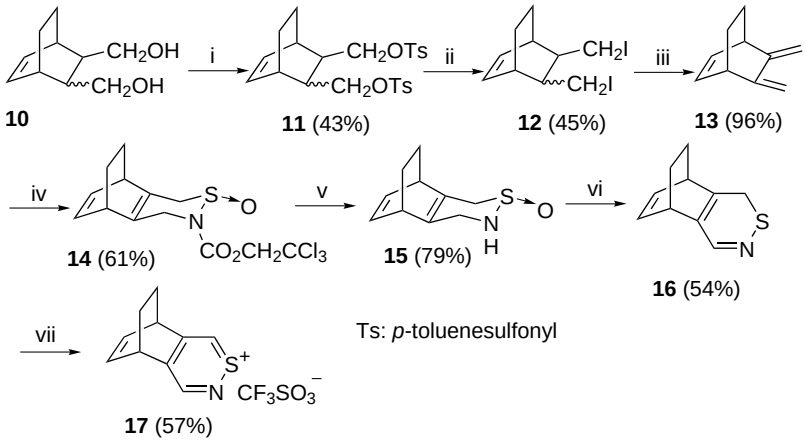
Scheme 3. *Reagents*: (i) SO_2Cl_2/70% $HClO_4$; (ii) NaOEt/EtOH; (iii) SO_2Cl_2/CF_3SO_3H/−30°C.



Scheme 4. *Reagents*: (i) SO_2Cl_2/70% $HClO_4$; (ii) NaOMe/MeOH; (iii) 2,3-dimethyl-1,3-butadiene/MeCN.



Scheme 2. *Reagents*: (i) $SOCl_2$/pyridine/ether; (ii) 1,3-butadiene; (iii) Zn/*t*-BuOH; (iv) PPSE/CH_2Cl_2.



Scheme 5. *Reagents*: (i) TsCl/pyridine; (ii) NaI/acetone; (iii) *t*-BuOK/*t*-BuOH; (iv) $Cl_3CCH_2OCONH_2/SOCl_2$/pyridine/ether; (v) Zn/*t*-BuOH; (vi) PPSE/CH_2Cl_2; (vii) SO_2Cl_2/CF_3SO_3H/0°C.

5-alkyl group (Scheme 4). The general method using SO_2Cl_2/70% $HClO_4$ afforded 1,2-thiazinylium salt **6c** as stable colorless needles.[10] The reactions of **6c** with nucleophiles were studied. The reaction with NaOMe gave 6-methoxy-1,2-thiazine (**7c**)[11] in high yield. We have been interested in the regiochemistry of [2⁺+4]-type polar cycloaddition of 1,2-thiazinylium salts with 1,3-dienes, as described above. In line with this interest, we investigated the cycloaddition of the salt **6c**. Treatment with 2,3-dimethyl-1,3-butadiene provided 5-*t*-butyl-1,6-(2,3-dimethyl-2-buteno)-6*H*-1,2-thiazinium perchlorate (**8c**), not **9c**, showing that the [2⁺+4] polar cycloaddition reaction of the salt **6c** occurred across the C=S⁺ bond, and not across the N=S⁺ bond, of the thiazinylium ring. The structure of **8c** was determined by ^{1}H NMR spectral data, showing the methylene protons β to the sulfur atom at δ 2.32 (dd, *J* 18 and 10 Hz) and 2.50 (dd, *J* 18 and 6 Hz) and a methine proton coupled with those methylene protons at δ 4.42 (dd, *J* 10 and 6 Hz).[12]

Finally, we performed the preparation of 5,8-ethano-5,8-dihydrobenzo[*d*]-1,2-thiazinylium salt which is expected to be resistant to the deprotonation at the 4,5-disubstituted moiety according to the Bredt's rule. 5,6-Dimethylenebicyclo[2.2.2]oct-2-ene **13** was prepared using the usual method, as shown in Scheme 5. The *p*-toluenesulfonylation and subsequent iodination of the diol **10** afforded 5,6-bis(iodomethyl)bicyclo[2.2.2]-oct-2-ene **12** in moderate yields.[13] The diiodide **12** was treated with a large excess of *t*-BuOK in *t*-BuOH under reflux conditions to give **13** in high yield. The general procedure for the preparation of thiazinylium salts with the diene **13** provided the desired 1,2-thiazinylium trifluoromethanesulfonate **17**[14] as a rather stable salt. We are now investigating the chemistry of this unique 4,5-disubstituted 1,2-thiazinylium salt **17**.

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7. Characterization data of **6a**: IR *v* 1090 (ClO_4^-); ^{1}H NMR δ 2.85 (3H, s, Me), 8.62 (1H, d, *J* 5 Hz, 4-H), 10.12 (1H, d, *J* 5 Hz, 3-H), 11.04 (1H, s, 6-H); MS *m*/*z* 111 ($M^+-ClO_4^-$).
8. Characterization data of **7a**: IR *v* 1120 (ether); ^{1}H NMR δ 0.88 (3H, t, *J* 7 Hz, Me), 2.13 (3H, s, Me), 3.28–3.39 (1H, m, CH_2), 3.63–3.70 (1H, m, CH_2), 5.08 (1H, s, 6-H), 6.23 (1H, d, *J* 4 Hz, 4-H), 8.07 (1H, d, *J* 4 Hz, 3-H); MS *m*/*z* 112 (M^+–OEt).
9. Characterization data of **6b**: ^{1}H NMR δ 2.74 (3H, s, Me), 2.82 (3H, s, Me), 10.03 (1H, s, 3-H), 10.77 (1H, s, 6-H).
10. Characterization data of **6c**: colorless prisms, mp 188–191°C, IR *v* 1110 (ClO_4^-), ^{1}H NMR δ 1.48 (9H, s, Me×3), 8.83 (1H, d, *J* 4 Hz, 4-H), 10.18 (1H, d, *J* 4 Hz, 3-H), 11.23 (1H, s, 6-H); ^{13}C NMR δ 29.52 (q×3), 38.81 (s), 137.13 (d), 165.17 (d), 175.97 (d); MS *m*/*z* 154 (M^+-ClO_4). Anal. calcd for $C_8H_{12}ClNO_4S$: C, 37.87; H, 4.77; N, 5.52. Found: C, 37.69; H, 4.72; N, 5.51.
11. Characterization data of **7c**: IR *v* 1060 (ether); ^{1}H NMR δ 1.23 (9H, s, Me×3), 3.27 (3H, s, OMe), 5.07 (1H, s, 6-H), 6.29 (1H, d, *J* 4 Hz, 4-H), 8.22 (1H, d, *J* 4 Hz, 3-H), ^{13}C NMR δ 29.38 (q×3), 35.96 (s), 52.76 (q), 75.98 (d), 115.63 (d), 145.57 (s), 153.61 (d); high-resolution mass calcd for $C_9H_{15}NOS$: 185.0874, found *m*/*z* 185.0877.

12. Characterization data of **8c**: white powder, mp 109–111°C, IR ν 1080 (ClO_4^-); ^{1}H NMR δ 1.28 (9H, s, Me×3), 1.80 (3H, s, Me), 1.87 (3H, s, Me), 2.32 (1H, dd, J 18 and 10 Hz, 7-H), 2.50 (1H, dd, J 18 and 6 Hz, 7-H), 4.02 (1H, d, J 18 Hz, 10-H), 4.42 (1H, dd, J 10 and 6 Hz, 6-H), 4.59 (1H, d, J 18 Hz, 10-H), 6.44 (1H, d, J 4 Hz, 4-H), 8.47 (1H, d, J 4 Hz, 3-H); ^{13}C NMR δ 19.58 (q), 20.91 (q), 28.40 (q×3), 30.72 (t), 35.36 (d), 38.26 (s), 40.00 (t), 117.04 (s), 118.02 (d), 129.40 (s), 163.02 (s), 170.78 (d); MS m/z 236 (M^+–ClO_4). Anal. calcd for $C_{14}H_{22}ClNO_4S1/2H_2O$: C, 48.76; H, 6.72; N, 4.06. Found: C, 48.70; H, 6.65; N, 4.05.
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14. Characterization data of **17**: brown powder, mp 95–98°C (dec.), IR ν 1160 (SO_3); ^{1}H NMR δ 1.49–1.60 (2H, m, CH_2), 1.78–1.92 (2H, m, CH_2), 4.68–4.70 (1H, m, CH), 4.76–4.79 (1H, m, CH), 6.65–6.71 (2H, m, olefinic H), 10.17 (1H, d, J 1 Hz, 4-H), 10.95 (1H, d, J 1 Hz, 1-H); ^{13}C NMR δ 24.27 (d), 24.47 (d), 42.44 (t), 42.71 (t), 134.26 (d), 134.34 (d), 159.25 (s), 159.78 (s), 160.42 (d), 169.74 (d).