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SYNTHESIS OF N-SUBSTITUTED OXAZOLINE-2-THIONE DERIVATIVES: REACTION OF TETRAAZAPENTALENE DERIVATIVES WITH α-HALOKETONES

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Summary: Tetraazapentalene derivatives (1: R=CH_3, CH_2=$CHCH_2$) reacted with various α-haloketones to give N-substituted oxazoline-2-thione derivatives (2, 4, 5, and 6).

The chemistry of π-hypervalent heterocyclic system has been of considerable current interest in relation to 6a-thia(S^{IV})pentalenes.[1] We have reported[2] a convenient one-pot synthesis of symmetrical tetraazapentalene derivatives (1) using the lithium thioureide/phenacyl chloride/alkyl isothiocyanate system. However, the chemical behavior of 1 has little been investigated.[3] In this communication, we report the reactions of 1 with α-haloketones such as dibenzoylbromomethane, 2-bromo-4,4-dimethyl-cyclohexa-1,3-dione, and phenacyl bromide.

A typical procedure for the reaction of 1a with dibenzoylbromomethane is as follows: Dibenzoylbromomethane (105 mg, 0.346 mmol) was added to a solution of 1a (90 mg, 0.346 mmol) in benzene (30 ml) with stirring at room temperature. The mixture was refluxed for 20h. The precipitate was filtered off and recrystallized from methanol, yielding 97 mg (95%) of 6,7-dihydro-2-methyl-5H-1,2,4-thiadiazolo[4,5-a]pyrimidine-3(2H)-thione hydrobromide (3a). The filtrate was concentrated in vacuo. The residue was chromatographed on silica gel with dichloromethane : hexane (4 : 1), and then recrystallized from chloroform-hexane to give a light yellow solid (2a) in 95% yield. 2a: Mp 115-116.5 °C; IR(KBr) 1670, 1630, 1610, and 1330 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ = 3.11 (s, 3H, NCH_3) and 7.10-7.60 (m, 10H, aromatic); MS m/z 295(M^+). Found; C, 68.89; H, 4.23; N, 4.71%. Calcd for $C_{17}H_{13}NO_2S$: C, 69.13; H, 4.44; N, 4.71%. 3a: Mp 254-256 °C(decomp); IR(KBr) 2900, 1630, 1500, 1380, 1370, 1310, 1260, 1215, and 1050 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ = 2.25 (m, 2H, $NCH_2C\underline{H}_2CH_2N$), 3.51 (s, 3H, NCH_3), 3.77 (m, 2H, $NCH_2CH_2C\underline{H}_2N$=C), 4.23 (t, 2H, $NC\underline{H}_2CH_2CH_2N$=C), and 11.29 (br, 1H, N-HBr). Found: C, 27.10; H, 3.75; N, 15.68%. Calcd for $C_6H_{10}N_3S_2Br$: C, 26.87; H, 3.76; N, 15.67%. The structures of products were determined on the basis of the following results. (i) All of the products gave satisfactory their IR, ^{1}H-NMR,[4] and mass spectral data, and their elemental analyses. (ii) Compound 6 was identified by a comparison of melting point with its

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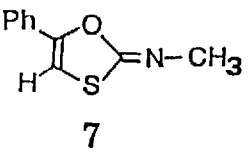
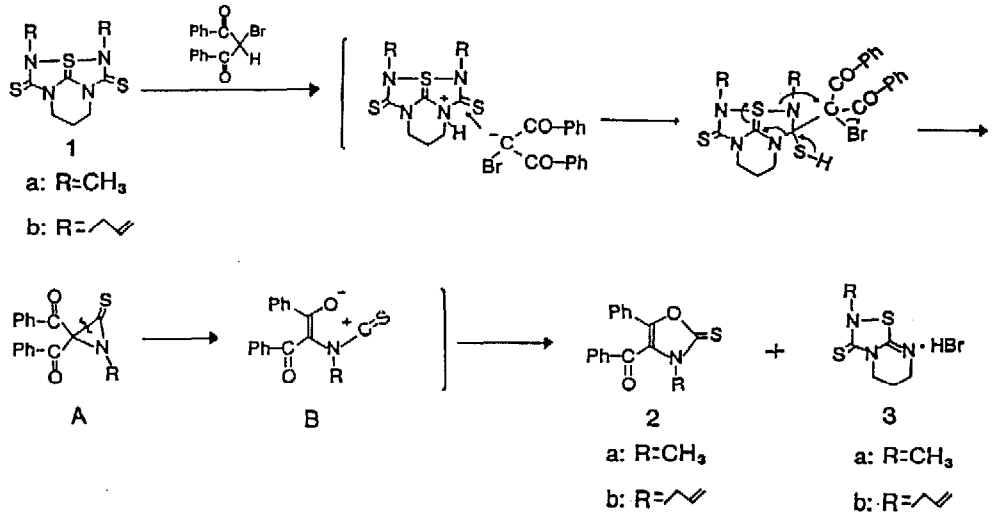
authentic specimen.[5] (iii) In the reaction of 1a with phenacyl bromide, there is the possibility that the isomer 7 can be formed by a nucleophilic attack of thiocarbonyl sulfur atom of 1a toward the sp^3 carbon atom of phenacyl bromide. This compound can be prepared by a separate experiment using the procedure of Kato et al.[6] Comparison of 7 thus prepared with 6 showed that they differ from each other in the spectral data and melting points. 7: Mp 99-102 °C (from n-hexane); IR(KBr) 3040, 1680, 1660, 1495, 1445, 1405, 1285, 1090, 1055, 1010, 885, 755, and 675 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ = 3.05 (s, 3H), 6.41 (s, 1H), and 7.34-7.63 (m, 5H); MS m/z (rel intensity) 191 (M^+, 54), 150 (19), 134 (17), 105 (100), and 77 (36). Found: C, 62.82; H, 4.56; N, 7.17%. Calcd for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32%. A plausible mechanism for the formation of 2 is shown in Scheme 1.



7

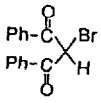
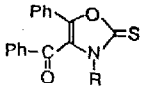
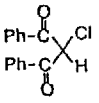
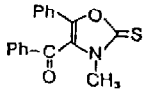
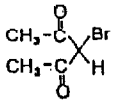
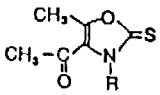
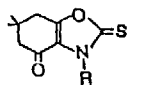
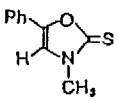
Scheme 1



The reaction is initiated by abstraction of the active methyne proton of α-haloketones by the nitrogen atom at the 4a-position[7] of 1 to give aziridine-2-thione intermediate (A). This intermediate may undergo the heterolytic cleavage[8] of the C-C bond of the aziridine ring to give an active ionic species (B). The subsequent ring closure gives the oxazoline-2-thione derivative 2. Similar treatment of 1 with other α-haloketones also afforded the corresponding oxazoline-2-thione derivatives. The results are given in Table 1. The yields of oxazoline-2-thione derivatives depended on the alkyl groups of the tetraazapentalene derivatives, the acidity of hydrogen on the carbon attached to halogen atom in α-haloketone, and also halogen atom. The compound 2a is not obtained by the reaction using PhCOCHXCOPh (X = Cl, Br)-NaH (or Et_3N)-CH_3NCS system.[9] Accordingly, the formation of 2 is attributable to

the structural characteristics of tetraazapentalene derivatives.

Table 1. Reactions of Tetraazapentalene Derivatives with α-Haloketones[a)]

Tetraazapentalene	α-Haloketone	Product		Time/h	Yield/%[b)]
1a			2a	20	95
1b			2b	20	40
1a			2a	29	3(50)[c)]
1a			4a	4	52
1b			4b	4	47(69)[c)]
1a			5a	45	47(53)[c)]
1b			5b	45	12(49)[c)]
1a			6	45	8(35)[c)]

a) The reaction was carried out under reflux in benzene. 1a (or 1b) : α-haloketone = 1 : 1 (molar ratio).
b) Isolated yields based on 1.
c) 1a (or 1b) : α-haloketone = 1 : 10 (molar ratio).

Related works are further in progress in our laboratory.

References and notes

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2) N. Matsumura, M. Tomura, Y. Tsuchiya, S. Yoneda, and M. Nakamura, Chem. Express, 1, 487 (1986); N. Matsumura, M. Tomura, R. Mando, Y. Tsuchiya, and S. Yoneda, Bull. Chem. Soc. Jpn., 59, 3693 (1986); N. Matsumura, M. Tomura, O. Mori, Y. Tsuchiya, S. Yoneda, and K. Toriumi, Bull. Chem. Soc. Jpn., 61, 2419 (1988).

3) N. Matsumura, M. Tomura, O. Mori, and S. Yoneda, Chem. Lett., 1987, 1065; N. Matsumura, M. Tomura, O. Mori, M. Ukawa, and S. Yoneda, Heterocycles, 1987, 3070; N. Matsumura, O. Mori, M. Tomura, and S. Yoneda, Chem. Lett., 1989, 39.

4) 2b: ^{1}H-NMR($CDCl_3$) δ = 3.85 (m, 2H, $NC\underline{H}_2CH=CH_2$), 5.16-5.38 (m, 2H, $NCH_2CH=C\underline{H}_2$), 5.92-6.07 (m, 1H, $NCH_2C\underline{H}=CH_2$), and 7.10-7.60 (m, 10H, aromatic). 4a: ^{1}H-NMR($CDCl_3$) δ = 2.39 (s, 3H, CH_3-C=C), 2.47 (s, 3H, acetyl), and 3.01 (s, 3H, NCH_3). 4b: ^{1}H-NMR($CDCl_3$) δ = 2.39 (s, 3H, CH_3-C=C), 2.48 (s, 3H, acetyl), 3.76 (m, 2H, $NC\underline{H}_2CH=CH_2$), 5.13-5.32 (m, 2H, $NCH_2CH=C\underline{H}_2$), and 5.86-6.00 (m, 1H, $NCH_2C\underline{H}=CH_2$). 5a: ^{1}H-NMR($CDCl_3$) δ = 1.17 (s, 6H, $C(CH_3)_2$), 2.41 (s, 2H, $C(CH_3)_2$-$C\underline{H}_2$-C=C), 2.60 (s, 2H, $C(CH_3)_2$-$C\underline{H}_2$-C=O), and 3.05 (s, 3H, NCH_3). 5b: ^{1}H-NMR($CDCl_3$) δ = 1.17 (s, 6H, $C(CH_3)_2$), 2.41 (s, 2H, $C(CH_3)_2$-$C\underline{H}_2$-C=C), 2.61 (s, 2H, $C(CH_3)_2$-$C\underline{H}_2$-C=O), 3.67 (m, 2H, $NC\underline{H}_2CH=CH_2$), 5.14-5.32 (m, 2H, $NCH_2CH=C\underline{H}_2$), and 5.86-6.00 (m, 1H, $NCH_2C\underline{H}=CH_2$). 6: ^{1}H-NMR($CDCl_3$) δ = 3.62 (s, 3H, NCH_3), 7.04 (s, 1H, C=CH), and 7.28-7.73 (m, 5H, aromatic).

5) 6: Mp 141-142 °C (lit. 140-141 °C); G. Kjellin and J. Sandstrom, Acta Chem. Scand., 23, 2879 (1969).

6) M. Ishida, K. Sugiura, K. Takagi, H. Hiraoka, and S. Kato, Chem. Lett., 1988, 1705. Procedure for the synthesis of 7 is as follows: To a suspension of 207 mg (2.0 mmol) of sodium imidazole in 25 ml of THF was added a solution of 157 mg (2.1 mmol) of methylisothiocyanate in 5 ml of THF under argon. The mixture was stirred for 20 h at room temperature. The solvent was removed under reduced pressure. To the residual dark yellow solid was added a solution of 202 mg (1.0 mmol) of phenacyl bromide in 25 ml of CH_3CN under argon. After the reaction mixture was stirred for 3 h at room temperature, triethylamine (202 mg, 2.0 mmol) was added, and the reaction mixture was refluxed for 6 h under argon. After the solvent was evaporated, the residue was poured into saturated aqueous NH_4Cl. The mixture was extracted with two 100 ml portions of CH_2Cl_2 and the combined extracts were washed with three 100 ml portions of brine and two 100 ml portions of water, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (silica gel, CH_2Cl_2) to give 7 in 36% yield based on phenacyl bromide.

7) The X-ray crystallographic analysis of 1 (R = CH_3CH_2) indicated that the N(3)-C(4) bond length (1.311 Å) is shorter than the N(4a)-C(4) bond length by 0.106 Å (N. Matsumura, M. Tomura, S. Yoneda, and K. Toriumi, Chem. Lett., 1986, 1047). This fact suggests that the basicity of the nitrogen atom at 3-position is lower than that at 4a-position. Therefore, the abstraction of the active proton is considered to take place at 4a-position of 1.

8) The aziridine ring bearing carbonyl group has been known to undergo the heterolytic cleavage of C-C bond upon thermolysis. I. J. Turchi and M. J. S. Dewar, Chem. Rev., 75, 389 (1975).

9) Typical procedure for the reactions using PhCOCHXCOPh (X = Cl, Br)-NaH (or Et_3N)-CH_3NCS systems is as follows: (a) PhCOCHClCOPh-NaH-CH_3NCS system; To a suspension of 40 mg (1.0 mmol) of sodium hydride in 20 ml of THF was added 200 mg (0.77 mmol) of dibenzoylchloromethane in THF (5 ml) at 0 °C under argon. The mixture was stirred for 15 min at room temperature and a solution of 57 mg of methylisothiocyanate (0.78 mmol) in 5 ml of THF was added. The mixture was stirred for 18 h at room temperature. After usual workup and purification with preparative TLC, compound 2a was not detected. (b) PhCOCHClCOPh-Et_3N-CH_3NCS system; Triethylamine (1.38 g, 13.7 mmol) was added to a solution of dibenzoylchloromethane (708 mg, 2.73 mmol) and methylisothiocyanate (200 mg, 2.73 mmol) in 30 ml of benzene with stirring. The reaction mixture was heated at reflux for 15 h. Usual workup and purification gave recovered dibenzoylchloromethane in 97% yield.

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