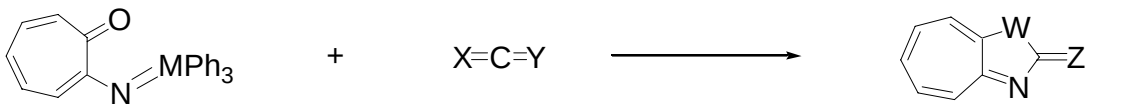
HETEROCYCLES, Vol. 55, No. 11, 2001, pp. 2131 - 2137, Received, 20th August, 2001

CONVENIENT PREPARATION OF HETEROAZULENES BY THE REACTION OF 2-AMINOTROPONE WITH HETEROCUMULENES IN THE PRESENCE OF A BASE

Yuhki Mitsumoto and Makoto Nitta*
Department of Chemistry, School of Science and Engineering, Waseda University, Shinjuku-ku, Tokyo 169-8555, Japan

Abstract-Reactions of 2-aminotropone with heterocumulenes, *N*,*N'*-diphenylcarbodiimide, phenyl isothiocyanate, phenyl isocyanate, and carbon disulfide, in the presence of *t*-BuOK afforded 1-phenylcycloheptaimidazole- 2(1H)-phenylimine, 1-phenylcyclohepataimidazole-2(1*H*)-thione, 1- phenylcyclohepta-imidazol-2(1*H*)-one along with 2*H*-cycloheptaoxazol-2-one, and 2H-cycloheptathiazol-2-one along with 2*H*-cycloheptaoxazole-2-thione in good to moderate yields, respectively.

The utility of (vinylimino)phosphoranes as useful building blocks for the synthesis of azaheterocycles has been demonstrated convincingly.[1-4] In this connection, we have demonstrated that the aza-Wittig reaction of (tropon-2-ylimino)pnictoranes (**1**) (M = P, As, Sb, and Bi) with heterocumulenes (**2a-d**) and the following cyclization reaction are useful for preparation of cyclohepta-annulated five-membered heterocycles (heteroazulenes) (**3a-d**) (Scheme 1).[5,6] Thus, the reactions are available as a new procedure for the preparation of 1-substituted cycloheptaimidazole-2(1*H*)-imines[7] such as **3a** and cycloheptaimidazol-2(1*H*)-ones,[8] which have strong analgesic and antiphlogistic activity, and the former compounds have been synthesized through the thermal reactions of 2-aminotropone (**4**) with substituted carbodiimides, active troponoid with guanidines, and 2-substituted aminotroponimine with substituted carbonimide dihalides.[7] Synthetic procedures of such heteroazulenes have been developed over several decades,[9] and their spectroscopic properties and functionality[10,11] as well as their biological activities have been investigated.[12] However, the reaction of 2-aminotropone (**4**) with heterocumulenes in the presence of a base has not been investigated so far. In the course of our exploration of a simple and convenient synthetic procedure for heteroazulenes, we investigated the reactions of **4** with heterocumulenes, *N*,*N'*-



1
M = P, As, Sb, Bi

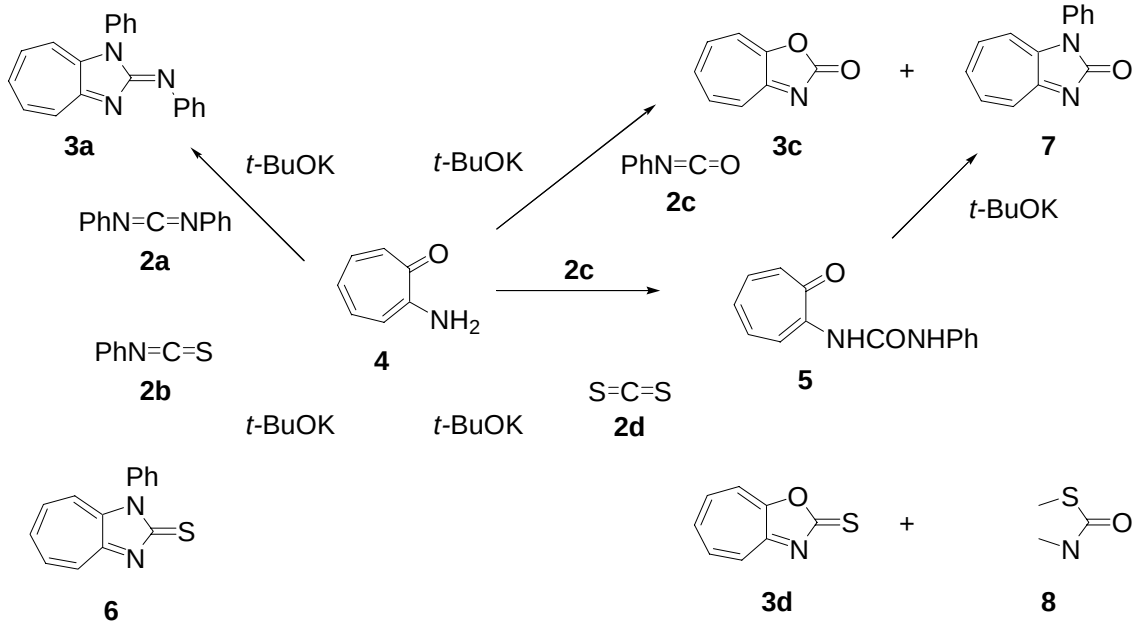
2a: X = Y = NPh
2b: X = S; Y = NPh
2c: X = O; Y = NPh
2d: X = Y = S

3a: W = Z = NPh
3b: W = O; Z = NPh
3c: W = Z = O
3d: W = O; Z = S

Scheme 1.

diphenylcarbodiimide (**2a**), phenyl isothiocyanate (**2b**), penyl isocyanate (**2c**), and carbon disulfide (**2d**), in the presence of *t*-BuOK to afford heteroazulenes in good to moderate yields. We now describe the results in detail.

The reaction of 2-aminotropone (**4**) and *N*,*N*′-diphenylcarbodiimide (**2a**) did not proceed at 0 °C to room temperature. However, the addition of *t*-BuOK in the mixture of **4** and **2a** at 0 °C caused rapid reaction to result in the formation of 1-phenylcycloheptaimidazole-2(1*H*)-phenylimine (**3a**) in good yield (Scheme 2, Table 1, Entry 1). Similarly, the reaction of **4** with phenyl isothiocyante (**2b**) does not proceed at 0 °C to room temperature, while the reaction proceeded quickly in the presence of *t*-BuOK at 0 °C to give 1-phenylcycloheptaimidazole-2(1*H*)-thione (**6**) (Entry 2). Although compound (**4**) reacts with phenyl isocyanate (**2c**) at room temperature to give *N*,*N*′-(tropon-2-yl)phenylurea (**5**) in good yield,[5] the reaction of **4** with **2c** in the presence of *t*-BuOK at 0 °C proceeded very quickly to give 2*H*-cycloheptaoxazol-2-one (**3c**) and 1-phenylcycloheptaimidazol-2(1*H*)-one (**7**) in modest combined yield (Table 1, Entry 3). Independent reaction of isolated urea (**5**)[5] with *t*-BuOK also proceeded rapidly at 0 °C to yield **7** in good yield (Table 1, Entry 4). Thus, the yield of **7** was improved through the reaction as follows. The thermal reaction of **4** with **2c** proceeded in refluxing THF for 4.5 h. Then, the reaction mixture was cooled to 0 °C, treated with *t*-BuOK for 10 min at 0 °C, and the subsequent neutralization of the mixture with aqueous 28% NH_4Cl solution afforded **7** and a trace amount of **3c** in good combined yield (Table 1, Entry 5). It is remarkable that compound (**4**) does not react with carbon disulfide (**2d**) at the temperature ranging from 0 °C to room temperature for 3 h, while the reaction occurred by addition of *t*-BuOK to the mixture at 0 °C to result in the formation of 2*H*-cycloheptaoxazole-2-thione (**3d**) and 2*H*-cycloheptathiazol-2-one (**8**) in a moderate combined yield. In this reaction, complete consumption of 2-aminotropone (**4**) was not accomplished under prolonged reaction time.



Scheme 2.

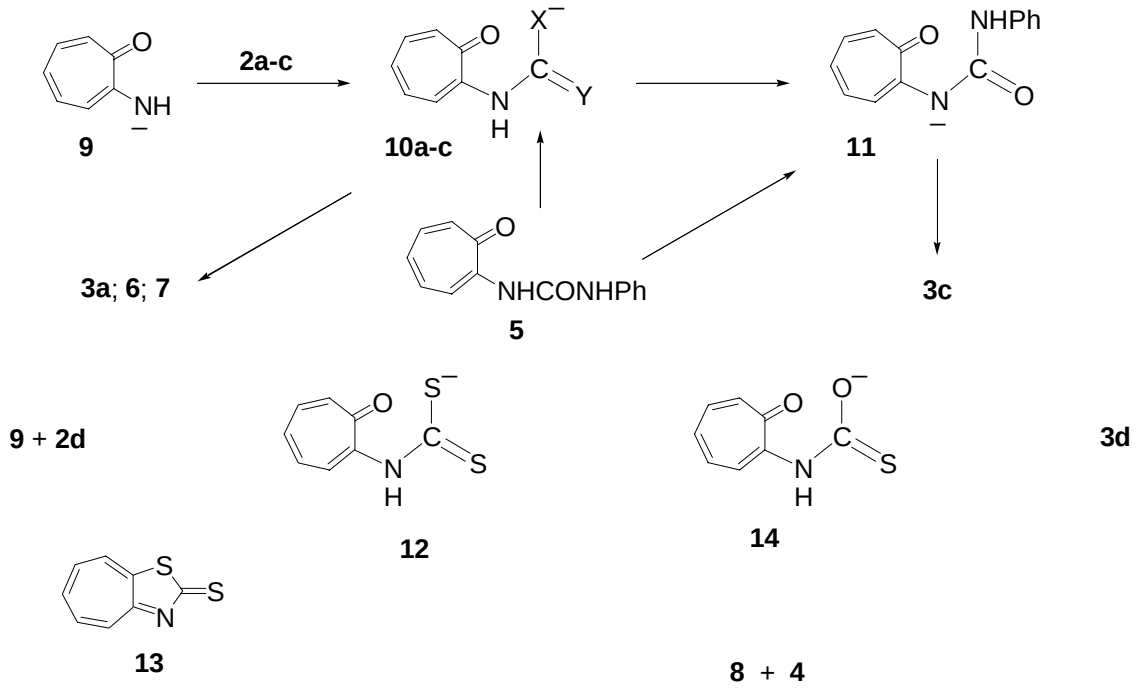
The assignment of the structures of known compounds (**3a,c**)[5,6] and (**7**),[5,13] which have been prepared by the reactions of **2a** with iminopnictoranes (**1**),[5] **4** with ethyl chloroformate,[13] and troponimine with phenyl isocyanate,[14] respectively, are based on a comparison of the physical data with those reported in the literatures. The structure of new compound (**6**) was assigned on the basis of the ^{1}H and ^{13}C NMR spectra, IR spectrum, MS spectral data, and analytical data, as well as a comparison of the physical data with those of the related compounds.[5,6] According to the IR spectrum of **6**, the absorption appearing at 1437 cm^{-1} is consistent with the assigned structure of the thiocarbonyl function.[5] The structure determination of a mixture of known compounds (**3d**)[5] and (**8**)[15] was accomplished by the independent synthesis of **3d**[5] and **8**,[15] which was obtained by the reaction of 2-chlorotropone with thiourea and subsequent hydrolysis.[11] The comparison of the ^{1}H NMR spectral data of independently prepared **3d** and **8** with that of a mixture of **3d** and **8** clearly supported the proposed structures.

Table 1. Reactions of 2-aminotropone (**4**) with heterocumulenes (**2a-d**) and reactions of **5** and **3d**

Entry	Reaction conditions				
	Compound	Cumulene	Temp/°C	Time	Product (Yield/%)[a]
1	**4**	**2a**[b]	0	20 min	**3a** (74)
2	**4**	**2b**	0	1.5 h	**6** (60)
3	**4**	**2c**	0	20 min	**3c** (9) **7** (42)
4	**5**	**----**	0	10 min	**7** (97)
5	**4**	**2c**	42-0	---	**3c** (0.6%) **7** (93)
6[c]	**4**	**2d**	0	2 h	**3d** (1) **4**(34) **8** (48)
7[d]	**4**	**2d**	0	2 h	**3d** (11) **4**(41) **8** (36)
8	**3d**[e]	**----**	rt	6 h	**4** (61) **8** (33)
9	**3d**[f]	**----**	rt	2.h	**4** (36) **8** (12)

a. Isolated yield based on 2-aminotropone (**4**) used. b. Prepared *in situ*. c. Reaction was quenched with aqueous 28% NH_4Cl solution. d. Reaction was quenched with H_2O. e. Reaction was carried out in 1N HCl solution. f. Reaction was carried out in 0.1N NaOH solution.

The pathways for the formation of products are outlined in Scheme 3. In general, the abstraction of the amino-proton of **4** by *t*-BuOK occurs to give anion (**9**), which attacks heterocumulenes (**2a-c**) to give **10a-c**. Then the anionic moieties of **10a-c** undergo cyclization to result in the formation of products (**3a**), (**6**), and (**7**). In the case of the reaction of phenyl isocyanate (**2b**) with **4** in the absence of *t*-BuOK, the urea-intermediate (**5**) is generated at first, then the *t*-BuOK-induced cyclization gives **6**. Since **7** is stable and it does not give **3c** under basic or acidic conditions, the formation of minor product (**3c**) is unclear at this stage. The pathway may be an abstraction of the proton of **5** leading to **11** and subsequent cyclization to afford **3c**. It is noteworthy that the reaction of **4** with **2d** gives a mixture of **3d** and **8** and recovery of **4**. The anion (**9**) reacts with carbon disulfide (**2d**) to give dithiocarbamate (**12**), which



Scheme 3.

probably exists in equilibrium with [**9** and **2d**]. Since the expected heteroazulene (**13**) is not isolated, thus, the formation of **3d** and **8** is not rationalized convincingly. A possible pathway is an exchange reaction of **12** with the hydroxide ion *via* dithiocarbamic acid to give **14**, which undergoes cyclization to result in the formation of 2*H*-cycloheptaoxazole-2-thione (**3d**). Independent reaction of **3d** under acidic or alkaline conditions is clarified to give **8** and 2-aminotropone (**4**) (Table 1, Entries 8 and 9). Furthermore, compound (**8**) is stable under acidic conditions and it does not afford **3d**.[15] Thus, it is clear that primary product (**3d**) in the reaction of **4** with **2d** undergoes rearrangement under the reaction conditions of basic media or under workup conditions of acidic media. Thus, the product composition of the reaction of **4** with **2d** would be rationalized.

In conclusion, the present study demonstrates that the reactions of 2-aminotropone (**4**) with heterocumulenes (**2a-d**) serve as a practical and convenient method for the preparation of heteroazulenes which involve a new heteroazulene (**6**).

EXPERIMENTAL

IR spectra were recorded on a Horiba FT-710 spectrophotometer. UV spectrum was recorded on a Shimadzu UV-3101PC spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL400 spectrometer and the chemical shifts are given relative to internal $SiMe_4$ standard: *J*-values are given in Hz. MS spectra were run on a JEOL JMS-AUTOMASS 150. Mps were measured on Yamato MP-21 apparatus and are uncorrected.

Reaction of 2-aminotropone (4) with *N,N'*-diphenylcarbodiimide (2a). A mixture of **2c** (1.07 g, 9

mmol) and Ph_3AsO (29 mg, 0.1 mmol) in benzene (10 mL) was heated under reflux for 2 h to prepare a solution of **2a** (4.5 mmol).[16] The solution was then cooled to 0 °C. To this solution were added a solution of **4** (368 mg, 3 mmol) in dry CH_2Cl_2 (10 mL) and *t*-BuOK (673 mg, 6 mmol) at rt, and the mixture was stirred for 20 min until **4** is completely consumed (monitored by TLC/SiO_2- AcOEt). The reaction mixture was then neutralized with aqueous 28% NH_4Cl solution and extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by TLC on SiO_2 (AcOEt) to give **3a** (Table 1, Entry 1).

General procedure for the reaction of 2-aminotropone (4) with heterocumulenes (2b,c). To a stirred solution of **4** (368 mg, 3 mmol) and **2** (9 mmol) in dry CH_2Cl_2 (10 mL) was added *t*-BuOK (673 mg, 6 mmol) at rt. After the solution was stirred for the periods as indicated in Table 1, the reaction mixture was neutralized with aqueous 28% NH_4Cl solution, and the mixture was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. After evaporation of the solvent, the residue was purified through TLC on SiO_2 (AcOEt) to give the products. The reaction conditions and the yields of the products are summarized in Table 1 (Entries 2 and 3). For 1-phenylcycloheptaimidazole-2(1*H*)-thione (**6**): orange prisms; mp 177-178 °C (MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (1H, d, *J*=9.8, H-4), 7.37 (2H, d, *J*=6.8, Ph), 7.51 (1H, dd, *J*=9.5, 9.5, H-6), 7.56-7.66 (4H, m, H-5, Ph), 7.89 (1H, dd, *J*=9.5, 10.7, H-7), 8.16 (1H, d, *J*=10.7, H-8); ^{13}C NMR (150 MHz) δ 116.9 (C-4), 128.3 (Ph), 129.9 (Ph), 130.0 (Ph), 130.4 (C-8), 134.1 (C-6), 135.0 (quart), 137.1 (C-5), 139.8 (C-7), 152.6 (quart), 164.1 (quart), 189.1 (quart); IR ($CHCl_3$) 1593, 1498, 1437, 1387, 1365, 1322, 1285 cm^{-1}; UV (log ε) (MeCN) 252 (4.69), 311 (3.51, sh), 445 (4.50) nm; MS (70 eV) (*m/z*) 238 (M^+, 32%), 237 (61), 77 (100). *Anal*. Calcd for $C_{14}H_{10}N_2S$: C; 70.57; H; 4.23, N; 11.76. Found: C; 70.38, H; 4.01, N; 11.53.

Preparation of 1-phenylcycloheptaimidazole-2(1*H*)-one (7) from urea (5) and *t*-BuOK. A solution of **5** (96 mg, 0.4 mmol) and *t*-BuOK (90 mg, 0.8 mmol) in CH_2Cl_2 (5 mL) was stirred for 5 min at 0 °C. The reaction mixture was then neutralized with aqueous 28% NH_4Cl and extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography on SiO_2 using AcOEt as the eluent to give the product (**7**) (Table 2, Entry 4).

Preparation of 1-phenylcycloheptaimidazole-2(1*H*)-one (3b) from urea (5) and *t*-BuOK. A solution of **4** (121 mg, 1 mmol) and **2c** (357 mg, 3 mmol) in dry THF (1 mL) was heated under reflux for 4.5 h until the starting material (**4**) was consumed completely. To this mixture was added dry THF (4 mL) and the mixture was cooled to 0 °C. To this mixture was added *t*-BuOK (224 mg, 2.0 mmol), and the mixture was stirred for 10 min. After the usual workup described above, and the subsequent purification by TLC on SiO_2 (AcOEt) afforded **3b** and **7** as summarized in Table 1 (Entry 5).

Reaction of 2-aminotropone (4) with carbon disulfide (2d). To a stirred mixture of **4** (363 mg, 3 mmol), carbon disulfide (5 mL), and CH_2Cl_2 (10 mL) was added *t*-BuOK (673 mg, 6 mmol), and the mixture was stirred for 2 h at 0 °C. The reaction mixture was neutralised with aqueous 28% NH_4Cl or

quenched with H_2O, extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. After evaporation of the solvent, the residue was purified through TLC on SiO_2 (AcOEt) to give a mixture of **3d** and **8** along with **4**. The results are summarized in Table 1 (Entries 6 and 7).

Isomerization of 2*H*-cycloheptaoxazol-2-thione (3d) in acidic media. A solution of **3d** (49 mg, 0.3 mmol) in 1N HCl (H_2O/EtOH-1/1, 7 mL) was stirred for 6 h at rt. After evaporation of EtOH, the mixture was neutralized with aqueous 9% $NaHCO_3$ solution and extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. Afater evaporation of the solvent, the resulting residue was separated by TLC on SiO_2 (AcOEt) to give **4** and **8** (Table 2, Entry 8).

Isomerization of oxazol-2-thione (3d) in alkaline media. A solution of **3d** (49 mg, 0.3 mmol) in 0.1 N NaOH (H_2O/EtOH-1/1, 4 mL) was stirred for 2 h at rt. The mixture was neutralized with aqueous 28% NH_4Cl and extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. Afater evaporation of the solvent, the resulting residue was separated by TLC on SiO_2 (AcOEt) to give **4** and **8** (Table 2, Entry 9).

ACKNOWLEDGMENT

The authors thank Materials Characterization Central Laboratory, Waseda University, for technical assistance with spectral data and elemental analyses.

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