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Condensation Reactions of Halogenated 2,4-, 2,5-, and 2,6-Dimethoxytropones with Guanidine

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Abstract: The condensation of halogenated 2,4-, 2,5-, and 2,6-dimethoxytropones with guanidine afforded the 2-amino-5-methoxy-1,3-diazazulenes. This can be explained in terms of the electronic control of nucleophilic attacking site by remote methoxyl group. This was also the case for the products, 4-bromo-6-hydroxy-7-methoxy-1,3-diazazulenes, in the reactions of 2,4,7-tribromo-5-methoxytropone with acetoamidine and with benzamidine.

Previously, we have reported the condensation reaction of 2,4-dichloro-5-methoxytropone with active methylene derivatives[1] and with amidine derivatives[2]. From the latter, we have synthesized 1*H*-cyclohepta-[1,2-*d*; 3,4-*d'*]- and 1*H*-cyclohepta[1,2-*d*; 4,5-*d'*]diimidazole derivatives[3], which possess the basic skeletons found in the fluorescent metabolites of marine organisms, paragracines[4] and zoanthoxanthins[5]. We thought the reaction should be extended to the tetrasubstituted tropones. Indeed, the reaction with 2,4-dichloro-5,7-dimethoxytropone (**1**), 3,5-dichloro-2,6-dimethoxytropone (**2**) and 2,5-dibromo-4,7-dimethoxytropone (**3**) with guanidine (**4**) occurred, in low yields though, disclosing a clear mesomeric effect from the remote methoxyl group which controlled the course of the reaction. Previously, such a reaction of polysubstituted tropones was not investigated due to a difficulty in obtaining materials. The results will be herein described.

As a 2,4-dimethoxyl derivative, **1** was condensed with **4** in the presence of sodium hydride. The sole product identified was 2-amino-4,6-dichloro-7-methoxy-1,3-diazazulene (**5**) in 25% yield. In this case, there are two possible ways of condensation, i. e., the 1,7-condensation and the 1,2-condensation, previous studies favored the 1,7-mode since the C-7 position of **1** was occupied by methoxyl group which is known to cause the normal substitution, while the C-2 position was occupied by chlorine which is a typical substituent to proceed in the cine mode[6]. The structure of **5** was clear in view of the ^{1}H NMR spectrum; the methoxyl signal disclosed an allylic coupling with the proton on the seven-membered ring whose chemical shift $\delta = 8.97$ was ascribable to the proton on the peri-position, C-8.

Similar treatment of **2** with **4** again gave **5** in 47% yield. Due to the base-sensitive 3-chloro-2-methoxytropone function in **2**, the reaction tends to accompany a benzenoid derivative; in case of the added base was potassium hydroxide, the sole product identified was 2,4-dichloro-5-methoxybenzoic acid (**6**).

In the case of **3**, again, 2-amino-6-bromo-4,7-dimethoxy-1,3-diazazulene (**7**), in 20% yield, was the sole product in the presence of potassium hydroxide, but the same reaction with sodium hydride gave, in addition to **7** in 21% yield, accompanied product, 4,7-dibromo-6-methoxy-1,3-diazazulene (**8**) in 8% yield. Particularly, the formation of **7** is interesting, since it is produced by the 1,2-mode with the tropone whose C-2 was occupied by *cine*-preferred bromine.

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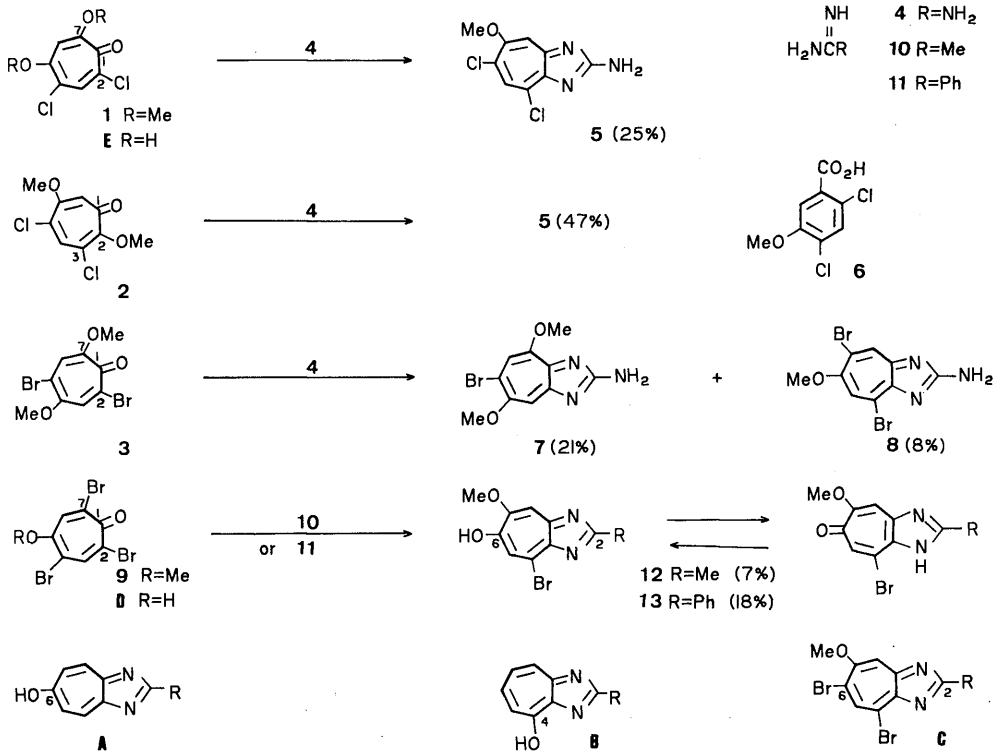
This can be explained as that the mesomeric effect of the remote methoxyl group determined the course of the reaction. The first step of the condensation must be the C-1 attack of the nucleophile. For the second step, intramolecular cyclization, nucleophilic attack by guanidine residue at the conjugate terminal to the electron-releasing methoxyl group should be unfavorable.



In this sense, a 2,7-dihalotropone having two different substituents at C-4 and C-5 positions would be worthy of studying. Such a derivative easily prepared was 2,4,7-tribromo-5-methoxytropone (**9**)[7,8]. Although attempted reactions of **9** with **4** were unsuccessful, the reactions of **9** with acetoamidine **(10)** and benzamidine **(11)** gave the single condensates (**12** and **13**) in 7% and 18% yield, respectively. The structures of **12** and **13** were clarified as 2-methyl and 2-phenyl derivatives of 4-bromo-6-hydroxy-7-methoxy-1,3-diazazulene or tautomeric 8-bromo-5-methoxy-6*H*-cyclohepta[*c*]imidazol-6-one by the comparison with the IR and UV spectral data[9] of 6-hydroxy-1,3-diazazulene (**A**) and the 4-hydroxy-1,3-diazazulene (**B**). Evidently, the formation of **12** and **13** involved an undesired hydrolysis step on the reactive 6-bromine in the proto-condensate (**C**). No other compound was detectable at all.

Previously, a matter of *cine*-substitution was principally understood by difference of 2-substituents[6,10]; methoxyl and dimethylamino groups are known to proceed in the normal mode, but halogens, tosyloxy, mesyloxy, and trialkylammonium groups are cine mode. As a secondary factor, a steric effect from 4- or 6-position[11] is pointed out to alter the course of the reaction. Moreover, solvent effect plays a decisive role to select a mode of the reaction[12]. However, no example like a present study which reveals electromeric effect from the distant substituent has been known.

In conclusion, the present results pointed out that since the *cine*-mode of nucleophilic substitutions in the

troponoid chemistry is a fundamental procedure, and currently an importance of troponoids in synthetic aspects is widely recognized[13], one should pay an attention for electronic effect of remote substituent in the synthetic designs.

Experimental

The elemental analyses were carried out by Miss S. Hirashima, of the Research Institute of Industrial Science, Kyushu University. The NMR spectra were measured by a JEOL FX 100 Spectrometer in $CDCl_3$ solution, unless otherwise specified, and the chemical shifts expressed were in δ units. The mass spectra were measured by a JEOL 01SG-2 Spectrometer. The IR spectra were taken as KBr disks using Jasco IR-A 102 Spectrometer. The UV spectra were measured by Hitachi Spectrophotometer.

Preparation of D. To a hot AcOH solution (8 cm^3) of 2-chloro-5-hydroxytropone[8] (314 mg), an AcOH solution (18 cm^3) of Br_2 (634 mg) was added with stirring and refluxed for 5 h. After cooling the mixture, the separated solid was collected by filtration to give yellow crystalline 2,4,7-tribromo-5-hydroxytropone **(D)**, mp 214.5—218°C (lit.[7] mp 240°C (decomp)), 490 mg (68%) [^{1}H NMR $\delta(CD_3OD)$=8.25 (1H, s) and 8.64 (1H, s)]. This **D** (1.46 g) was dissolved in AcOH (19 cm^3) containing conc HCl (19 cm^3), and heated at 140°C in a sealed tube. After 10 h, the mixture was cooled and deposited solid was collected by filtration to give 3,5-dichloro-6-hydroxytropolone (**E**), pale yellow crystals, mp 173—175°C, 766 mg (91%) [Found : C, 40.27 ; H, 2.28% ; M. W., 205.9520, 207.9503, 209.9480.. Calcd for $C_7H_4O_3Cl_2$: C, 40.61 ; H, 1.95% ; 205.9535, 207.9505, 209.9481. ^{1}H NMR $\delta(CD_3OD)$=7.20 (1H, s) and 8.11 (1H, s). IR ν : 3000, 1570, 1400, 1340, and 1195 cm^{-1}. UV λ_{max}^{MeOH} : 244 nm (ε=20000), 339 (5600), 377 (6400), and 388 (5900)].

Preparation of 1 and 2. An acetone solution (400 cm^3) of **E** (1.5 g) was treated with ethereal CH_2N_2 at 0—5°C. Then the solvent was evaporated in vacuo, and the residue was chromatographed on a silica-gel column to afford **1**, mp 170—171°C, 189 mg (11%) [Found : M. W., 233.9860, 235.9834, 237.9778. Calcd for $C_9H_8O_3Cl_2$: 233.9850, 235.9821, 237.9789. ^{1}H NMR δ = 4.02 (3H, s), 4.06 (3H, s), 6.75 (1H, s), and 8.05 (1H, s). ^{13}C NMR δ = 56.8, 57.9, 103.5, 118.0, 135.4, 137.8, 157.7, 162.2, and 170.7. IR ν : 1580 and 1450 cm^{-1}. UV $\lambda_{max}^{CHCl_3}$: 257 nm (ε = 18000), 346 (5800, sh), 370 (6500), and 388 (4500)], and **2**, pale yellow crystals, mp 155—156°C, 97 mg (6%) [Found : C, 45.59 ; H, 3.43%. Calcd for $C_9H_8O_3Cl_2$: C, 45.99 ; H, 3.54%. ^{1}H NMR δ = 3.87 (3H, s), 4.00 (3H, s), 6.56 (1H, s), and 7.47 (1H, s). ^{13}C NMR δ = 56.8, 59.6, 114.9, 130.5, 130.9, 132.9, 159.0, 160.0, and 176.9. UV $\lambda_{max}^{CHCl_3}$: 260 nm (ε = 13000) and 325 (2300)].

Preparation of 3. To an acetone solution (500 cm^3) of 3,6-dibromo-5-hydroxytropolone[14] (1.5 g), ethereal CH_2N_2 was added under ice-cooling. The mixture was then evacuated to remove the solvent, and the residue was purified on a silica-gel column chromatography to give **3**, pale yellow crystals, mp 140—142°C, 344 mg (21%) [Found : M. W., 321.8842, 323.8822, 325.8801. Calcd for $C_9H_8O_3Br_2$: 321.8842, 323.8822, 325.8801. ^{1}H NMR δ = 3.17 (6H, s), 7.17 (1H, s), and 8.09 (1H, s). ^{13}C NMR δ = 56.9, 59.2, 118.1, 118.6, 130.4, 137.0, 152.2, 155.4, and 171.8. IR ν : 1580 and 1460 cm^{-1}].

Condensation of 1 with 4. An anhydrous DMF solution (8 cm^3) of **1** (50 mg) was added dropwise to a DMF solution (7 cm^3) of hydrochloride of **4** (44.8 mg) and 50% NaH (108 mg) in an ice bath under N_2 atmosphere. After continued stirring for 12 h, the mixture was then evaporated in vacuo, and the residue was purified with preparative thin-layer chromatography (PTLC ; $CHCl_3$: MeOH : conc NH_4OH = 20 : 1.5 : 1) to give pale yellow needles, mp 219—221°C (decomp), **5**, 13.1 mg (25%) [Found : M. W., 242.9950, 244.9943. Calcd for $C_9H_7ON_3Cl_2$: 242.9965, 244.9937. ^{1}H NMR $\delta(CF_3COOD)$ = 4.47 (3H, s), 8.48 (1H, s), and 8.97 (1H, s). ^{13}C NMR δ = 61.6, 112.9, 134.7, 143.7, 145.4, 145.7, 149.3, 157.5, and 171.7. IR ν : 1390 and 1200 cm^{-1}].

Condensation of 2 with 4. An anhydrous DMF solution (8 cm^3) of **2** (92 mg) was added dropwise to a DMF solution (7 cm^3) of hydrochloride of **4** (89.4 mg) and 50% NaH (48 mg) in an ice bath under N_2

atmosphere. After stirring for 3 h at 0—5°C, the solvent was removed by evaporation. The residue was purified on PTLC ($CHCl_3$: MeOH : conc NH_4OH = 80 : 20 : 1) to give **5**, 44.8 mg (47%), which was identical with the sample obtained from **1** and **4**.

Attempted Reaction of 2 and 4 in the Presence of Potassium Hydroxide. An anhydrous EtOH (20 cm^3) of **2** (90 mg), hydrochloride of **4** (73.2 mg) and excess of KOH was refluxed with stirring under N_2 atmosphere. After 10 min, the mixture was evaporated in vacuo to remove the solvent, and purified on PTLC ($CHCl_3$: MeOH : conc NH_4OH = 80 : 20 : 1) to give colorless crystals, mp 207—210°C (lit.[15] mp 190°C), **6**, 25 mg (29%).

Condensation of 3 with 4. **a)** An anhydrous EtOH solution (20 cm^3) of **3** (90 mg) and hydrochloride of **4** (53 mg) and excess KOH was refluxed for for 30 min under N_2 atmosphere. The solvent was evaporated in vacuo, and the residue was purified on PTLC ($CHCl_3$: MeOH : conc NH_4OH = 80 : 20 : 1) to give pale yellow crystals, mp 200—201°C, 15.7 mg (20%), **7** [Found : M. W., 282.9950, 284.9929. Calcd for $C_{10}H_{10}O_2N_3Br$: 282.9938, 284.9934. ^1H NMR δ(CF_3COOD) = 4.37 (3H, s), 4.50 (3H, s), 8.26 (1H, s), and 9.00 (1H, s). ^{13}C NMR δ(CF_3COOD) = 61.1 (2C), 110.2, 132.4, 134.0, 142.9, 145.3, 154.5, 157.5, and 168.6. IR ν : 1450, 1430, and 1200 cm^{-1}. UV λ_{max}^{MeOH} : 258 nm (ε = 16000, sh), 273 (18000), 295 (6800, sh), 360 (7100), and 426 (7400)].

b) An anhydrous DMF solution (8 cm^3) of **3** (50 mg) was added to a DMF solution (7 cm^3) of hydrochloride of **4** (32.5 mg), and 50% NaH (8.2 mg) under ice-cooling. The mixture was then purified on PTLC ($CHCl_3$: MeOH : conc NH_4OH = 85 : 15 : 1) to give **7**, 21%, and pale yellow needles, **8**, 4 mg (8%) [Found : m/z, 331, 333, 335 (M^+). 316.8808, 318.8809, 320.8786. Calcd for $C_7H_5ON_3Br_2$: 316.8801, 318.8781, 320.8764 (M^+-15). ^1H NMR δ(CF_3COOD) = 4.48 (3H, s), 8.50 (1H, s), and 9.42 (1H, s). IR ν : 1490 and 1360 cm^{-1}].

Condensation of 9 with 10. An anhydrous DMF solution (30 cm^3) of **9** (150 mg), hydrochloride of **10** (232 mg), and excess of KOH was refluxed for 17 h with stirring under N_2 atmosphere. The solvent was removed in vacuo, and the resultant residue was purified on a silica-gel column to give pale yellow needles, **12**, mp 258—259°C, 7 mg (7%) [Found : M. W., 267.9828, 269.9832. Calcd for $C_{10}H_9O_2N_2Br$: 267.9845, 269.9832. ^1H NMR δ(CD_3OD) = 2.40 (3H, s), 3.98 (3H, s), 7.07 (1H, s), and 8.25 (1H, s). IR ν : 1680 and 1595 cm^{-1}. UV λ_{max}^{MeOH} : 205 nm (ε = 8300), 240 (42000), 272 (5500, sh), 281 (5300, sh), 303 (2900), and 316 (2600)].

Condensation of 9 with 11. An anhydrous DMF (15 cm^3) of **9** (90 mg), the hydrochloride of **11** (45 mg) and 50% NaH (18 mg) was stirred for 3 h in an ice bath. The solvent was then evaporated in vacuo, and the residue was purified on PTLC ($CHCl_3$: AcOEt = 2 : 1) to give **13**, pale yellow crystals, mp 295—296°C (decomp), 14.5 mg (18%) [Found : M. W., 330.0023, 331.9996. Calcd for $C_{15}H_{11}O_2N_2Br$: 330.0005, 331.9985. ^1H NMR δ = 4.06 (3H, s), 7.95 (5H, m), 8.04 (1H, s), and 8.43 (1H, s). IR ν : 1670 and 1600 cm^{-1}. UV $\lambda_{max}^{CHCl_3}$: 253 nm (ε = 14000) and 308 (6200)].

References

1) H. Takeshita, A. Mori, and T. Minami, *Bull. Chem. Soc. Jpn.*, **57**, 621 (1984).
2) H. Takeshita, A. Mori, T. Minami, and H. Kondo, *Heterocycles*, **14**, 793 (1980).
3) M. Yasunami, Y. Sasagawa, and K. Takase, *Chem. Lett.*, **1980**, 205.
4) Y. Komoda, S. Kaneko, M. Yamamoto, M. Ishikawa, A. Itai, and Y. Iitaka, *Chem. Pharm. Bull.*, **23**, 2464 (1975).
5) L. Cariello, S. Crescenzi, G. Prota, F. Giordano, and L. Mazzarella, *J. Chem. Soc., Chem. Commun.*, **1973**, 99.
6) T. Nozoe, S. Seto, and T. Sato, *Proc. Jpn. Acad.*, **30**, 473 (1954) ; R. D. Haworth and P. B. Tenker, *J. Chem. Soc.*, **1955**, 911.
7) T. Nozoe, Y. Kitahara, and H. Abe, *Proc. Jpn. Acad.*, **29**, 347 (1953) ; R. S. Coffey and A. W. Johnson, *J. Chem. Soc.*, **1958**, 1741.
8) T. Nozoe and Y. Kitahara, *Proc. Jpn. Acad.*, **29**, 347 (1953). They recorded mp 174°C, however, we obtained mp 212°C (decomp). Here, we record its ^1H NMR ; δ = 4.02 (3H, s), 8.07 (1H, s), and 8.57 (1H, s).
9) T. Nozoe, T. Mukai, and T. Asao, *Bull. Chem. Soc. Jpn.*, **35**, 1188 (1962) ; J. Nakazawa, Y. Saito, and N. Soma,

Ann. Sankyo Res. Lab., **21**, 47 (1969).

10) T. Nozoe, S. Seto, K. Takase, S. Matsumura, and T. Nakazawa, *Nippon Kagaku Kaishi,* **86**, 346 (1965).

11) T. Nozoe, S. Seto, S. Matsumura, and T. Asao, *Proc. Jpn. Acad.*, **32**, 339 (1956); T. Nozoe, S. Seto, and S. Nozoe, ibid., **32**, 472 (1956).

12) T. Nozoe, H. Takeshita, and K. Tajiri, *Bull. Chem. Soc. Jpn.*, **56**, 3679 (1983).

13) H. Takeshita, A. Mori, and Y. Shimada, *Kyushu Daigaku Sogo Rikogaku Kenkyuka Hokoku*, (1986) in press; T. Uyehara, T. Furuta, Y. Kabasawa, and T. Kato, *J. Chem. Soc., Chem. Commun.*, **1986**, 539; J. H. Rigby, J-A. Z. Wilson, and C. Senanayake, *Tetrahedron Lett.*, **27**, 3329 (1986); J. H. Rigby, T. L. Moore, and S. Rege, *J. Org. Chem.*, **51**, 2398 (1986); R. L. Funk and G. L. Bolton, *J. Am. Chem. Soc.*, **108**, 4655 (1986); M. Ando, K. Wada, H. Kusaka, N. Kataoka, M. Yasunami, and K. Takase, Abstract Papers of 29th Simposium of Terpenes, Essential Oils, and Aromatic Compounds, Tsu, 1985, p 310.

14) H. Takeshita, T. Kusaba, and A. Mori, *Bull. Chem. Soc. Jpn.*, **55**, 1659 (1982).

15) S. R. Patel, K. C. Kshatrieya, and K. S. Nargund, *J. Univ. Bombay,* **17A**, Pt. 3, 13 (1948) (C. A. **43**, 6633c).