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AN ANION-PROMOTED REARRANGEMENT OF 2-(o- AND p-NITROBENZYLOXY)TROPONES TO α-HYDROXYLATED 2-(o- AND p-NITROBENZYL)TROPONES. A READY INTRODUCTION OF ARALKYL GROUP INTO THE TROPONOID NUCLEUS

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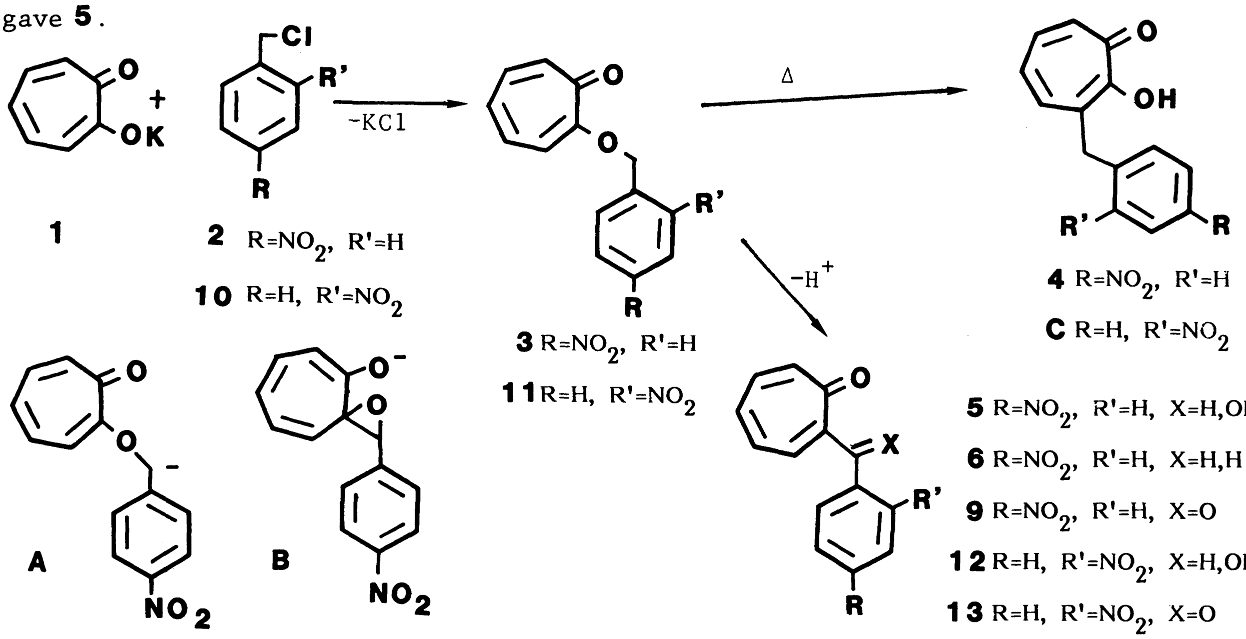
During the preparation of 2-(o- and p-nitrobenzyloxy)tropones from o- and p-nitrobenzyl chlorides and potassium tropolonate, a concomittant formation of α-hydroxylated 2-(o- and p-nitrobenzyl)tropones and 3-(o- and p-nitrobenzyl)tropolones was recognized. This alkali-promoted reaction has no precedent analogy in the troponoid chemistry. From the 2-(p-nitrobenzoyl)tropone, a tetrahydrobenzodiazaheptalenone, 6-(p-nitrophenyl)-5,7,11a,12-tetrahydrocyclohepta[b](1,5)benzodiazepin-7-one, was prepared.

Previously, we reported a thermally-induced radical reaction of 2-(arylmethoxy)tropone to the 3- and 5-(arylmethyl)tropolones.1) The mechanism of the rearrangement was clarified by the kinetic analysis and isotope-labelling experiments. Similar rearrangements also occurred when 2-(hetarylmethoxy)tropones were heated in decalin; 2-(2-furylmethoxy)tropone to 3- and 5-(2-furylmethyl)tropolones and 3- and 5-(5-methyl-2-furyl)tropolones,2) and 2-(2-thienylmethoxy)tropones to 3- and 5-(2-thienylmethyl)tropolones.3) During the preparation of 2-(nitrobenzyloxy)tropones by the thermal reaction, we found an unprecedent rearrangement in the troponoid chemistry to form a C-C bond. We will herein describe an anion-promoted, novel reaction of 2-(nitrobenzyloxy)tropones.

When a hexamethylphosporic triamide (HMPA) solution of potassium tropolonate (**1**)4) and p-nitrobenzyl chloride (**2**) was stirred at room temperature for 5 h, three isomeric products (**3**, **4**, and **5**)5) were isolated by silica-gel column chromatography in 68%, 1%, and 8% yields, respectively. On the other way, when an HMPA solution of **1** was added dropwise to a solution of **2**, the product was predominantly **3** with very small amount of **4** and **5**. The structures of **3** (colorless plates, mp 164–166 °C) and **4** (yellow crystals, mp 167–169 °C) were identified to be 2-(p-nitrobenzyloxy)tropone and 3-(p-nitrobenzyl)tropolone, a formal rearrangement product of **3**: The NMR of **3** revealed a methylene signal at lower field, δ=5.24, and nine aromatic protons, while the ^{1}H NMR spectrum of **4** showed a methylene signal at higher field, 4.21, and eight aromatic protons. The ^{13}C NMR chemical shifts for the methylene carbons of **3** and **4** supported this conclusion.

The third product, **5** (yellow crystals, mp 170–172 °C), has secondary hydroxyl group [ν: 3230 cm^{-1}] and a tropone ring system [λ_{max}^{MeOH}: 275 nm (ε=14000) and 315 (10500)]. In the ^{1}H NMR, a singlet signal ascribable to the newly-formed methine proton appeared. As expected, its ^{13}C NMR spectrum revealed, except for an sp^3-carbon, a reasonable similarity to that of 2-(p-nitrobenzyl)tropone (**6**) which could be prepared, together with 4-(p-nitrobenzyl)tropone (**7**), by thermolysing 2-(p-nitrobenzylsulfonyl)tropone (**8**).6-8) In addition, the benzoyl derivative (**9**), a manganese(IV) oxide oxidation product of **5**, showed no singlet proton signal in the low field, where β-proton of the benzoyl group should appear. All these data have shown **5** to be the α-hydroxylated derivative of **6**, 2-[hydroxy(p-nitrophenyl)methyl]tropone.

When **3** was kept at room temperature in HMPA, no reaction occurred after 5 h, but when **3** was refluxed in 1,2-dichlorobenzene, **4** was formed in good yield. Furthermore, when **3** was added into an HMPA solution of sodium hydride, the mixture instantly caused a change in color to yield **5** in 72%, but none of **4**. Clearly, the formation of **5** was facilitated by a base, and **3** might not be the precursor of **4** already formed during the preparation. Thus, **4** should be formed by direct C-attack. On the other hand, from the mesomeric effect of the nitro group, an anion can be generated on the benzylic carbon (**A**), which could be transformed into the epoxide (**B**) by an assistance of potassium ion. The following C-O bond cleavage gave **5**.



1

2 R=NO$_2$, R'=H
10 R=H, R'=NO$_2$

3 R=NO$_2$, R'=H
11 R=H, R'=NO$_2$

4 R=NO$_2$, R'=H
C R=H, R'=NO$_2$

5 R=NO$_2$, R'=H, X=H,OH
6 R=NO$_2$, R'=H, X=H,H
9 R=NO$_2$, R'=H, X=O
12 R=H, R'=NO$_2$, X=H,OH
13 R=H, R'=NO$_2$, X=O

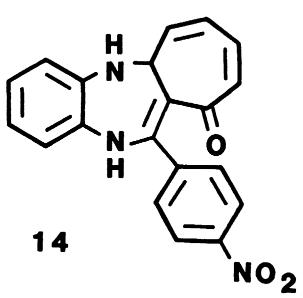
A

B

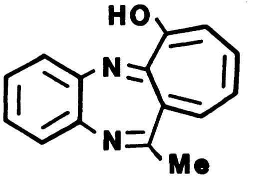
This alkali-promoted reaction was also applicable to the ortho-isomer of **3**: By the reaction of **1** with o-nitrobenzyl chloride (**10**) in HMPA, 2-(o-nitrobenzyloxy)tropone (**11**, yellow needles, mp 151–153 °C) was obtained in 88% yield together with and 2-[hydroxy(o-nitrophenyl)methyl]tropone (**12**, brown crystals, mp 165–167 °C).9) An alkali treatment of **11** with sodium hydride in HMPA afforded **12** in 66% yield. An oxidation of **12** yielded 2-(o-nitrobenzoyl)tropone (**13**, yellow crystals, mp 131–133 °C).

The rearrangement must also be applicable to other species which can produce a carboanion on that position. It may be even likely that the heteroatom linked to the tropone ring needs not to be oxygen; e.g., sulfur or nitrogen derivatives may work as well. In general, Grignard reaction with various tropones has been used for preparation of 2-substituted tropones,[10] but it is true that the yields of the desired products were not sufficiently good due to the accompanied formation of ring-contracted phenyl derivatives; e.g., phenylmagnesium bromide and 2-methoxytropone gave triphenylmethanol.[11] It has been a common knowledge that 2-alkoxytropones are unstable under basic conditions to cause a ring-contraction to benzenoids. However, in a bulky aprotic polar solvent such as HMPA, tropones showed no tendency of the ring-contraction. This characteristic property of troponoids[12] will make various reinvestigations promising.

Finally, as a preliminary experiment to synthesize a diazaheptalene or 1,2-diazazulene derivative, a condensation of **9** with 1,2-diaminobenzene or hydrazine hydrate was carried out. The former gave red crystalline compound (**14**) [λ_{max}^{MeOH}: 220 nm (ε=37600), 269 (20600), 324 (8900), and 417 (11000)] in 96% yield. However, its structure was not the desired 6-(p-nitrophenyl)cyclohepta[b](1,5)-benzodiazepine but 6-(p-nitrophenyl)-5,7,11a,12-tetrahydrocyclohepta[b](1,5)-benzodiazepin-7-one.[13] Furthermore, the latter formed none of desired 3-(p-nitrophenyl)-1,2-diazazulene.[14] These two results indicate the Michael-type conjugate addition to be exclusive in the nucleophilic reaction of **9**. Studies on the related aspect will be a matter of independent paper in future.[15]



14



I

The followings are NMR spectral data of new compounds.

3: δ(H)=5.24(2H, s), 6.6–7.0(3H, m), 7.1–7.2(2H, m), 7.60(2H, d, J=9 Hz), and 8.19(2H, d, J=9 Hz). δ(C)=69.7, 115.5, 124.1(2C), 127.8(2C), 129.3, 132.5, 136.8, 138.0, 141.3, 148.0, 164.1, and 180.8.

4: δ(H)=4.21(2H, s), 6.99(1H, ddd, J=9.5, 6, 5 Hz), 7.2–7.6(3H, m), 7.38(2H, d, J=9 Hz), and 8.08(2H, d, J=9 Hz). δ(C)=40.9, 120.5, 123.9(2C), 127.7, 130.0 (2C), 136.9, 139.5, 140.1, 147.0, 147.3, 167.9, and 173.6.

5: δ(H)=3.40(1H, br s, OH), 5.86(1H, s), 6.9–7.2(4H, m), 7.46(1H, d, J=5.5 Hz), 7.58(2H, d, J=9 Hz), and 8.12(2H, d, J=9 Hz). δ(C)=75.2, 123.7(2C), 127.5 (2C), 134.4, 135.4, 135.9, 137.0, 142.2, 147.5, 149.5, 153.3, and 187.5.

6: δ(H)=4.03(2H, s), 6.9–7.3(5H, m), 7.40(2H, d, J=9 Hz), and 8.09(2H, d, J=9 Hz). δ(C)=40.9, 123.6(2C), 129.9(2C), 133.4, 133.6, 135.7(2C), 136.1, 141.0, 147.0, 152.7, and 186.1.

9: δ(H)=7.0–7.5(5H, m), 7.91(2H, d, J=9 Hz), and 8.23(2H, d, J=9 Hz). δ(C)=124.1 (2C), 130.0(2C), 134.2, 136.8, 137.0, 137.5, 141.0, 143.9, 150.1, 150.5, 186.2, and 195.1.

11: δ(H)=5.55(2H, s), 6.7–7.1(3H, m), 7.4–7.8(2H, m), and 8.0–8.2(2H, m). δ(C) =67.7, 114.9, 125.2, 128.5, 128.8(2C), 132.7, 134.8, 136.8(2C), 137.9, 146.7, 164.2, and 180.8.

12: δ(H)=6.36(1H, s) and 6.9–8.0(9H, m). δ(C)=70.4, 124.8, 128.8, 129.2, 133.5, 134.2, 134.5, 134.9, 136.7, 141.7, 148.9, 153.0(2C), and 187.4.

13: δ(H)=6.9–7.3(4H, m), 7.4–7.8(3H, m), and 8.0–8.2(2H, m). δ(C)=123.9, 124.8, 129.0, 130.3, 133.4, 134.1, 135.6, 137.8, 138.5, 140.1, 144.3, 146.5, 185.6, and 193.7.

14: δ(H)=3.31(1H, dd, J=5.5, 1 Hz), 6.1–6.3(2H, m), 6.6–7.1(5H, m), 7.66(2H, d, J=9 Hz), and 8.26(2H, d, J=9 Hz). δ(C)=52.2, 105.3, 114.5, 117.0, 119.2, 122.2, 123.2, 123.7(2C), 125.4, 126.4, 129.0(3C), 131.7, 132.8, 145.1, 147.1, 148.7, and 193.5.

References

1) H. Takeshita, H. Mametsuka, A. Chisaka, and N. Matsuo, Chem. Lett., 1981, 73.

2) H. Takeshita and H. Mametsuka, Heterocycles, 22, 663 (1984).

3) H. Takeshita, H. Mametsuka, and H. Motomura, in preparation.

4) When the sodium tropolonate was employed, the reaction mixture darkened and the isolable products were **3** and **4** in only 7% and 1.6% yields, respectively.

5) All new compounds described in this text gave satisfactory elemental analyses.

6) H. Takeshita, N. Matsuo, and H. Mametsuka, Bull. Chem. Soc. Jpn., 57, 2321 (1984).

7) Calculations of the $\Delta\delta$(5-6), the chemical shift differences for the carbons of the seven-membered rings between **5** and **6**, gave: 1.4(C-1), 0.6(C-2), 1.3(C-3), 1.8(C-4), 1.0(C-5), 1.0(C-6), and 0.2(C-7).

8) We thank Mr. Norihide Matsuo, M. Eng., for this experiment.

9) In this case, expected 3-(o-nitrobenzyl)tropolone (**C**) was not detected in the mixture, but subsequent thermolysis of **11** at 200 ^{o}C slowly produced a thermolysate whose ^{1}H NMR [δ=4.46(2H, s), 7.2–7.6(7H, m), and 7.94(1H, dd, J=9, 2 Hz)] strongly suggested a formation of **C**. However, due to instability under the conditions, its purification was unsuccessful.

10) T. Nozoe, T. Mukai, and J. Minegishi, Proc. Jpn. Acad., 27, 419 (1951); W. von E. Doering and C. F. Haskey, J. Am. Chem. Soc., 74, 5688 (1952).

11) T. Nozoe, T. Mukai, J. Minegishi, and T. Fujisawa, Sci. Repts. Tohoku Univ., Ser. I, 37, 388 (1953); T. Mukai, Bull. Chem. Soc. Jpn., 31, 852 (1958).

12) Benzenoid analogs, salicylaldehyde or other phenolic compounds carrying electron-attractive substituents, seem to be worth trying, but at least to date every attempt was unsuccessful.

13) Synthesis of a compound in this family, 11-hydroxy-6-methylcyclohepta[b](1,5)-benzodiazepine (or tautomeric 12(H)-6-methylcyclohepta[b](1,5)benzodiazepin-11-one), **i**, has been reported. See K. Imafuku, A. Yamane, and H. Matsumura, J. Heterocyclic Chem., 18, 335 (1981).

14) 6-Isopropyl derivative is known. See S. Matsumoto, Sci. Repts. Tohoku Univ., Ser. I, 42, 222 (1958). In a sense, cyclohepta[c]pyrazolones should be included in this category, but these derivatives are all known to exist in the tautomeric tropone form; e.g., S. Itô, K. Takase, N. Kawabe, and H. Sugiyama, Bull. Chem. Soc. Jpn., 39, 256 (1966); T. Nozoe, T. Asao, E. Takahashi, and K. Takahashi, ibid., 39, 1310 (1966); L. J. Luskus and K. N. Houk, Tetrahedron Lett., 1972, 1925.

15) We thank the Ministry of Education, Science, and Culture for a financial assistance, the Grant-in-Aid for Scientific Research to A. M. (No. 60470025).

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