Oxidative Cyclization of Azo-coupling Products of 3-Isopropenyltropolone and 3-Cinnamoyltropolone with Bromine

Wen Tao GAO*, Shu Fen ZHANG, Jin Zong YANG

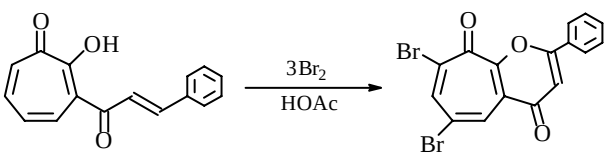
State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian, 116012

Abstract: A new method to synthesize heterocycle-fused troponoid compounds by oxidizing azo-coupling products of 3-isopropenyltropolone and 3-cinnamoyltropolone with bromine in the presence of pyridine was reported for the first time. Reaction of azo-couping products of 3-isopropenyl tropolone **1a~f** and 3-cinnamoyltropolone **3a~d** with excess bromine afforded heterocycle-fused troponoid compounds **2a~f**, **4a~d**, respectively.

Keywords: 3-isopropenyltropolone, 3-cinnamoyltropolone, oxidation, cyclization, bromine.

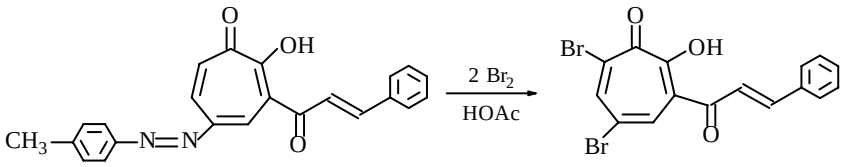
Heterocycle-fused troponoids are a kind of compounds with physiological activity such as anticancer[1], germicide[2], antiphlogistic[3], antihypertension[4] and antidiabetic[5]. Troponoid compounds can be synthesized in many ways, among which one was to oxidize the side chain of tropolone for cyclization. For instance, it was reported that flavone-like heterocycle-fused troponoid compounds, 2-aryl-4, 9-dihydrocyclohepta [b]pyran-4, 9-diones were obtained by oxidative cyclization of 3-cinnamoyltropolones with selenium dioxide and with 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone[6~8]; Jin Renhao *et al.* has reported that 3-isopropenyltropolone could be oxidized to 2-methyl-8-hydrocyclohepta[b]furan-8-one[9], Wang Daolin *et al.* synthesized 2-aryl-4, 9-dihydrocyclo hepta[b]pyran-4, 9-diones in one-step reaction by treatment of 3-acetyltropolone with substituted benzaldehydes in the presence of triethyl orthoformate and with perchloric acid as the oxidant[10, 11]. When we were investigating the electrophilic substitution of 3-cinnamoyltropolone, it was observed that 3-cinnamoyltropolone was oxidized in acetic acid by three molar equivalents of bromine to 6, 8-dibromo-2-phenyl-4, 9-dihydrocyclohepta [b] pyran-4, 9-dione[12] (**Scheme 1**).

Scheme 1



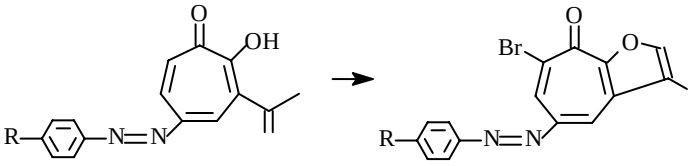
But when azo-coupling product of 3-cinnamoyltropolone was used as starting material under the same conditions, dibromo-substituted electrophilic substitution product in which phenylazo group in 5 position was replaced by bromine was obtained instead of the anticipated closed-ring compound[12] (**Scheme 2**).

Scheme 2



In order to supply more optional substrates to synthesize heterocycle-fused troponoid compounds with physiological activity, we examined the reaction in alkaline medium and got satisfying result. 3-Isopropenyl-5-substituted phenylazo tropolone **1a~f** and 3-cinnamoyltropolone-5-substituted phenylazotropolone **3a~d** were used as substrates to react with two molar equivalents of bromine in pyridine at 0~30°C for 1~24 hours, **2a~f** and **4a~d** were afforded, respectively. The reaction equations were shown as follows (**Scheme 3** and **Scheme 4**):

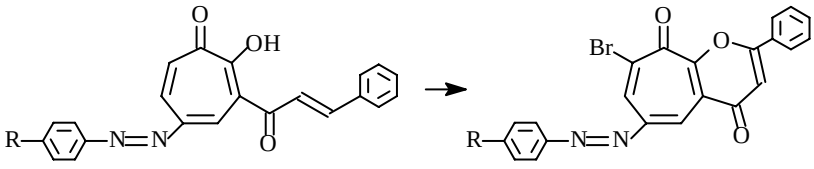
Scheme 3



1 a~f **2 a~f**

R=H, CH_3, OCH_3, Br, Cl, NO_2

Scheme 4



3 a~d **4 a~d**

R=H, CH_3, OCH_3, Br

The products **2a~f** and **4a~d** were new compounds whose structures were confirmed by IR, ^{1}H-NMR and elemental analysis.

Result and Discussion

Azo-coupling products of 3-isopropenyltropolone **1a~f** and 3-cinnamoyltropolone **3a~d** were dissolved in pyridine respectively and pyridine solution containing 2 molar equivalents of bromine was dropped into the reaction mixture at room temperature. After stirring for 1~24 hours, **2a~f** and **4a~d** were obtained in yields of 37.4%~68.2% and 33.0%~74.3%, respectively. The structures of compounds **2a~f** and **4a~d** were analyzed. When the compounds were developed on TLC plate (silica gel: GF254, developing agent: ethyl acetate), there was only one spot with no tailing; The compounds had negative reaction to iron trichloride in methanol solution; The absorption peak of the hydroxyl group disappeared in IR. All these facts showed that the hydroxyl group in tropolone ring had taken part in the reaction. From the results, it is considered that bromine substitution in 7 position of azo-coupling products was the first step of the reaction and then the remaining bromine was used as oxidant for cyclization.

Acknowledgment

This work was supported by Natural Science Foundation of Liaoning Province.

References and Notes

1. T. Tsuruo, H. Iido, S. Tsukagoshi, Y. Sakirai, *Cancer Res*., **1979**, *39*, 1063.
2. T. Tanaka, A. Hagashi, Y. Miki, JP 74, 85230.
3. T. Amano, A. Hagashi, J. Sawada, M. Sasajima, U.S.A. 4189607 (*C.A.***1980**, 93:7880r).
4. F. Bagli Jehan, Bogri Tibor. U.S.A. 4258188 (*C.A.***1981**, 95:7341g).
5. A. Treasurywala, B. Palameta, T. Boogri, J. Bagli. U.S.A.4337265 (*C.A.***1982**, 97:162818c).
6. K. Imafuku, K. Yamaguchi, *Bull. Chem. Soc. Jpn*., **1981**, *54*, 2855.
7. M. Honda, K. Imafuku, *Bull. Chem. Soc. Jpn.*, **1985**, *58*, 508.
8. K. Imafuku, A. Yamane, H. Matsumura., *Yuki Gosei Kagaku Kyokai Shi*, **1980**, *38*, 308.
9. Jin RenHao. *Masters Thesis*, Yanbian University, Yanji, **1988.**
10. D. L. Wang, Z. T. Jin, B. Z. Yin, K. Imafuku, *J. Heterocyclic Chem*., **1990**, *27*, 891.
11. W. T. Gao, Chemical Research and Application, **1995**, *7* (4), 404.
12. W. T. Gao, Z. T. Jin, B. Z. Yin, K. Imafuku, *J. Heterocyclic Chem*., **1989**, *26*, 371.
13. The IR, ^{1}H-NMR spectra of the new compounds, measured by means of Perkin-Elmer1700 and DMX-300 in $CDCl_3$ are provided here:
    2a: *Anal*. Cald. For $C_{16}H_{11}N_2BrO_2$: C, 56.02; H, 3.21; N, 8.16. Found: C, 56.24; H, 3.16;N, 8.27. V_{max}: 1593cm^{-1}. δ_H: 2.40 (3H, s, -CH_3), 7.27~9.15 (8H, m, ArH, PhH, C=CH) ppm.
    2b: *Anal*. Cald. For $C_{17}H_{13}N_2BrO_2$: C, 57.18; H, 3.64; N, 7.84. Found: C, 57.31; H, 3.56; N, 7.97.V_{max}: 1595cm^{-1}. δ_H: 2.39 (3H, s, -CH_3), 2.48 (3H, s, -CH_3), 7.27~9.16 (7H, m, ArH, PhH, C=CH) ppm.
    2c: *Anal*. Cald. For $C_{17}H_{13}N_2BrO_3$: C, 54.73; H, 3.49; N, 7.51. Found: C, 54.89; H, 3.38; N, 7.72. V_{max}: 1597cm^{-1}. δ_H: 2.39 (3H, s, -CH_3), 3.94 (3H, s, -OCH_3), 7.04~9.16 (7H, m, ArH, PhH, C=CH) ppm.
    2d: *Anal.* Cald. For $C_{16}H_{10}N_2Br_2O_2$: C, 45.54; H, 2.37; N, 6.64. Found: C, 45.71; H, 2.26; N, 6.82. V_{max}: 1596cm^{-1}. δ_H: 2.41 (3H, s, -CH_3), 7.27~9.14 (7H, m, ArH, PhH, C=CH) ppm.
    2e: *Anal*.Cald.For $C_{16}H_{10}N_2BrClO_2$: C, 50.90; H, 2.65; N, 7.42. Found: C, 51.17; H, 2.47; N, 7.60. V_{max}: 1598cm^{-1}. δ_H: 2.42 (3H, s, -CH_3), 7.27~9.16 (7H, m, ArH, PhH, C=CH) ppm.
    2f: *Anal*. Cald. For $C_{16}H_{10}N_3BrO_4$: C, 49.52; H, 2.58; N, 10.82. Found: C, 49.65; H, 2.39; N,

10.98. V_{max}: 1599cm^{-1}. δ_H: 2.43 (3H, s, -CH_3), 7.27~9.18 (7H, m, ArH, PhH, C=CH) ppm.
4a: *Anal*. Cald. For $C_{22}H_{13}N_2BrO_3$: C, 61.01; H, 3.00; N, 6.47. Found: C, 61.23; H, 2.89; N, 6.62. V_{max}: 1605, 1634cm^{-1}. δ_H: 7.21~9.05 (13H, m, ArH, PhH, C=CH) ppm.
4b: *Anal*. Cald. For $C_{23}H_{15}N_2BrO_3$,: C, 61.78; H, 3.36; N, 6.26. Found: C, 61.88; H, 3.29; N, 6.42. V_{max}: 1607, 1637cm^{-1}. δ_H: 2.47 (3H, s, -CH_3), 6.93~9.12 (12H, m, ArH, PhH, C=CH) ppm.
4c: *Anal*. Cald. For $C_{23}H_{15}N_2BrO_4$: C, 59.65; H, 3.24; N, 6.05. Found: C, 59.79; H, 3.13; N, 6.22. V_{max}: 1609, 1638cm^{-1}. δ_H: 3.92 (3H, s, -OCH_3), 7.02~9.00 (12H, m, ArH, PhH, C=CH) ppm.
4d: *Anal*. Cald. For $C_{22}H_{12}N_2Br_2O_3$: C, 43.40; H, 2.34; N, 5.47. Found: C, 43.55; H, 2.26; N, 5.45. V_{max}: 1604, 1635cm^{-1}. δ_H: 7.28~9.12 (12H, m, ArH, PHH, C=CH) ppm.

Received 16 June 1998