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Study on Unexpected Cycloaddition Reactions of Imines with THF

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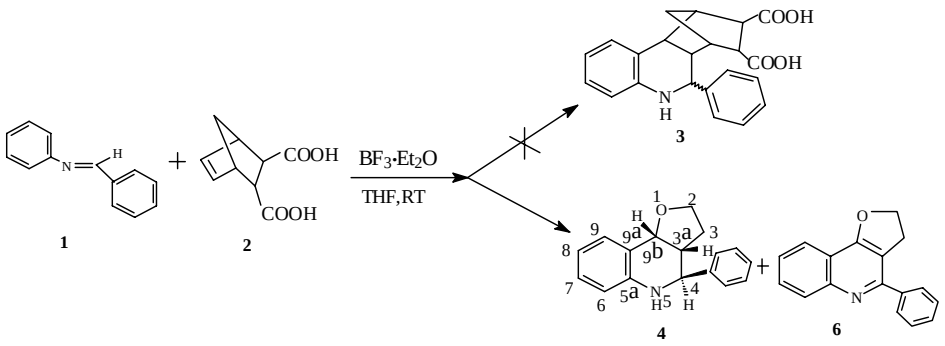
Abstract: An unexpected tricyclic compound 2,3,3a,4,5,9b-hexahydrophenylfuro[3,2-c] quinoline **4** and its aromatized product **6** were obtained when the cycloaddtion of imine **1** and substituted norbornene **2** was carried out in THF with a catalytic amount of boron trifluoride. The structures of the products were determined by spectral data, and the mechanism of reaction was substantiated by the imitation reaction.

Keywords: Imine, THF, cycloaddition reaction.

The synthesis of nitrogen-containing heterocyles through cycloaddition reaction of imines has stimulated much preparative and mechanistic work[1,2,3]. When we attempted to synthesize a polycyclic compound **3** by addition reaction of imine **1** and 5-norbornene-2,3-dicarboxylic acid **2**, however, unexpected tricyclic compounds **4** and **6** were obtained instead of the designed product **3** (**Scheme 1**). Here tetrahydrofuran (THF) served as the source of dihydrofuran which underwent cycloaddition with **1** giving **4** and **6**.

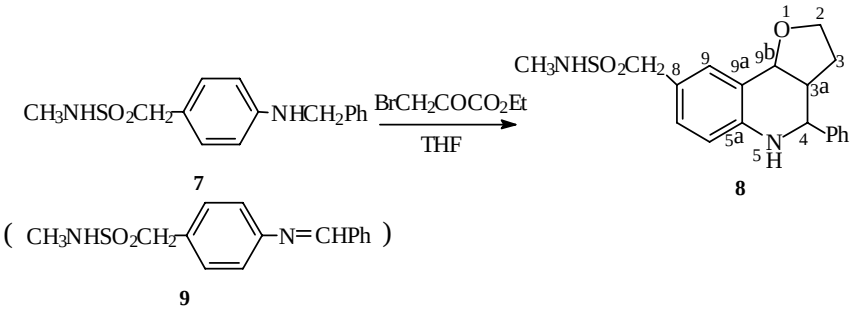
Scheme 1



An analogous reaction was noted previously in this laboratory[4] (**Scheme 2**). Here the starting material **7** must have been oxidatively transformed to the Schiff base (**9**) before its cycloaddition with dihydrofuran (from THF). Thus the cycloaddition reactants (**9** and dihydrofuran) were all generated *in situ* while the bromoester apparently played

the role of an acidic catalyst (probably furnishing HBr by some side-reactions).

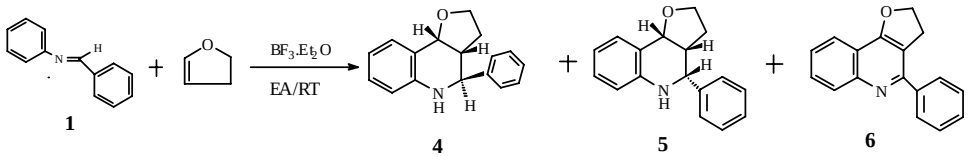
Scheme 2



Our present work (**Scheme 1**) involved the following experimental procedure: To a solution of imine **1** (181mg, 1mmol) dissolved in anhydrous THF (15mL) with a catalytic amount of boron trifluoride ($BF_3{\cdot}Et_2O$) at 0°C was added 5-norbornene-2,3-dicarboxylic acid **2** (182mg, 1mmol) dissolved in anhydrous THF (5mL) dropwise. The reaction mixture was then stirred for 10 hours at room temperature. Following the general work-up, compound **4** (m.p.111-112°C) was isolated as the major product in the yield of 21.5%. A small amount (5%) of oily product **6** was obtained and 60% of starting material **1** was recovered. The structures of the product **4** and **6** were confirmed by ^{1}HNMR, ^{13}CNMR, DEPT, MS, ^{1}H-^{1}HCOSY, and ^{13}C-^{1}HCOSY[6].

In order to further vindicate the proposed structures of compounds **4, 6** and to explain the mechanism of the reaction, we prepared compound **4, 5** and **6** from the reaction of imine with 2,3-dihydrofuran[5]. (**Scheme 3**)

Scheme 3

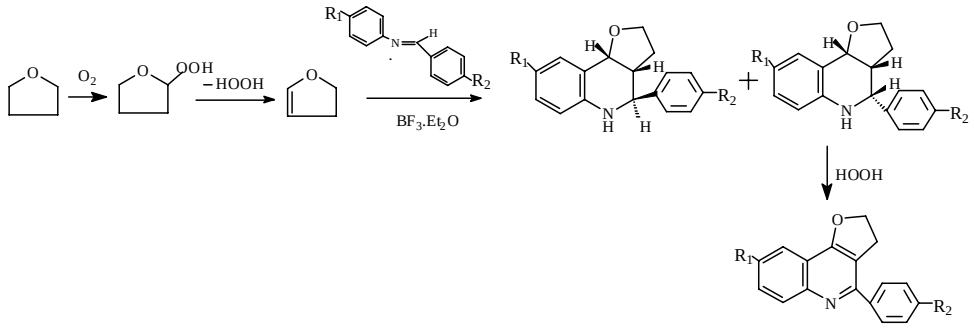


It was found that when **5** in chloroform was exposed to the air for a while, part of the sample was oxidized to give **6,** indicating that compound **6** was the auto-oxidation product of compound **5.** The conversion of **5** into **6** was also effected by the treatment with H_2O_2. On the contrary, compound **4** was not oxidized under the same conditions. The requirement of an all-*cis* configuration for the oxidative the removal of the hydrogens has interesting mechanistic implications.

On the basis of all experimental facts, the mechanism of the reaction depicted in

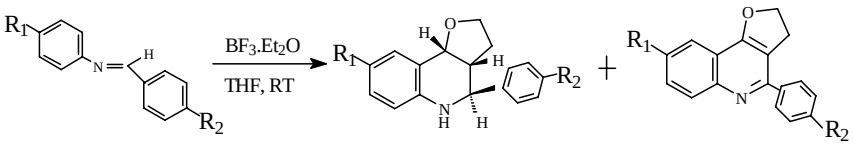
Scheme 1 was proposed as follows: (**Scheme 4**)

Scheme 4



Some other examples can be found in **Scheme 5**. The major products **10** and **11** were obtained in the yield of 19.8% and 18.6% respectively. The corresponding aromatized product **12** was isolated in 4.5% yield, while **13** was formed only in trace amounts. (**Scheme 5**)

Scheme 5



10 R_1=Cl, R_2=CH_3 **12** R_1=Cl, R_2=CH_3

11 R_1=H, R_2=CH_3 **13** R_1=H, R_2=CH_3

Acknowledgment

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References and notes

1. S. Laschat. *Liebigs Ann. /Recueil*., **1997**, 1.
2. E. F. Elslager, D. F. Worth, *J. Heterocycl. Chem.*, **1969**, *6*, 597.
3. B. Crousse, J. P. Begue, D. B. Delpon, *Tetrahedron Lett*., **1998**, *39*, 5765.
4. Y. Zhang, Y. Z. Jiang, X. T. Liang, *Chin. Chem. Lett*., **1998**, *9*, 705.
5. J. Zhao, S. F. Chen, X. T. Liang, *Chin. Chem. Lett*., **1998**, *9*, 983.
6. Experimental data of products:

Compound 4: white solid, m.p.118-119°C. ^{1}HNMR (500MHz,$CDCl_3$): δ (ppm) 7.49 (td, 2H, J=7.0,1.2Hz), 7.39 (m, 3H), 7.33 (td, 1H, J=7.0,1.2), 7.10 (td, 1H, J=7.6, 2.4Hz), 6.67 (dd, 1H, J=7.6, 2.4Hz), 5.27 (d, 1H, J=7.9Hz), 4.71 (s, 1H), 3.82 (dt, 1H, J=8.4, 2.7Hz), 3.74 (dt, 1H, J=8.4, 2.7Hz) , 2.82 (m, 1H), 2.24 (m, 1H), 1.58 (m, 1H). ^{13}C NMR (500MHz, $CDCl_3$): δ (ppm) 24.62, 45.71, 57.49, 66.79, 75.00 , 114.95, 119.21 , 126.50 , 127.64, 128.33, 128.63, 130.09. MS *m/z* (%): 251 (M^+,18), 220 (8), 206 (42), 180 (11), 146 (30), 130 (64), 91 (93),77 (100).
Compound 5: white solid, m.p. 99-100°C; ^{1}H NMR (500MHz, $CDCl_3$): δ (ppm) 7.38-7.49 (m, 6H), 7.13 (m, 2H), 6.92 (m, 1H), 6.72 (m, 1H), 4.65 (s, 1H), 4.03 (m, 6H), 3.84 (m, 2H), 2.64 (m, 1H), 2.03 (m, 1H), 1.69 (m, 1H). ^{13}C NMR (500MHz, $CDCl_3$): δ (ppm) 28.89, 43.01, 57.96, 65.28, 74.17, 114.95, 118.75, 128.15, 128.29, 128.64, 128.91, 131.14. MS *m/z* (%): 251 (M^+, 52), 220 (17), 206 (100), 146 (36), 130 (60), 91 (86), 77 (80).
Compound 6: light yellow oil , ^{1}HNMR (500 Mhz , $CDCl_3$): δ (ppm) 8.18 (m, 2H), 7.83 (d, 1H , J=8.17), 7.70 (t, 1H, J=7.70) , 7.42-7.57 (m, 5H), 3.76 (t, 2H, J=6.58), 3.06 (t, 2H, J=6.58). MS *m/z* (%): 247 (M^+ , 52), 231 (45), 217 (100), 115 (40), 89 (44).
Compound 10: white solid, m.p.103-105°C. ^{1}HNMR (300MHz, $CDCl_3$): δ (ppm) 7.38 (d, 1H, J=2.4), 7.35 (d, 2H, J=7.2), 7.22 (d, 2H, J=7.2), 7.06 (dd, 1H, J=2.4, 8.4), 6.57 (d, 1H, J=8.4), 4.55 (d, 1H, J=5.1), 3.97-4.05 (m, 1H), 3.77-3.86 (m, 1H), 3.74 (d, 1H, 10.8), 2.47 (m, 1H), 2.38 (s, 3H), 1.96-2.08 (m, 1H), 1.65-1.74 (m, 1H); MS: *m/z* 299 (M+).
Compound 11: white solid, m.p.111-112°C. ^{1}HNMR (300MHz, $CDCl_3$): δ (ppm) 7.39 (dd, 1H, J=1.5,7.8), 7.33 (d, 2H, J=7.8), 7.20 (d, 2H, J=7.8), 7.13 (dt, 1H, J=1.5, 7.8), 6.80 (dt, 1H, J=1.5, 7.8), 6.62 (d, 1H, J=7.8), 4.60 (d, 1H, J=5.1), 4.00 (bs, 1H), 3.99-4.05 (m, 1H), 3.80-3.88 (m, 1H), 3.77 (d, 1H, J=10.8), 2.41-2.47 (m, 1H), 2.38 (s, 3H), 2.02 (m, 1H), 1.72 (m, 1H). MS:*m/z* (%) 265 (M+, 72), 220 (100), 194 (10), 146 (30), 105 (51).
Compound 12: ^{1}H NMR (300MHz, $CDCl_3$): δ (ppm) 8.12 (d, 1H, J=8.7), 7.81 (d, 1H, J=2.4), 7.63 (dd, J=2.4, 8.7), 7.47 (d, 2H, J=7.8), 7.28 (d, 2H, J=7.8), 3.78 (t, 2H, J=6.3), 3.07 (t, 2H, J=6.3), 2.42 (s, 3H).
MS: *m/z* 295 (M+).

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