HETEROCYCLES, Vol. 76, No. 1, 2008, pp. 811 - 817. © The Japan Institute of Heterocyclic Chemistry
Received, 10th December, 2007, Accepted, 15th January, 2008, Published online, 18th January, 2008. COM-07-S(N)4

# SYNTHESIS OF DIAZIRINE POSSESSING AN ACETOPHENONE DERIVATIVE AS A VALUABLE INTERMEDIATE FOR A FLAVONOID PHOTOAFFINITY PROBE‡

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‡Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

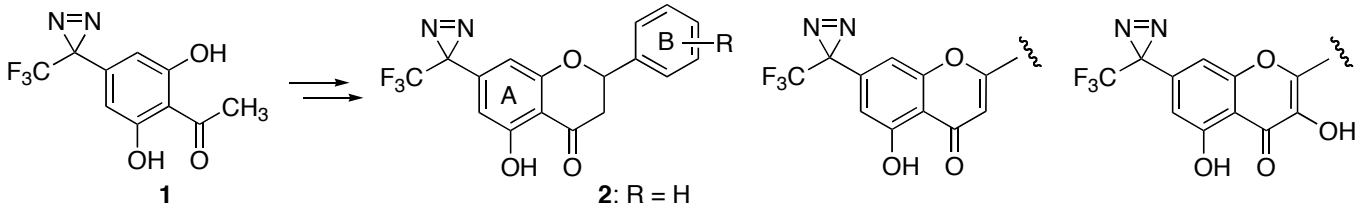
**Abstract** – A novel acetophenone derivative with a diazirine moiety is prepared as a potential intermediate for a flavonoid photoaffinity probe. The transformation to the flavanone derivative with a diazirine moiety on the A-ring is also demonstrated.

## INTRODUCTION

Flavonoids are typical phenolic constituents of plants, which exhibit a variety of bioactivities such as anti-inflammatory, antitumor, and antimicrobial activities.[1] Flavonoids have also attracted attention as neuroprotective agents[2] and enhancers for memory.[3] Therefore, preparing molecular probes that would be beneficial for chemical biological research of flavonoids are of great interest. Photoaffinity labeling is one of the most powerful methods to investigate ligand-receptor interactions as well as to aid in the discovery of target biomolecules.[4] Therefore, photoactivatable flavonoids, which contain a photolabile group such as an azide, benzophenone, or diazirine moiety, are very valuable in photoaffinity labeling studies. However, only a few synthetic studies on photoactivatable flavonoids have been reported.[5]

During the course of our synthetic study on catechin derivatives, we have found that A-ring phenolic hydroxy groups are not crucial for bioactivity.[6] Considering the structural similarities between catechins and flavonoids, we postulated that the A-ring functionalization of flavonoids with a photoactivatable group is plausible without losing bioactivity. This hypothesis led us to design flavonoid photoaffinity probes containing the diazirine moiety, which is known as a structurally concise and powerful photoactivatable group,[7] on the A-ring (Scheme 1).

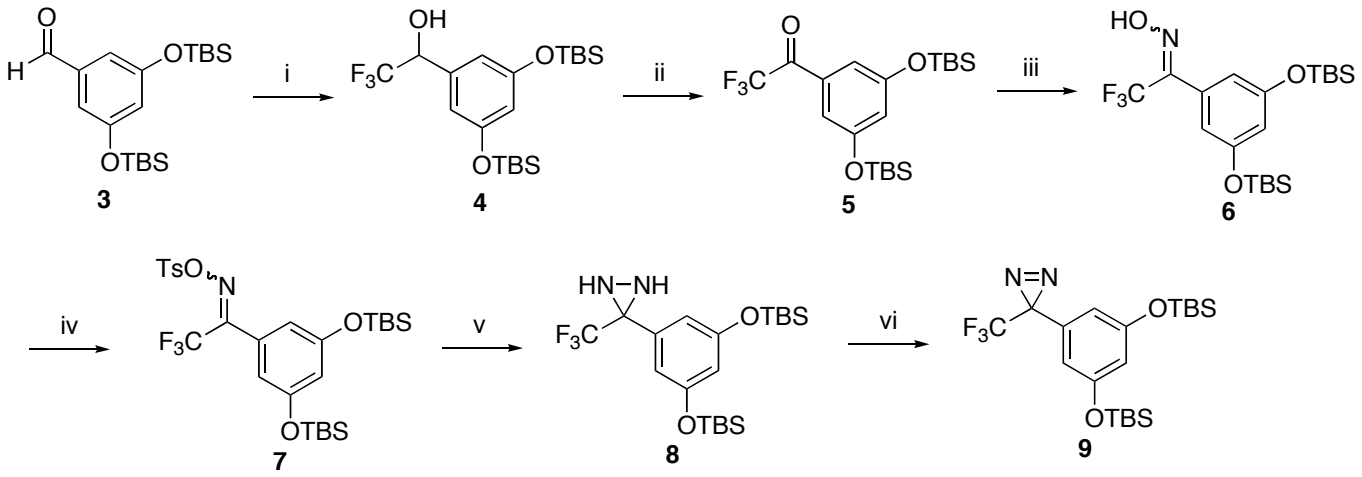
In our total synthesis of flavone C-glycoside, an acetophenone derivative was employed as the potential precursor for the A-ring of the target flavone.[8] Therefore, we envisioned that acetophenone derivative **1** with a diazirine moiety would be a valuable intermediate for flavonoid photoaffinity probes (Scheme 1). Herein, the synthesis of key intermediate **1** and the transformation to the flavanone probe molecule **2** are described.




**Scheme 1**

## RESULTS AND DISCUSSION

The synthesis of key phenyl diazirine **9** began from aryl aldehyde **3**[9] where both of the phenolic hydroxyl groups were protected with TBS groups. Treatment of $TMSCF_3$ in the presence of a catalytic amount of TBAF afforded alcohol **4**, and a subsequent Dess–Martin oxidation of **4** yielded ketone **5**. After conversion to tosylated oxime **7** via **6**, diaziridine **8** was obtained by the treatment with liquid $NH_3$. Oxidation of **8** with iodine afforded phenyl diazirine **9** in 66% total yield via six steps from **3**. Although a methyl group has been frequently employed for phenolic hydroxyl group protection in diazirine syntheses,[10] a silyl protecting group is also applicable in the synthesis as shown in Scheme 2.

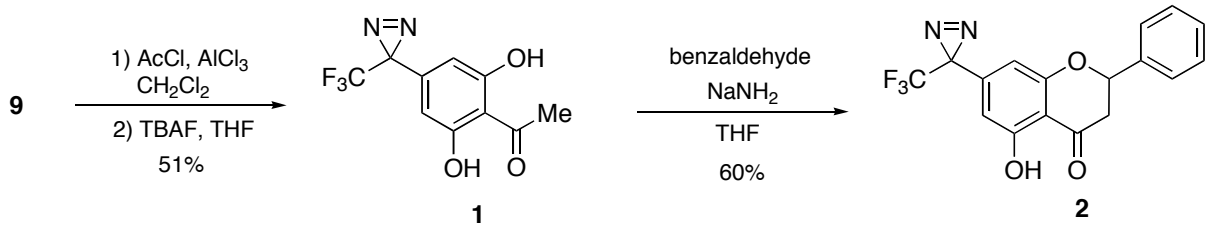



Reagents: i, $TMSCF_3$,TBAF, THF; 2.0 M HCl, MeOH, 79%; ii, Dess-Martin periodinane, TFA, $CH_2Cl_2$, 96%; iii, $NH_2OH$•HCl, pyridine, 97%; iv, TsCl, $Et_3N$, DMAP, $CH_2Cl_2$, 99%; v, liq. $NH_3$, $Et_2O$, 94%; vi, $I_2$, $Et_3N$, $CH_2Cl_2$, 97%.

**Scheme 2**

Next, we focused on the introduction of the acetyl group to **9** (Scheme 3). Treatment of acetyl chloride in the presence of $AlCl_3$ allowed the Friedel–Crafts acylation to proceed smoothly and selectively at the *para*-position of the diazirine moiety.[11] Successive deprotection of the TBS groups afforded desired acetophenone derivative **1**, which contained the two of phenolic hydroxy groups and the ketone moiety, all of which correspond to the flavonoid framework. Therefore, compound **1** should be a valuable intermediate for flavonoid related compounds, including chalcones and catechins.

Further investigation of the transformation to the flavonoid framework clearly showed the potential of **1** as a key intermediate, as depicted in Scheme 3. Aldol condensation with benzaldehyde and a successive oxy-Michael addition to the chalcone intermediate afforded flavanone derivative **2**, which is the first example of a flavonoid photoaffinity probe possessing a photolabile moiety on the A-ring.[12]




**Scheme 3**

In conclusion, the synthesis of diazirine possessing acetophenone derivative **1** and transformation to photoactivatable flavanone **2** was successful. Compound **2** might be applicable in photo-crosslinking experiments to discover target proteins of bioactive flavanones. Further transformations of **1** to a variety of bioactive flavonoids are currently underway.

## EXPERIMENTAL

$^1$H NMR spectra were obtained on JEOL EX-270 at 270 MHz with chemical shifts reported as ppm from tetramethylsilane as an internal standard. $^{13}$C NMR spectra were also measured on JEOL EX-270 at 68 MHz. The mass spectra were measured on a JEOL MStation JMS-700 spectrometer. Unless otherwise noted, all reactions were conducted in an argon atmosphere. Column chromatography was carried out with silica gel 60N spherical (63-210 mesh, KANTO CHEMICAL).

### 1-[3,5-Bis(*tert*-butyldimethylsilyloxy)phenyl]-2,2,2-trifluoroethanol (4).

$TMSCF_3$ (0.5 M THF solution, 5.7 mL, 2.85 mmol) and TBAF (1.0 M THF solution, 5.4 μL, 5.4 μmol) were added to 3,5-bis(*tert*-butyldimethylsilyloxy)benzaldehyde (**3**) (209 mg, 0.57 mmol), and the mixture was stirred at 0 °C for 5 min under an Ar atmosphere. Then MeOH (3.8 mL) and 2.0 M HCl (1.9 mL) were added to the mixture. After being stirred at rt for 5 min, the reaction mixture was neutralized with

satd. aq. $NaHCO_3$ and evaporated under reduced pressure. The residue was extracted with $Et_2O$. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/EtOAc=10/1) to give a mixture that included compound **4**. Further purification of the mixture by column chromatography (*n*-hexane/EtOAc=100/1 to 100% EtOAc) afforded **4** (190 mg, 79%) as a colorless oil.

**4:** IR (neat) 1454, 1591, 2860, 2932, 3441 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.19 (s, 12H), 0.97 (s, 18H), 4.89 (q, *J* = 6.6 Hz, 1H), 6.37 (s, 1H), 6.52 (s, 2H); $^{13}C$ NMR (68 MHz, $CDCl_3$) δ –4.5, 18.2, 25.6, 72.7 (q, *J* = 30.8 Hz), 112.6, 113.2, 124.1 (q, *J* = 284.8 Hz, $CF_3$), 135.8, 156.7; FAB (*m/z*) 437 $(M+H)^+$; HRMS *m/z* calcd. for $C_{20}H_{36}F_3O_3Si_2$: 437.2155 $(M+H)^+$, found: 437.2144.

**1-[3,5-Bis(*tert*-butyldimethylsilyloxy)phenyl]-2,2,2-trifluoroethanone (5).**

1-[3,5-Bis(*tert*-butyldimethylsilyloxy)phenyl]-2,2,2-trifluoroethanol (**4**) (138 mg, 0.316 mmol) and Dess–Martin periodinane (402 mg, 0.948 mmol) were mixed in $CH_2Cl_2$ (5 mL) under an Ar atmosphere. TFA (71 μL) was added to the mixture. After stirring at rt for 8 h, the reaction mixture was evaporated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/EtOAc = 5/1) to afford **5** (616 mg, 96%) as a yellow oil.

**5:** IR (neat) 1585, 1721, 2860, 2932 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.22 (s, 12H), 0.98 (s, 18H), 6.66 (t, *J* = 2.0 Hz, 1H), 7.13 (d, *J* = 2.0 Hz, 2H); $^{13}C$ NMR (68 MHz, $CDCl_3$) δ –4.5, 18.2, 25.6, 114.7, 116.6 (q, *J* = 291.5 Hz, $CF_3$), 119.5, 131.3, 157.2, 180.3 (q, *J* = 36.6 Hz); FAB (*m/z*) 435 $(M+H)^+$; HRMS *m/z* calcd. for $C_{20}H_{34}F_3O_3Si_2$: 435.1999 $(M+H)^+$, found: 435.1995.

**1-[3,5-Bis(*tert*-butyldimethylsilyloxy)phenyl]-2,2,2-trifluoroethanone oxime (6).**

1-[3,5-Bis(*tert*-butyldimethylsilyloxy)phenyl]-2,2,2-trifluoroethanone (**5**) (1.11 g, 2.54 mmol) and $NH_2OH$•HCl (883 mg, 12.7 mmol) were dissolved in pyridine (20 mL) under an Ar atmosphere. After stirring at 60 °C for 3 h, the reaction mixture was evaporated under reduced pressure. The residue was dissolved in $CH_2Cl_2$, and washed with $H_2O$ and brine. The combined organic layer was dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/EtOAc=10/1) to afford **6** (1.10 g, 97%) as colorless solids.

**6:** IR (neat) 1587, 1607, 1775, 2932 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.20 (s, 12H), 0.97 (s, 18H), 6.44 (q, *J* = 2.0 Hz, 1H), 6.61 (t, *J* = 2.0 Hz, 1H), 8.62 (s, 1H); $^{13}C$ NMR (68 MHz, $CDCl_3$) δ –4.5, 18.2, 25.6, 113.5, 114.1, 120.5 (q, *J* = 271.2 Hz, $CF_3$), 127.0, 147.2 (q, *J* = 34.3 Hz), 156.6; FAB (*m/z*) 450 $(M+H)^+$.

**1-[3,5-Bis(*tert*-butyldimethylsilyloxy)phenyl]-2,2,2-trifluoroethanone *O*-(*p*-toluenesulfonyl)oxime (7).**

1-[3,5-Bis(*tert*-butyldimethylsilyloxy)phenyl]-2,2,2-trifluoroethanone oxime (**6**) (1.09 g, 2.43 mmol), *p*-TsCl (695 mg, 3.65 mmol), $Et_3N$ (509 μL, 3.65 mmol) and DMAP (6 mg, 48.6 μmol) were dissolved in $CH_2Cl_2$ (60 mL) under an Ar atmosphere. After stirring at rt for 16 h, the reaction mixture was added to

0.2 M citric acid aqueous solution, and then extracted with $CH_2Cl_2$. The combined organic layer was washed with $H_2O$, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/EtOAc=10/1) to afford **7** (1.46 g, 99%, *E*/*Z* mixture) as a brown oil.

**7:** IR (neat) 1584, 2860, 2931 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.18 (s, 7H), 0.20 (s, 5H), 0.97 (s, 18H), 2.4-2.5 (m, 3H), 6.4-6.5 (m, 3H), 7.3-7.5 (m, 2H), 7.8-8.0 (m, 2H); $^{13}C$ NMR (68 MHz, $CDCl_3$) δ –4.5, 18.2, 21.8, 25.6, 113.3, 113.9, 115.4, 115.5, 119.5 (q, $J$ = 277.1 Hz, $CF_3$), 125.6, 129.2, 129.8, 131.3, 131.4, 145.9, 146.0, 153.7 (q, $J$ = 33.5 Hz), 156.7, 156.9; FAB (*m*/*z*) 604 $(M+H)^+$, HRMS *m*/*z* calcd. for $C_{27}H_{41}F_3NO_5SSi_2$: 604.2196 $(M+H)^+$, found: 604.2211.

**3-[3,5-Bis(*tert*-butyldimethylsilyloxy)phenyl]-3-(trifluoromethyl)diaziridine (8).**

1-[3,5-Bis(*tert*-butyldimethylsilanyloxy)phenyl]-2,2,2-trifluoroethanone *O*-(*p*-toluenesulfonyl)oxime (**7**) (3.18 g, 5.27 mmol) was dissolved in $Et_2O$ (5 mL). The mixture was added to liquid ammonia (excess) at –78 °C under an Ar atmosphere. After stirring at –78 °C for 1 h, the mixture was warmed to rt. The reaction mixture was washed with $H_2O$ and brine. The combined organic layer was dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/EtOAc=20/1) to afford **8** (2.22 g, 94%) as a yellow oil.

**8:** IR (neat) 1589, 2860, 2932, 3262 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.19 (s, 12H), 0.97 (s, 18H), 2.18 (d, $J$ = 8.6 Hz, 1H), 2.72 (d, $J$ = 8.6 Hz, 1H), 6.39 (br s, 1H), 6.70 (br s, 2H); $^{13}C$ NMR (68 MHz, $CDCl_3$) δ –4.5, 18.2, 25.6, 58.1 (q, $J$ = 36.6 Hz), 113.1, 113.7, 123.5 (q, $J$ = 278.0 Hz, $CF_3$), 133.3, 156.8; FAB (*m*/*z*) 449 $(M+H)^+$, HRMS *m*/*z* calcd. for $C_{20}H_{36}F_3N_2O_2Si_2$; 449.2368 $(M+H)^+$, found: 449.2230.

**3-[3,5-Bis(*tert*-butyldimethylsilyloxy)phenyl]-3-(trifluoromethyl)-3*H*-diazirine (9).**

3-(3,5-Bis(*tert*-butyldimethylsilyloxy)phenyl)-3-(trifluoromethyl)diaziridine (**8**) (838 mg, 1.87 mmol) was dissolved in $CH_2Cl_2$ (5 mL) under an Ar atmosphere. Iodine (712 mg, 2.81 mmol) and $Et_3N$ (780 mL, 5.61 mmol) were added to the solution. After stirring at rt for 30 min, the reaction mixture was added to 1 M aq. NaOH (77 mL) and vigorously stirred for 5 min. Then the mixture was extracted with $CH_2Cl_2$, washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography (100% *n*-hexane) to afford **9** (815 mg, 97%) as a yellow oil.

**9:** IR (neat) 1443, 1585, 2860, 2932 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.18 (s, 12H), 0.96 (s, 18H), 6.22 (br s, 2H), 6.34 (br s, 1H); $^{13}C$ NMR (68 MHz, $CDCl_3$) δ -4.5, 18.2, 25.6, 29.4 (q, $J$ = 42.0 Hz), 111.5, 113.4, 122.1 (q, $J$ = 271.2 Hz, $CF_3$), 131.0, 157.1; FAB (*m*/*z*) 447 $(M+H)^+$, HRMS *m*/*z* calcd. for $C_{20}H_{34}F_3N_2O_2Si_2$; 447.2111 $(M+H)^+$, found: 447.2076.

**1-[2,6-Dihydroxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl]ethanone (1).**

3-(3,5-Bis(*tert*-butyldimethylsilyloxy)phenyl)-3-(trifluoromethyl)-3*H*-diazirine (**9**) (67 mg, 150 μL) was dissolved in $CH_2Cl_2$ under an Ar atmosphere. AcCl (13 μL, 180 μmol) and $AlCl_3$ (24 mg, 180 μmol) were

added to the mixture at 0 °C. After stirring at rt for 1 h, the reaction mixture was added to ice water and extracted with $CH_2Cl_2$. The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in THF (1 mL) under an Ar atmosphere. TBAF (1.0M solution in THF, 306 μL, 306 μmol) was added to the mixture at 0 °C. After stirring at rt for 15 min, the reaction mixture was added to satd. aq. $NH_4Cl$, and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/EtOAc=3/1) to afford **1** as yellow solids.

**1:** IR (neat) 1597, 1616, 1636, 2930, 3350 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 2.75 (s, 3H), 6.15 (s, 2H), 9.85 (s, 2H); $^{13}C$ NMR (68 MHz, $CDCl_3$) δ 28.1 (q, $J$ = 40.8 Hz), 33.5, 106.3, 110.4, 116.4, 121.6 (q, $J$ = 274.9 Hz, $CF_3$), 132.7, 137.2, 161.4, 205.2; FAB (*m/z*) 261 $(M+H)^+$, HRMS *m/z* calcd. for $C_{10}H_8F_3N_2O_3$; 261.0487 $(M+H)^+$, found: 261.0515.

**5-Hydroxy-2-phenyl-7-[3-(trifluoromethyl)-3*H*-diazirin-3-yl]chroman-4-one (2)**

1-(2,6-Dihydroxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)ethanone (**1**) (50 mg, 192 μmol) and $NaNH_2$ (45 mg, 1.15 mmol) were dissolved in THF (3 mL) under an Ar atmosphere. Benzaldehyde (20 μL, 192 μmol) was added to the mixture at 0 °C. After stirring at rt for 17 h, the reaction mixture was added to satd. aq. $NH_4Cl$, and extracted with $Et_2O$. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/EtOAc=2/1) to afford **2** (40 mg, 60%) as yellow solids.

**2:** IR (neat) 1674, 2922 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 2.92 (dd, $J$ = 3.0, 17.5 Hz, 1H), 3.16 (dd, $J$ = 13.0, 17.5 Hz, 1H), 5.47 (dd, $J$ = 3.0, 13.0 Hz, 1H), 6.28 (s, 1H), 6.32 (s, 1H), 7.45 (s, 5H), 11.7 (s, 1H); $^{13}C$ NMR (68 MHz, $CDCl_3$) δ 28.4 (q, $J$ = 40.8 Hz), 43.6, 79.5, 105.7, 107.5, 108.1, 121.6 (q, $J$ = 275.1 Hz, $CF_3$), 126.1, 129.2, 137.6, 139.4, 161.4, 162.0, 197.5; FAB (*m/z*) 349 $(M+H)^+$; HRMS *m/z* calcd. for $C_{17}H_{12}F_3N_2O_3$ 349.0800 $(M+H)^+$, found 349.0829.

## ACKNOWLEDGEMENTS

This work was financially supported by the 21st Century COE Program.

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‡ This paper is also dedicated to the memory of the late professor Kiyoshi Tanaka, who passed away on December 8, 2004.

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