# Stereoselective Synthesis of Methyl (*Z*)-(4,4-Difluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-ylidene)acetate Using a Dianion Horner–Wadsworth–Emmons Reagent

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**Stereoselective synthesis of methyl (*Z*)-(4,4-difluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-ylidene)acetate (1a) is described. *Z*-selectivity of the Horner–Wadsworth–Emmons (HWE) reaction was obtained based on an investigation of the reaction conditions for introduction of a methylidene group onto the 5-position of benzazepine.**

**Key words** arginine vasopressin antagonist; dianion; Horner–Wadsworth–Emmons reaction

Methyl (*Z*)-(4,4-difluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-ylidene)acetate (**1a**) is a useful intermediate for the synthesis of non-peptide arginine vasopressin (AVP) antagonists.[1)] For example, YM-35471 (**2**), a potent AVP antagonist, has been synthesized from key intermediate **1a**. However, an opposite geometrical isomer (**1b**) forms as a by-product when the methylidene group is introduced at the 5-position of benzazepine. Therefore, an improvement of the *Z*-selectivity in olefination is required for large-scale synthesis of this intermediate and for further studies of compound **2** (Fig. 1).

In a preceding paper,[1)] we tried to introduce the methylidene group at the 5-position of 1-(4-aminobenzoyl)-4,4-difluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-one (**3**) by a Horner–Wadsworth–Emmons (HWE) reaction[2,3)] or a Peterson reaction.[4)] However, at best the yield of the *Z*-isomer (**4a**) was only three times that of the *E*-isomer (**4b**) (Fig. 2). We have subsequently studied the HWE reaction further, since it showed better *Z*-selectivity than the Peterson reaction, using 4,4-difluoro-1-tosyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-one (**5**) as a substrate (Fig. 3), because it is a versatile intermediate for synthesis of compound **2**.

The general reaction pathway is shown in Chart 1. A mixture of compounds **8a**, **b** and **9a**, **b** were obtained by condensation of compound **5** and 1.2 eq of HWE reagents **6** and **7**, respectively. When the HWE reagents were prepared, the 2.4 and 1.2 eq of the bases were used for **6** and **7**, respectively. Subsequent removal of the tosyl group and esterification of **8a**, **b** with methanol in the presence of sulfuric acid afforded compounds **1a**, **b** in one step. The geometries of the two isomers **1a**, **b** were determined by NMR spectroscopy, based on nuclear Overhauser effect (NOE) difference spectra. As illustrated in Fig. 3, an NOE is observed between the hydrogen of the methylidene group and the hydrogen at the 6-position of the benzazepine ring in **1a**, while no NOE is observed in **1b**. The *Z*/*E* ratio of the two isomers was determined by HPLC analysis just after completion of the reaction, and by HPLC and $^1$H-NMR after purification by crystallization. For the $^1$H-

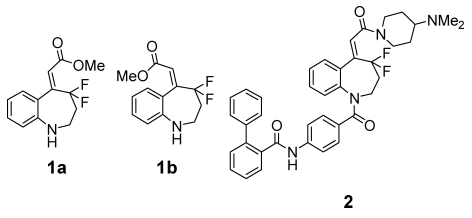


Fig. 1

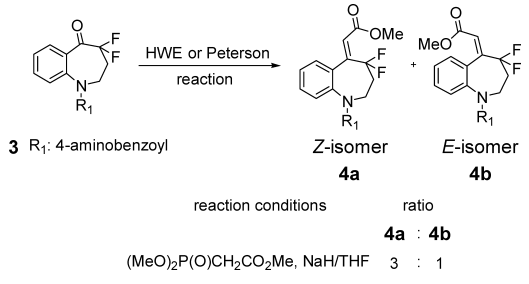


Fig. 2

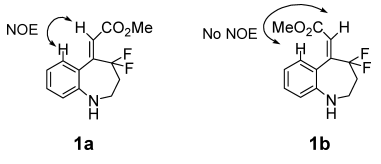


Fig. 3

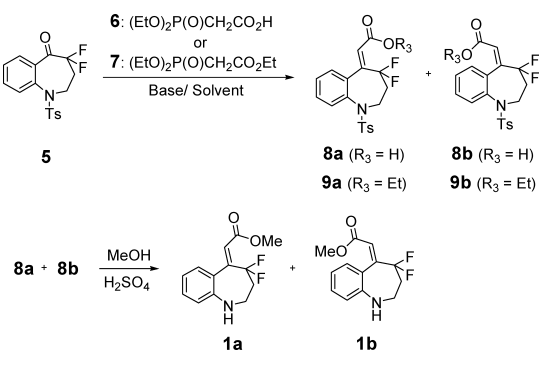


Chart 1

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Table 1. *Z*/*E* Ratio of the HWE Reaction for Compound **5**

| No. | Reagent | Base[a)] | Solvent[b)] | Ratio[c)] *Z* : *E* |
|---|---|---|---|---|
| 1 | **7** | NaH | THF | 0.5 : 1 |
| 2 | **6** | NaH | THF | 3.6 : 1 |
| 3 | **6** | LDA | THF | 3.9 : 1 |
| 4 | **6** | *n*-BuLi | THF | 3.9 : 1 |
| 5 | **6** | LiHMDS | THF | 3.5 : 1 |
| 6 | **6** | KHMDS | THF | 4.7 : 1 |
| 7 | **6** | NaHMDS | THF | 9.7 : 1 |
| 8 | **6** | NaH | DMF | 2.3 : 1 |
| 9 | **6** | LiHMDS | DMF | 2.6 : 1 |
| 10 | **6** | KHMDS | DMF | 6.7 : 1 |
| 11 | **6** | NaHMDS | DMF | 8.0 : 1 |

*a*) LDA; lithium diisopropylamide, *n*-BuLi, *n*-butyllithium, HMDS; hexamethyldisilazide. *b*) THF; tetrahydrofuran, DMF; *N*,*N*-dimethylformamide. *c*) The *Z*/*E* ratio of the two isomers was determined by HPLC analysis just after completion of the reaction.

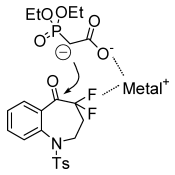


Fig. 4

NMR analysis, the intensity of the $^1$H-NMR signal at the methylidene position was used as a measure of the isomer ratio.

The *Z*/*E* ratio of the crude products after the reaction is summarized in Table 1. The HWE reagent prepared from ethyl diethylphosphonoacetate (**7**) gave the *E*-isomer preferentially (Reaction No. 1, Table 1). However, the reaction using a dianion HWE reagent (prepared from diethylphosphonoacetic acid (**6**) proceeded with *Z*-selectivity (No. 2), in contrast to the same kind of reaction with a monoanion HWE reagent (No. 1).[5] An approximately 7.2-fold increase in *Z*-selectivity was observed using the dianion HWE reagent. On the basis of these results, we postulated that interaction between a fluorine atom and the HWE reagent through the alkaline metal facilitates formation of the *Z*-isomer, as shown in Fig. 4.

Stereoselectivity can be controlled by interactions between an alkaline metal and a fluorine atom in organic fluorine compounds,[6,7] and such phenomena are commonly observed between organic fluorine compounds and bases containing Li as the alkaline metal. Thus, we investigated the HWE reaction using bases containing Li (Reactions Nos. 3—5, Table 1). These reagents exhibited a similar *Z*-selectivity to that of NaH (No. 2), and further improvement in selectivity was not observed. However, the *Z*-selectivity was significantly increased through use of KHMDS and NaHMDS as bases (Reaction Nos. 6, 7, Table 1). In particular, the HWE reaction using NaHMDS in THF (No. 7) gave the best results (*Z* : *E*=9.7 : 1). Moreover, a comparison of solvents showed that stereoselectivity for the *Z*-isomer in THF (Nos. 2—7) was better than that in DMF (Nos. 8—11). Consequently, an approximately 19-fold improvement in the *Z*/*E* ratio was achieved through optimization of the HWE reagent, base and solvent.

The minor (*E*)-isomer (**1b**) was removed effectively by means of extraction after completion of the reaction. As a result, the key intermediate (**1a**) was obtained in a practically pure form (*Z* : *E*=50 : 1). Hence, we were able to obtain methyl (*Z*)-(4,4-difluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-ylidene)acetate (**1a**) stereoselectively using a dianion HWE reagent. This method may be useful for synthesis of **1a** as an intermediate in the synthesis of AVP receptor antagonists.

## Experimental

$^1$H- and $^{13}$C-NMR spectra were obtained on a JNM-400 spectrometer. Chemical shifts are expressed in $\delta$ (ppm) values with tetramethylsilane as the internal standard. Abbreviations of $^1$H-NMR signal patterns are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. Mass spectra were obtained on a JEOL JMS-DX300 spectrometer.

**General Procedure for Synthesis of (*Z*)-(4,4-Difluoro-1-tosyl-1,2,3,4-tetrahydro-1*H*-1-benzazepin-5-ylidene)acetic Acid (8a) and (*E*)-(4,4-Difluoro-1-tosyl-1,2,3,4-tetrahydro-1*H*-1-benzazepin-5-ylidene)acetic Acid (8b)** A solution of sodium hexamethyldisilazide (6.6 ml of a 1 M solution in tetrahydrofuran; THF, 6.6 mmol) was added dropwise to a solution of diethylphosphonoacetic acid (670 mg, 3.42 mmol) in THF (5 ml) at −60 °C, and the mixture was stirred at −60 °C for 2 h under an Ar atmosphere. 4,4-Difluoro-1-tosyl-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one (**5**)[1] (1.00 g, 2.85 mmol) in THF (10 ml) was added dropwise and the temperature of the mixture was increased slowly to 0 °C for 20 h (**8a** : **8b**=9.7 : 1). The reaction mixture was diluted with ethyl acetate (AcOEt, 50 ml) and brine (50 ml), and then extracted with $H_2O$ (50 ml×2). The aqueous layer was washed with AcOEt (50 ml×4) and acidified with 1 M HCl (50 ml) at 4 °C. The mixture was extracted with AcOEt (50 ml×2) and the organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from ethanol to afford the title compound as a crystal (685 mg, 1.74 mmol, 61% yield, **8a** : **8b**=50 : 1). $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.50 (3H, s), 3.34 (2H, br), 3.85 (2H, br), 5.82 (1H, s), 7.26—7.33 (4H, m), 7.39—7.46 (2H, m), 7.52 (2H, d, *J*=7 Hz), 12.99 (1H, br). $^{13}$C-NMR (DMSO-$d_6$) $\delta$: 20.9 (s), 36.7 (t), 38.8 (s), 39.6 (s), 44.7 (s), 119.9 (t), 126.6 (s), 126.9 (s), 128.7 (s), 128.9 (s), 129.5 (s), 129.8 (s), 129.9 (s), 135.1 (s), 136.6 (s), 137.0 (s), 139.4 (t), 143.5 (s), 166.1 (s). FAB-MS *m*/*z*: 392 $[M-H]^-$.

**Methyl (*Z*)-(4,4-Difluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-ylidene)acetate (1a) and Methyl (*E*)-(4,4-Difluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-ylidene)acetate (1b)** The mixture of **8a**, **b** (1.01 g, 2.57 mmol) and concentrated $H_2SO_4$ (2.05 ml) was stirred at room temperature for 14 h, and then stirred at 80 °C for 4.5 h. After cooling to room temperature, methanol (1.5 ml) was added dropwise, and the mixture was stirred at 80 °C for 3 h. The reaction mixture was diluted with $CHCl_3$ (15 ml) and alkalinized with 17% NaOH aqueous solution at 4 °C. The organic layer was washed with brine (10 ml×3), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column using hexane–AcOEt (4 : 1) as the eluent to give 37 mg (0.15 mmol, 6%) of **1b** as a colorless amorphous substance. $^1$H-NMR ($CDCl_3$) $\delta$: 2.52—2.63 (2H, m), 3.41 (2H, t, *J*=7 Hz), 3.80 (3H, s), 6.17 (1H, s), 6.60 (1H, d, *J*=7 Hz), 6.81 (1H, t, *J*=7 Hz), 7.14 (1H, t, *J*=7 Hz), 7.21 (1H, d, *J*=7 Hz), 7.25 (1H, s). FAB-MS *m*/*z*: 254 $[M+H]^+$.

Further elution yielded 311 mg (1.23 mmol, 48%) of **1a** as a colorless amorphous substance. $^1$H-NMR ($CDCl_3$) $\delta$: 2.52—2.62 (2H, m), 3.42 (2H, t, *J*=7 Hz), 3.80 (3H, s), 5.82 (1H, s), 6.60 (1H, d, *J*=7 Hz), 6.81 (1H, d, *J*=7 Hz), 7.14 (1H, t, *J*=7 Hz), 7.21 (1H, d, *J*=7 Hz), 7.25 (1H, s). $^{13}$C-NMR ($CDCl_3$) $\delta$: 39.7 (s), 41.4 (t), 51.7 (s), 116.5 (s), 117.3 (s), 119.8 (s), 120.8 (s), 122.5 (t), 129.4 (s), 129.5 (s), 143.8 (t), 147.9 (s), 166.4 (s). FAB-MS *m*/*z*: 254 $[M+H]^+$.

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