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One-pot Synthesis of 2,3-Benzodiazepines from Arynes and β-Diketones

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Novel one-pot synthesis of 2,3-benzodiazepines from aryne precursors was accomplished. Tofisopam, well-known anxiolytics, could be synthesized via C–C bond insertion of 4,5-dimethoxybenzyne with 2-ethyl-1-(3,4-dimethoxyphenyl)-butane-1,3-dione, followed by the reaction with hydrazine hydrate in a one-pot operation. This protocol is applicable to the synthesis of other biologically active 2,3-benzodiazepines, such as Girisopam and Nerisopam.

Synthesis of 2,3-benzodiazepines **1** was first aimed at finding active papaverine-related derivatives with cardiovascular activity. These substances act as tranquillizing agents, and they show no muscle-relaxant and anticonvulsant character in rodents.[1] The most active derivative, Tofisopam (Grandaxin1) (**1a**) was found to be a highly active nonsedative, anxiolytic in humans.[2] Other 2,3-benzodiazepines such as Girisopam (**1b**) and Nerisopam (**1c**) were also found to be biologically active (Figure 1).

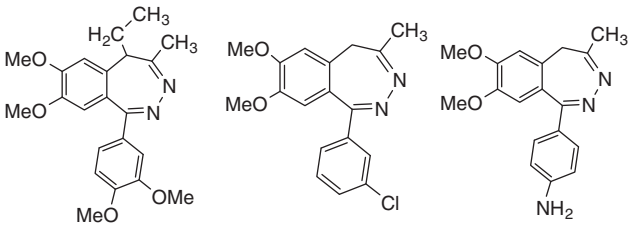


Figure 1.

These 2,3-benzodiazepines were generally synthesized by four-step reactions starting from arylacetones or arylethanols.[3] Although synthesis of 1,4-dimethyl-2,3,4,5-tetrahydro-(1*H*)-1,4-benzodiazepin-5-one by reaction of benzyne prepared from *o*-trimethylsilylphenyl triflate **2** and KF with 1,3-dimethyl-2-imidazolidinone was reported by Yoshida et al., there is no report on the straightforward synthesis of 2,3-benzodiazepines **1**.[4] Recently, we have reported the direct synthesis of 4-substituted 2-naphthols by the reaction of benzyne with 1,3-diketones, intermediates of which were 2-acetylmethylbenzophenones.[5] Given our interest in the synthesis of nitrogen-containing heterocycles,[6] we speculated on the possibility of a short-step synthesis of 2,3-benzodiazepines such as **1a**, **1b**, and **1c** from arynes as shown in Figure 2. Herein, we report the one-pot synthesis of 2,3-benzodiazepines **1** by sequential two-step reaction starting from 2-trimethylsilylphenyl triflates **2** and aroylacetones **3**.

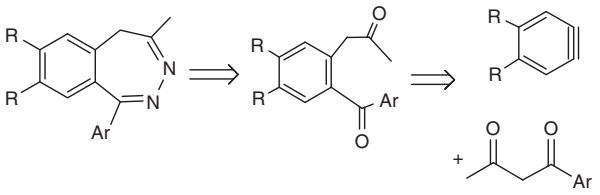
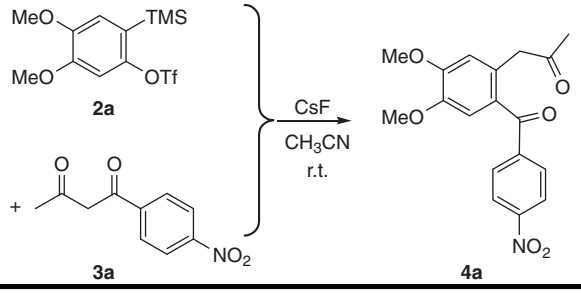


Figure 2.

We first attempted the reaction of 4,5-dimethoxy-2-trimethylsilylphenyl triflate (**2a**) with 4-nitrobenzoylacetone (**3a**)[7] in the presence of CsF in acetonitrile to optimize the reaction conditions. Treatment of **2a** with **3a** in the presence of CsF in acetonitrile at rt resulted in the formation of 2-acetylmethyl-4,5-dimethoxy-4′-nitrobenzophenone (**4a**) in 21% yield (Table 1, Entry 1). The results are shown in Table 1.

Table 1. Reaction of **2a** with *p*-nitrobenzoylacetone (**3a**)



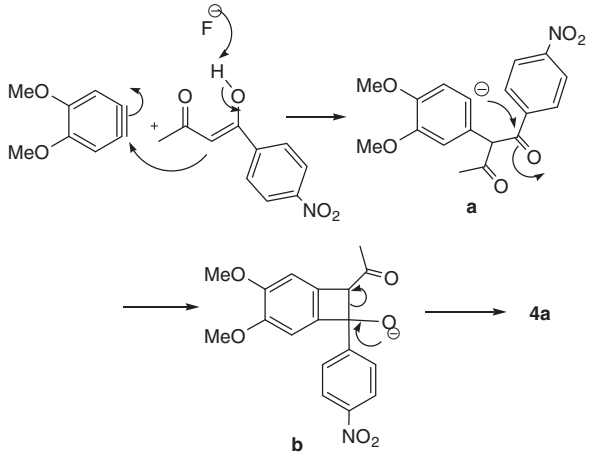
Entry	**2** /equiv	Temp /°C	Time /h	Product **4a** /%
1	0.7	rt	18	21
2	1.1	rt	15	32
3	1.1	40	8	43
4	1.7	rt	10	61
5	1.7	40	6	56
6	2.0	rt	10	52

When 1.1 equiv of **2a** was treated with **3a** at rt for 15 h, **4a** was obtained in 32% yield (Entry 2). When the reaction was carried out at 40 °C, **4a** was obtained in 43% yield (Entry 3). When 1.7 equiv of **2a** was reacted with **3a** at rt, **4a** was obtained in 61% yield,[8] whereas elevated temperature resulted in the formation of **4a** in 56% yield (Entries 4 and 5). Using excess amount of **2a** resulted in the formation of less amount of **4a** (Entry 6).

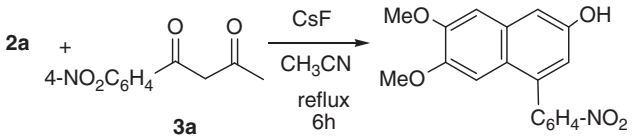
The reaction would proceed as follows: fluoride-induced enolate attacked aryne to give the corresponding anion **a**, which intramolecularly attacked aroyl carbonyl carbon to give four-membered intermediate **b**. Ring-opening of the intermediate **b** gave ortho-substituted benzophenone **4a** (Scheme 1).

When the reaction was carried out in refluxing acetonitrile, an intramolecular aldol reaction followed by dehydration proceeded to give 6,7-dimethoxy-4-(4-nitrophenyl)-2-naphthol (**5a**) in 52% yield (Scheme 2).

Since the optimum conditions were obtained (rt, 1.7 equiv of **2a**, 10 h), we then tried the synthesis of other 2-(acetylmethyl)-benzophenones **4**. Treatment of **2a** with 3-chlorobenzoylacetone



Scheme 1.



Scheme 2.

Table 2. Reaction of **2** with benzoylacetones **3**

2a: R= OMe
2b: R= Me
2c: R= -OCH_2O-
2d: R= F

3a: Ar= 4-$NO_2C_6H_4$
3b: Ar= 3-ClC_6H_4

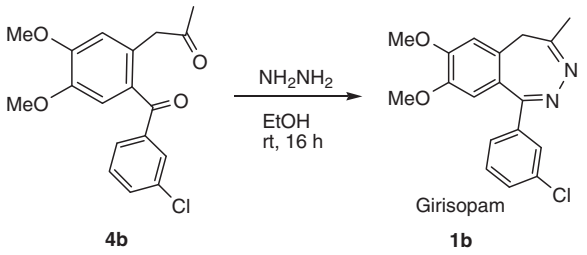
4a: R= OMe, Ar= 4-$NO_2C_6H_4$
4b: R= OMe, Ar= 3-ClC_6H_4
4c: R= Me, Ar= 4-$NO_2C_6H_4$
4d: R= -OCH_2O-, Ar= 4-$NO_2C_6H_4$
4e: R= F, Ar= 4-$NO_2C_6H_4$
4f: R= F, Ar= 3-ClC_6H_4

Entry	2	3	4	Product yield/%
1	**2a**	**3a**	**4a**	61
2	**2a**	**3b**	**4b**	63[a]
3	**2b**	**3a**	**4c**	51
4	**2c**	**3a**	**4d**	41
5	**2d**	**3a**	**4e**	42
6	**2d**	**3b**	**4f**	56

[a]Less than 10% of 3-(3-chlorophenyl)-3-hydroxy-6,7-dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one was obtained as a side product.

(**3b**) and CsF resulted in the formation of 2-acetylmethyl-4,5-dimethoxy-3′-chlorobenzophenone (**4b**) in 63% yield. By using substituted triflates **2a**–**2d**, other benzophenones **4** were synthesized in moderate yields (Table 2).

To confirm that the present method provides a general short-step synthesis of 2,3-benzodiazepines, we then tried the reaction of **4b** with hydrazine hydrate in ethanol. As expected, Girisopam (**1b**) was obtained in 65% yield (Scheme 3). Crystals suitable for X-ray diffraction were obtained from ethanol. ORTEP drawing of **1b** was shown in Figure 3.[9]



Scheme 3.

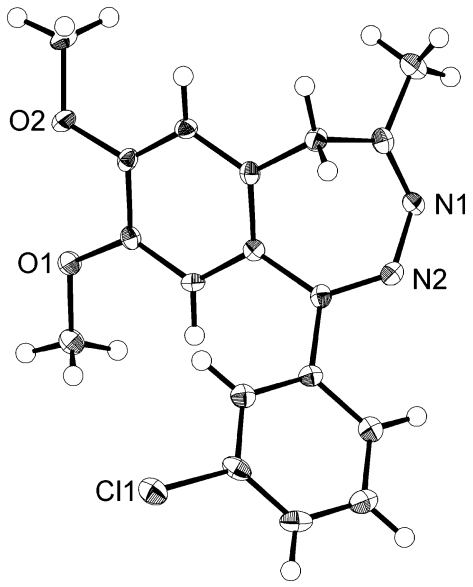
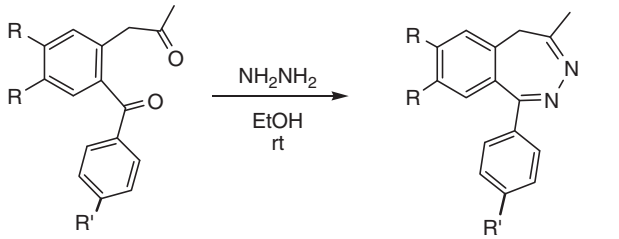


Figure 3. ORTEP drawing of Girisopam (**1b**).

Table 3. Synthesis of 2,3-benzodiazepines **1**



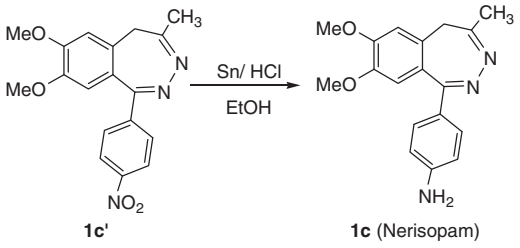
4a: R= OMe, R'= NO_2
4c: R= Me, R'= NO_2
4d: R= -OCH_2O-, R'= NO_2

1c': R= OMe, R'= NO_2
1d : R= Me, R'= NO_2
1e : R= -OCH_2O-, R'= NO_2

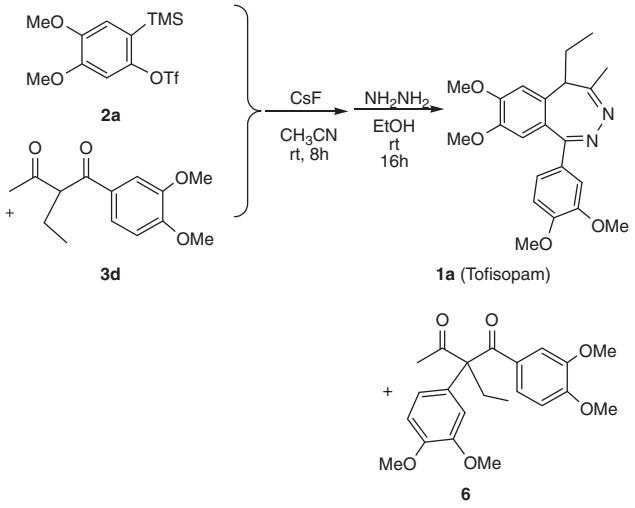
Entry	4	Benzodiazepine 1	Yield /%
1	**4b**	**1c′**	60
2	**4d**	**1d**	43
3	**4e**	**1e**	43

Other benzodiazepines were synthesized in a similar manner (Table 3). Reduction of **1c′** with Sn/HCl gave Nerisopam **1c** in 65% yield (Scheme 4).

We finally tried the one-pot synthesis of Tofisopam (**1a**) known as Grandaxin, which was previously synthesized by four-step reactions starting from 1-(3,4-dimethoxyphenyl)-1,3-dibromobutane.[10] Treatment of 2-ethyl-1-(3,4-dimethoxyphenyl)-1,3-



Scheme 4.



Scheme 5.

butanedione (**3d**) with triflate **2a** in the presence of CsF at 60 °C for 10 h, followed by the addition of hydrazine hydrate in refluxing EtOH resulted in the formation of Tofisopam **1a** and diketone **6** in 45 and 22% yields, respectively. Girisopam **1b** was also synthesized in a similar manner (48%) (Scheme 5).

Thus, we have successfully developed the one-pot synthesis of 2,3-benzodiazepines via a completely different strategy from aryne precursors. This one-pot synthesis would provide a wide variety of biologically active 2,3-benzodiazepine derivatives.

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8 Typical reaction: To a solution of 4-nitrobenzoylacetone (**3a**) (0.30 mmol) and CsF (1.50 mmol) in acetonitrile (3 mL) was added triflate **2a** (0.51 mmol) in acetonitrile (2 mL).[9] After being stirred for 15 h at rt, 5 mL of water was added to the reaction mixture and the mixture was concentrated to 6 mL, extracted with dichloromethane (5 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give brown oil, which was chromatographed over silica gel by elution with hexane–ethyl acetate (3:1) to afford 2-acetylmethyl-4,5-dimethoxy-4′-nitrobenzophenone (**4a**) (0.18 mmol). **4a**: pale yellow solid. Mp 157–159 °C. ^{1}H NMR ($CDCl_3$): δ 2.25 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.02 (s, 2H, CH_2), 6.75 (s, 1H, Ar), 6.85 (s, 1H, Ar), 7.92 (d, 2H, $J = 8.4$ Hz, Ar), 8.31 (d, 2H, $J = 8.4$ Hz, Ar). ^{13}C NMR ($CDCl_3$): δ 30.13 (CH_3), 48.43 (CH_2), 56.35 (OCH_3), 56.42 (OCH_3), 114.68, 115.34, 123.70, 128.54, 130.27, 131.03, 144.18, 147.13, 150.06, 152.28 (Ar), 195.51 (C=O), 205.76 (C=O). Anal. Calcd for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99; N, 4.08%. Found; C, 62.89; H, 4.91; N, 4.20%.

9 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

10 Compound **1b**: Mo Kα radiation, monoclinic, $P2_1/n$, $a = 9.978(5)$ Å, $b = 5.761(3)$ Å, $c = 27.575(14)$ Å, $\alpha = 90°$, $\beta = 99.238(6)°$, $\gamma = 90.00°$. $Z = 4$, 10377 measured reflections, 3059 independent reflections, $R1 = 0.0609$, $wR2 = 0.1166$. Crystallographic data for **1b** have been deposited with Cambridge Crytallographic Data Centre as supplementary publication No. CCDC 943505. Copies of the data can be obtained free of charge via http://www.ccdc.ac.uk/conts/retreving.html.

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