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Synthesis of 2,3-Benzodiazepines and 2,3-Benzodiazepin-4-ones from Arynes and β-Diketones

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Abstract: 2,3-Benzodiazepines were synthesized by two step or one-pot reactions from aryne precursors. Reaction of 2-(trimethylsilyl)aryl triflates with β-diketones in the presence of CsF gave ortho-substituted benzophenones. Treatment of benzophenones with hydrazine hydrate resulted in the formation of 2,3-benzodiazepines in moderate yields. Tofisopam, well known anxiolytics, could be synthesized via C-C bond insertion of 3,4-dimethoxybenzyne with 2-ethyl-1-(3,4-dimethoxyphenyl)butane-1,3-dione, followed by the reaction with hydrazine hydrate in one pot operation. 2,3-Benzodiazepin-4-ones were also synthesized by the reaction of β-keto esters with triflates in the presence of CsF, followed by the addition of hydrazine hydrate. Substituted isoquinolines were synthesized by the reaction of ortho substituted benzophenones with ammonium hydroxide.

Introduction

Arynes are highly reactive intermediates that have been widely used in organic synthesis.[1] Reaction of aryne with β-keto compounds provides a useful tool on the

synthesis of *ortho*-substituted ketones via carbon-carbon insertion reaction.[2] Benzodiazepines have received considerable attention in recent times because of their psychoactive ability.[3] Especially, 2,3-benzodiazepines (**1**) act as tranquillizing agents without any muscle relaxant and anti convulsant character in rodents.[4] Synthesis of 2,3-benzodiazepines **1** was firstly aimed at finding active papaveine-related derivatives with cardiovascular activity. The most active derivative, Tofisopam (Grandaxin) **1a** was found to be a highly active non-sedative, anxiolytic in humans.[5] Other 2,3-benzodiazepines and 2,3-benzodiazepin-3-ones such as Girisopam, Nerisopam, and BDZ-2 were also found to be biologically active (Figure 1).[6]

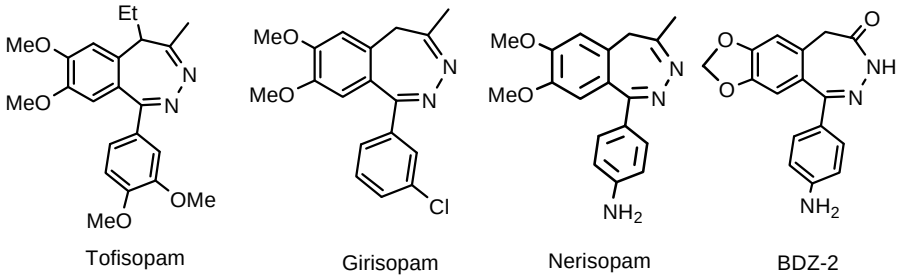


Figure 1. Biologically active 2,3-benzodiazepines

These 2,3-benzodiazepines were previously synthesized by four-step reactions starting from arylacetones or arylethanols.[7] Recently, we have reported the synthesis of 4-aryl-2-naphthols by the reaction of 2-(trimethylsilyl)phenyl triflate (**2**) with *β*-diketones and CsF via intramolecular cyclization.[8] Given our interest in the synthesis of nitrogen-containing heterocycles,[9] we speculated on the possibility of a short step synthesis of 2,3-benzodiazepines and communicated the synthesis of 2,3-benzodiazepines starting from 2-(trimethylsilyl)aryl triflates **2**, aroylacetones (**3**), and hydrazine hydrate.[10] The advantage of this method include short step reaction, commercial availability of starting materials (triflates, β-diketones, and β-ketoesters), and the possibility of one-pot synthesis. Herein, we report the full details of one-pot

synthesis of 2,3-benzodiazepines and 2,3-benzodiazepin-4-ones such as Tofisopam, Girisopam and Girisopam derivatives starting from triflates **2**, aroylacetones **3**, and β-ketoesters as shown in Figure 2.

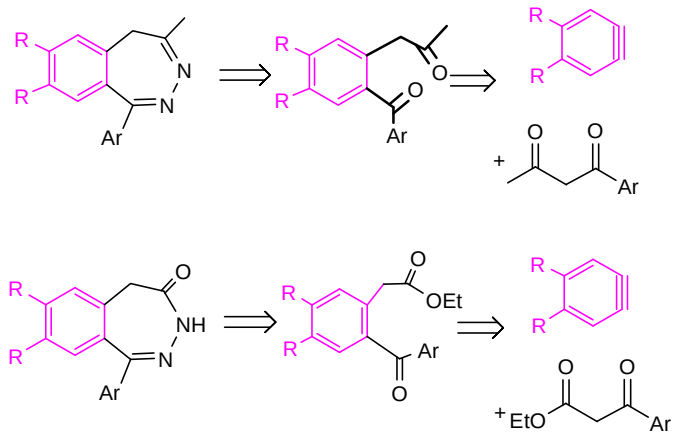


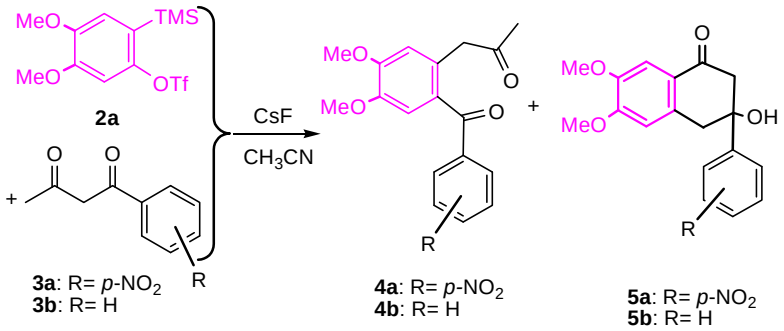
Figure 2. Retrosynthetic analysis of 2,3-benzodiazepines

Results and Discussion

Synthesis of ortho-substituted acetophenones

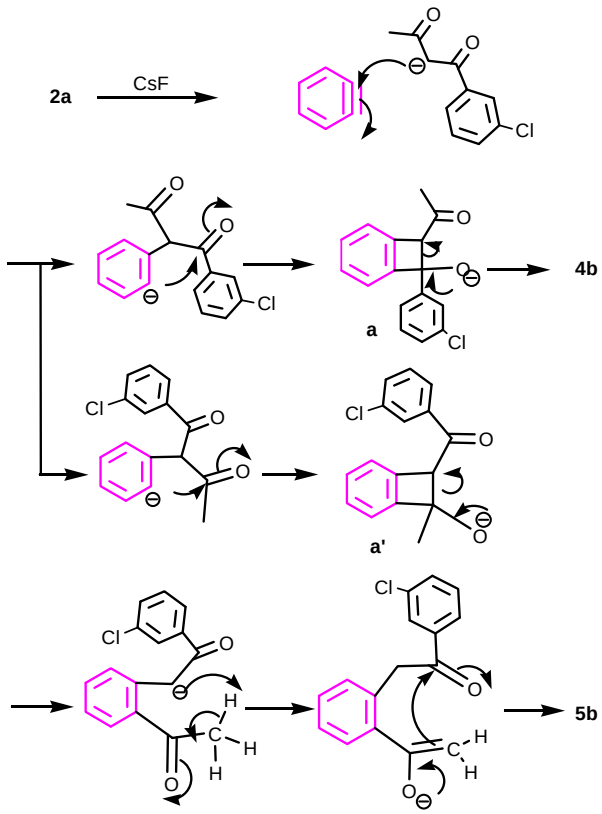
To standardize the reaction conditions, a series of experiments were performed under varying reaction parameters, such as time and temperature for a representative reaction of 4,5-dimethoxy-2-trimethylsilylphenyl triflate (**2a**). Treatment of **2a** with 4-nitrobenzoylacetone **3a** in the presence of CsF in acetonitrile at rt for 18 h resulted in the formation of 2-acetylmethylbenzophenone (**4a)** in 21% yield (Table 1, Entry 1). The results are shown in Table 1.

Table 1. Reaction of 2a with benzoylacetone 3a and 3b



Entry	**2a** (equiv)	**3a** or **3b**	Temp (°C)	Time (h)	Products **4**	(%)	**5**	(%)
1	0.7	**3a**	rt	18	**4a**	21	**5a**	0
2	1.1	**3a**	rt	12	**4a**	32	**5a**	0
3	1.1	**3a**	40	8	**4a**	43	**5a**	0
4	1.7	**3a**	rt	8	**4a**	63	**5a**	0
5	1.7	**3a**	40	8	**4a**	56	**5a**	0
6	1.7	**3b**	rt	8	**4b**	61	**5b**	8

When 1.1 equiv. of **2a** was treated with **3a** at rt for 12 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 63% yield, whereas elevated temperature resulted in the formation of **4a** in 56% yield (Entries 4 and 5). When **3b** was used as a substrate, **4b** was obtained in 61% along with **5b** (8%, Entry 6), which might be formed via intramolecular aldol condensation of regioisomer (**a'**) as shown in Scheme 1.

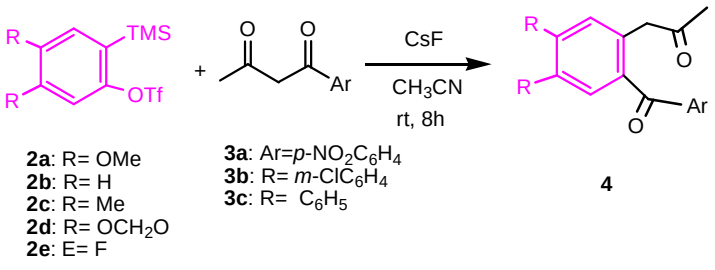


Scheme 1. Formation mechanism of 4b and 5b from triflate 2a and diketone 3b.

Since the optimum conditions were obtained (rt, 1.7 eq of **2**, 8 h), we then tried the synthesis of other 2-acetylmethylbenzophenones **4**. Treatment of **2b** with 4-nitrobenzoylacetone **3a** and CsF resulted in the formation of 2-acetylmethyl-4,5-dimethoxybenzophenone **4c** in 42% yield. By using substituted triflates **2a-2e**, other benzophenones **4a-4h** were synthesized in moderate yields (Table 2).

Table 2. Synthesis of compounds 4 from 2, 3, and CsF.

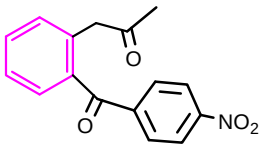
Table 2.



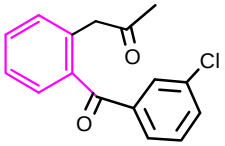
2a: R= OMe
2b: R= H
2c: R= Me
2d: R= OCH_2O
2e: E= F

3a: Ar=*p*-$NO_2C_6H_4$
3b: R= *m*-ClC_6H_4
3c: R= C_6H_5

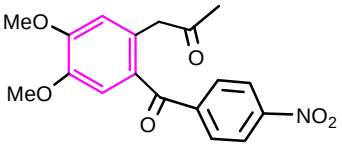
4



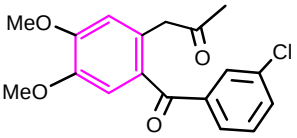
4a 63%



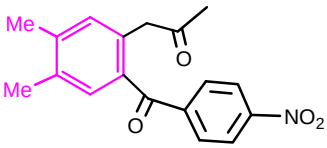
4b 51%



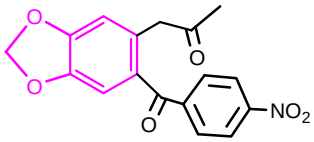
4c 42%



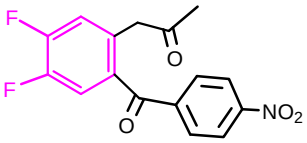
4d 42%



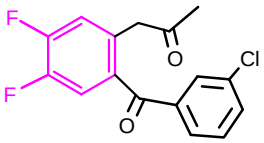
4e 41%



4f 41%



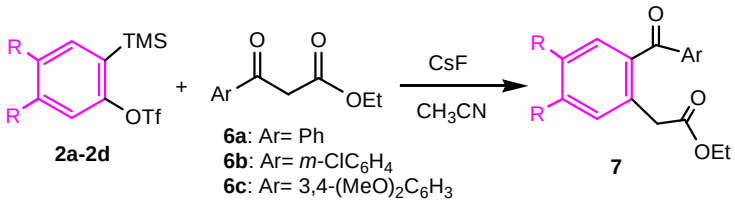
4g 42%



4h 56%

Similarly, CsF mediated reaction of β-ketoesters (**6**) with triflates **2**, following the conditions reported by Stoltz et al.,[2] afforded the 2-aroylarylacetate esters (**7**). (Table 3.) Yields were better than those using aroylacetones **3** as substrates due to regioselective addition to the aroyl carbons of β-ketoesters (Table 1).

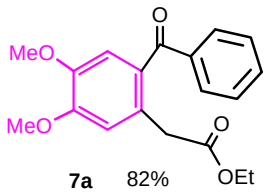
Table 3. Synthesis of ethyl 2-aroylarylacetates 7 from 2,6, and CsF.



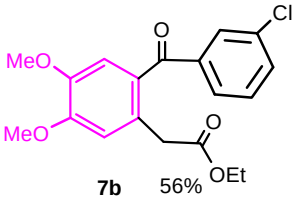
2a-2d

6a: Ar= Ph
6b: Ar= *m*-ClC_6H_4
6c: Ar= 3,4-$(MeO)_2C_6H_3$

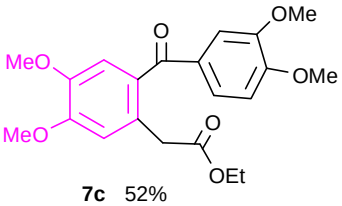
7



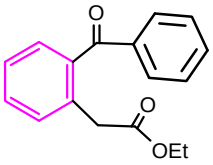
7a 82%



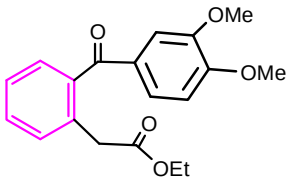
7b 56%



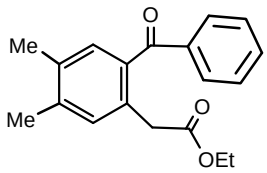
7c 52%



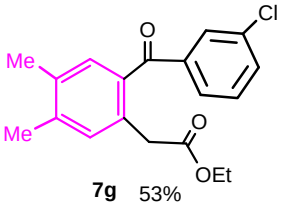
7d quant.



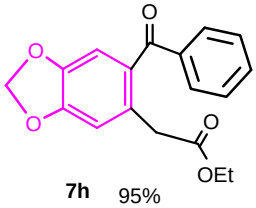
7e 56%



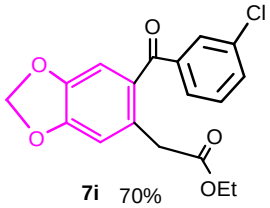
7f 47%



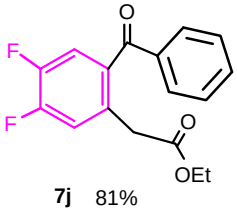
7g 53%



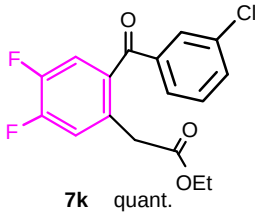
7h 95%



7i 70%



7j 81%

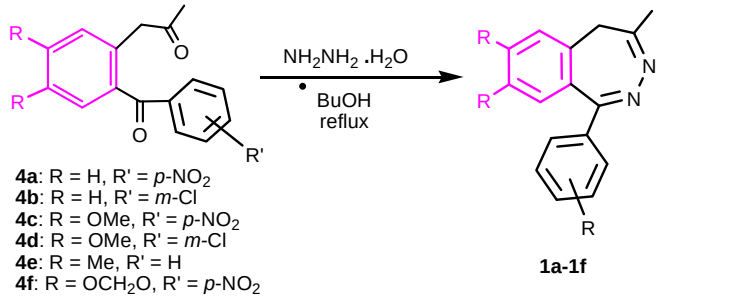


7k quant.

Reaction of ortho-substituted benzophenones with hydrazone

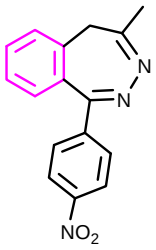
To confirm the present method provides a general short-step synthesis of 2,3-benzodiazepines, reaction of **4a** with hydrazine hydrate in refluxing butanol was tried. As expected, benzodiazepine **1a** was obtained in 63% yield. Other diazepines **1b-1f** were synthesized in moderate yields (Table 3).

Table 4. Synthesis of benzodiazepines

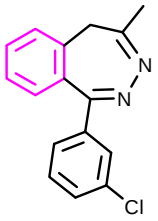


4a: R = H, R' = *p*-NO_2
4b: R = H, R' = *m*-Cl
4c: R = OMe, R' = *p*-NO_2
4d: R = OMe, R' = *m*-Cl
4e: R = Me, R' = H
4f: R = OCH_2O, R' = *p*-NO_2

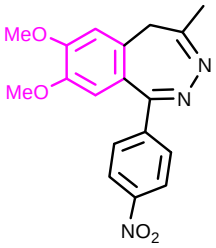
1a-1f



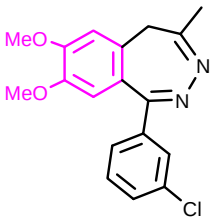
1a 32%



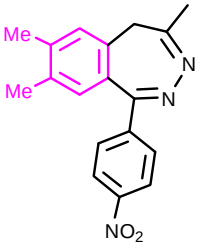
1b 45%



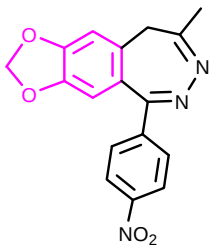
1c 63%



1d 65%

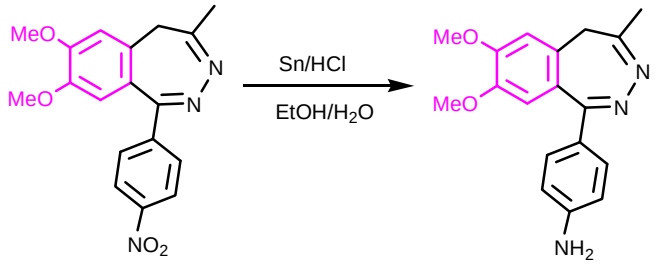


1e 43%



1f 55%

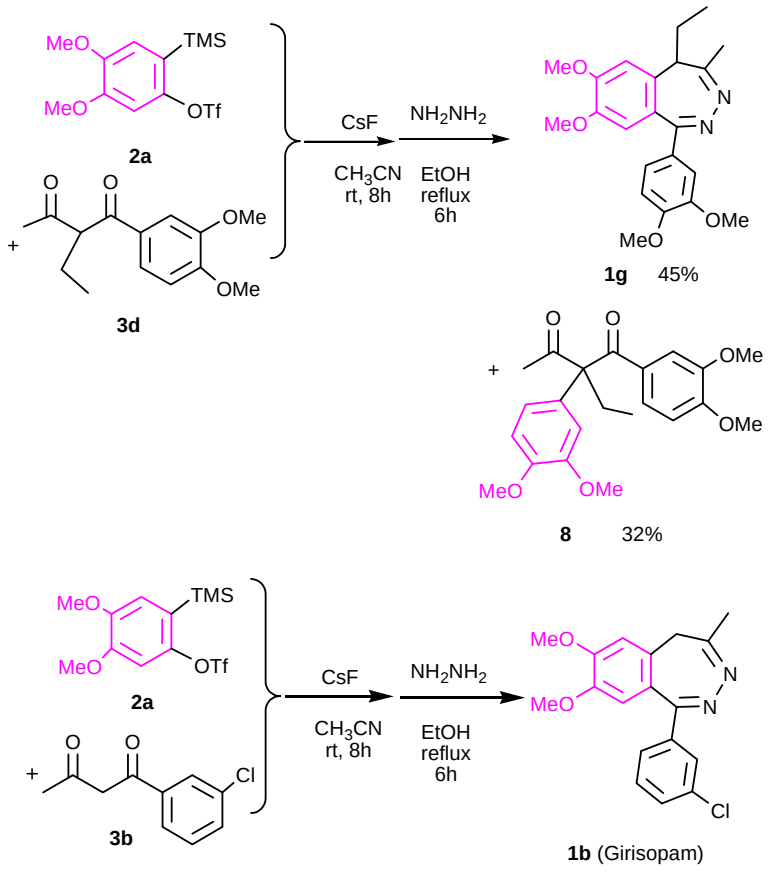
Nerisopam (**1c'**) has also shown anxiolytic and neuroleptic activity in animal studies,[4] which could be easily synthesized by reduction of **1c** by Sn/HCl in 86% yield (Scheme 2).



1c **1c'** (Nerisopam)

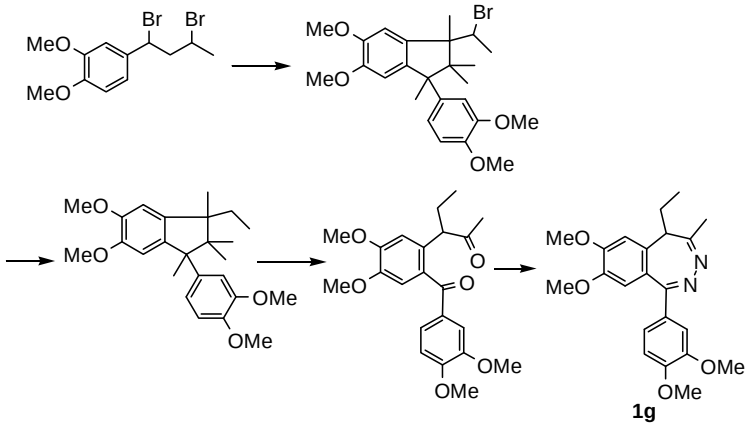
Scheme 2. Synthesis of Nerisopam 1c'.

Since our method provides a short-step synthesis of benzodiazepines, we have tried the preparation of Tofisopam (**1g**) in one-pot operation. Treatment of triflate **2a** with 2-ethyl-1-(3,4-dimethoxyphenyl)butane-1,3-dione (**3d**) in the presence of CsF for 8 h followed by the addition of hydrazine hydrate in refluxing EtOH resulted in the formation of Tofisopam **1g** and 2-ethyl-1,2-bis(3,4-dimethoxyphenyl)butane-1,3-dione (**8**) in 45% and 32% yields, respectively. Similarly, Girisopam **1b** was synthesized in one-pot operation (33%) (Scheme 3).



Scheme 3. Synthesis of Tofisopam 1g and Girisopam 1b.

Previously, Müllar et al. synthesized Tofisopam **1g** starting from 1-(3,4-dimethoxyphenyl)-1,3-dibromobutane via four-step reaction (Scheme 4).[11] Thus, the present method provides a versatile synthesis of benzodiazepines in one-pot operation.

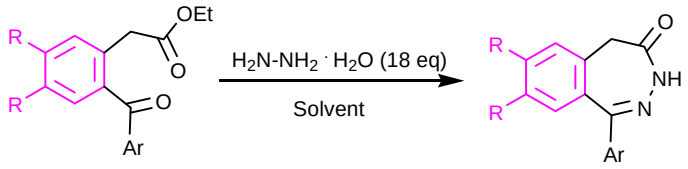


Scheme 4. Reported synthesis of Tofisopam 1g

Synthesis of 2,3-benzodiazepin-4-ones

Since 2,3-benzodiazepin-4-ones (**9**) were generally synthesized from substituted arylacetic acid via 4 step reactions,[6] we have tried the two-step synthesis of **9** from aryne precursors. First step was already shown in Table 3, thus, the reaction of ethyl 2-aroylphenylacetate **7** with hydrazine hydrate was tried. Treatment of aroylacetate ester **7a** with hydrazine hydrate in refluxing butanol for 8 h resulted in the formation of 2,3-benzodiazepin-4-one **9a** in 83% yield. As shown in Table 5, other reaction of ethyl aroylacetates**7b-7g** with hydrazine hydrate gave the corresponding 2,3-benzodiazepin-4-ones **9** in 53-83% yields.

Table 5. Synthesis of 2,3-benzodiazepine-4-ones.



7 **9**

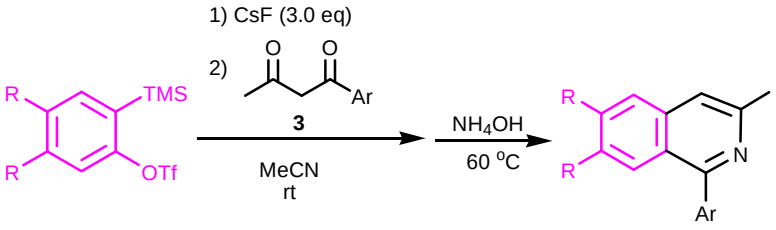
7	R	Ar	Solv.	Temp./°C	**9**	Yield/%
7a	MeO	C_6H_5	BuOH	reflux	**9a**	83
7b	MeO	*m*-ClC_6H_4	BuOH	reflux	**9b**	53
7c	H	3,4-$(MeO)_2C_6H_3$	EG	160	**9c**	60
7d	Me	*m*-ClC_6H_4	EG	160	**9d**	72
7e	-OCH_2O-	C_6H_5	BuOH	reflux	**9e**	59
7f	-OCH_2O-	*m*-ClC_6H_4	BuOH	reflux	**9f**	60
7g	F	C_6H_5	BuOH	reflux	**9g**	29

Synthesis of substituted isoquinolines

Since Stoltz et al. synthesized one-pot synthesis of 3-hydroxyisoquinolines from aryne precursors **2b** and β-keto esters,[12] we applied this method to the one-pot synthesis

of 1-aryl-3-alkylsubstituted isoquionolines. 1-Phenylisoquinolines are important ligands for the synthesis of palladium, platinum, iridium complexes, which show novel red phosphorescence and applied to the synthesis of organic electroluminescent devices.[13] Treatment of triflate **2a** with 4-nitrobenzoylacetone **3a** in the presence of CsF at rt for 8 h followed by the addition of ammonium hydroxide for additional 10 h at 60 ^{o}C resulted in the formation of 1-(4'-nitrorophenyl)-3-methyl-6,7-dimethoxyisoquinoline (**10a**) in 32% yield. As shown in Table 6, substituted isoquinolines **10** were synthesized in one-pot operation starting from commercially available **2** and diketones **3**.

Table 6. One-pot synthesis of substituted isoquinolines



2a: R= OMe
2b: R= H
2d: R= OCH_2O

3a: Ar=*p*-$NO_2C_6H_4$
3b: Ar= *m*-ClC_6H_4

10a: R= OMe, Ar= *p*-$NO_2C_6H_4$
10b: R= OMe, Ar= *m*-ClC_6H_4
10c: R= H, Ar= *p*-$NO_2C_6H_4$
10d: R= OCH_2O, Ar= *p*-$NO_2C_6H_4$

Entry	**2**	Time 1	**3**	Time 2/ hr	**10**	Yield /%
1	**2a**	8	**3a**	10	**10a**	32
2	**2a**	1.4	**3b**	48	**10b**	25
3	**2b**	1	**3a**	24	**10c**	54
4	**2d**	1.5	**3a**	2	**10d**	30

Conclusion

We have developed a completely new method on the synthesis of 2,3-benzodiazepines and 2,3-benzodiazepin-4-ones from (2-trimethylsilyl)aryltriflates. The reaction requires only two-step reaction. A completely different strategy for the one-pot synthesis 1-arylisoquinolines from aryne precursors was accomplished.

Experimental Section

General: All chemicals were obtained from commercial suppliers and were used without further purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and flash column chromatography was performed with silica (Merck, 70-230 mesh). NMR spectra (^{1}H at 400 MHz; ^{13}C at 100 MHz) were recorded in $CDCl_3$, and chemical shifts are expressed in ppm relative to internal TMS for ^{1}H and ^{13}C NMR. Melting points were uncorrected.

Reaction of Triflate 2a with 4-Nitrobenzoylacetone at rt

To a solution of 4-nitrobenzoylacetone **3a** (79 mg, 0.22 mmol) and CsF (100 mg, 0.66 mmol) in acetonitrile (3 mL) was added triflate **2a** (86 mg, 0.24 mmol) in acetonitrile (2 mL). 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 x 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'-nitro)benzophenone **4a** (22 mg, 0.064 mmol).

When 1.7 eq of **2a** (182 mg, 0.51 mmol), CsF (227 mg, 1.5 mmol), and **3a** (62 mg, 0.30 mmol) were used at rt for 15h, **4a** (65 mg, 0.19 mmol) was obtained in 63% yield. Other reaction was carried out in a similar manner.

4a: Yellow oil; ^{1}H NMR ($CDCl_3$) δ = 2.26 (s, 3H, CH_3), 4.12 (s, 2H, CH_2), 7.30 (d, J = 7 Hz, 1H, ArH), 7.34-7.36 (m, 2H, ArH), 7.51-7.55 (m, 1H, ArH), 7.98 (d, J = 9 Hz, 2H, ArH), 8.31 (d, J = 9 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ = 30.0, 48.0, 123.4, 126.5, 123.4, 126.5, 130.3, 131.1, 131.9, 132.2, 134.8, 136.9, 143.0, 150.0, 196.4, 205.1;

HRMS: m/z Calcd for $C_{16}H_{13}NO_4$ 283.0845. Found: 283.0835 (M^+).

4b: Yellow oil; ^{1}H NMR ($CDCl_3$) δ = 2.20 (s, 3H, CH_3), 4.02 (s, 2H, CH_2), 7.33 - 7.42 (m, 4H, ArH), 7.51 (t, *J* = 8 Hz, 1H, ArH), 7.55 (d, *J* = 8 Hz, 1H, ArH), 7.67 (d, *J* = 8 Hz, 1H, ArH), 7.80 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ = 29.9, 48.1, 126.5, 128.5, 129.6, 130.1, 130.3, 131.4, 132.1, 132.7, 134.6, 134.7, 137.2, 139.5, 196.8, 205.3; HRMS: Calcd for $C_{16}H_{13}ClO_2$ *m/z* (%)= 272.0604 (M^+, 100), 274.0575 (M^{+2}, 32). Found *m/z* = 272.0604 (M^+, 100), 274.0583 (M^{+2}, 32).

5b: Yellow oil; ^{1}H NMR ($CDCl_3$) δ = 2.12 (s, 1H, OH), 3.02 (d, *J* = 17 Hz, 1H, CH_2), 3.21 (d, *J* = 16 Hz, 1H, CH_2), 3.28 (d, *J* = 16 Hz, 1H, CH_2), 3.58 (d, *J* = 17 Hz, 1H, CH_2), 7.28-7.42 (m, 5H, ArH), 7.54 (d, *J* = 7 Hz, 1H, ArH), 7.57 (s, 1H, ArH), 8.08 (d, *J* = 8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ = 43.5, 51.33, 74.98, 122.9, 125.3, 127.0, 127.2, 128.0, 129.5, 130.0, 131.6, 134.3, 134.7, 140.0, 147.8, 196.2 (s, C=O). HRMS: Calcd for $C_{16}H_{13}ClO_2$ *m/z* (%)= 272.0604 (M^+, 100), 274.0575 (M^{+2}, 32). Found *m/z* = 272.0601 (M^+, 100), 274.0553 (M^{+2}, 32).

4c: pale yellow solid. mp 157-159^{o}C (ref[14] mp 156-158^{o}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 Hz, Ar), 8.31 (d, 2H, *J* = 8 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ = 30.1 (CH_3), 48.4 (CH_2), 56.4 (OCH_3), 56.4 (OCH_3), 114.7, 115.3, 123.7, 128.5, 130.3, 131.0, 144.2, 147.1, 150.1, 152.3 (Ar), 195.5 (C=O), 205.8 (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.

4d: Pale yellow solid; mp 100-101^{o}C (ref.[4] mp 108-110^{o}C. ^{1}H NMR ($CDCl_3$) δ = 2.23 (s, 3H, CH_3), 3.78 (s, 3H, CH_3O), 3.94 (s, 2H, CH_2), 3.96 (s, 3H, OCH_3), 6.76 (s, 1H, ArH), 6.93 (s, 1H, ArH), 7.40(t, *J* = 8 Hz, 1H, ArH), 7.56 (d, *J* = 8 Hz, 1H, ArH), 7.64 (d, *J* = 8.0 Hz, 1H, ArH), 7.77 (s, 1H, ArH).

4e: Yellow oil; ^{1}H NMR ($CDCl_3$) δ = 2.23 (s, 6H, CH_3), 2.30 (s, 3H, CH_3), 4.03 (s, 2H, CH_2), 7.05 (s, 1H, ArH), 7.10 (s, 1H, ArH), 7.94 (d, *J* = 9 Hz, 2H, ArH), 8.31 (d, *J* = 9 Hz, 2H,ArH). ^{13}C NMR ($CDCl_3$) δ = 19.3, 19.8, 29.9, 47.8, 123.4, 130.9, 132.1, 132.7, 133.8, 134.1, 135.0, 141.5, 143.7, 149.8, 196.4, 205.7. HRMS: m/z Calcd for $C_{18}H_{17}N_3O_2$ 307.1321. Found: 307.1322 (M^+).

4f: Yellow solid; mp 150-152ºC (ref.[15] mp 151-154ºC). ^{1}H NMR ($CDCl_3$) δ = 2.25 (s, 3H, CH_3), 4.01 (s, 2H, CH_2), 6.06 (s, 2H, OCH_2O), 6.76 (s, 1H, ArH), 6.81 (s, 1H, ArH), 7.91 (d, *J* = 8 Hz, 2H, ArH), 8.31 (d, *J* = 8 Hz, 2H, ArH).

4g: Orange oil; ^{1}H NMR ($CDCl_3$) δ = 2.24 (s, 3H, CH_3), 4.09 (s, 2H, CH_2), 7.12 (dd,$^{3}J_{HF}$ = 11 Hz, $^{4}J_{HF}$ = 7 Hz, 1H, ArH), 7.19 (dd,$^{3}J_{HF}$ = 10 Hz, $^{4}J_{HF}$ = 8 Hz, 1H, ArH), 7.96 (d, *J* = 9 Hz, 2H), 8.33 (d, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$) δ = 30.0, 47.2, 119.7 (d, *J* = 18 Hz,), 121.4 (d, *J* = 18 Hz), 123.6, 131.0, 132.7 (dd, *J* = 5 Hz), 133.3 (dd, *J* = 5 Hz), 142.2, 148.8 (dd, $^{1}J_{CF}$ = 365 Hz, $^{2}J_{CF}$ = 13 Hz), 150.3, 151.3 (dd, $^{1}J_{CF}$ = 370 Hz, $^{2}J_{CF}$ = 13 Hz), 194.4, 204.4. ^{19}F NMR ($CDCl_3$) δ = -138.66 (ddd, $^{3}J_{FF}$ = 21 Hz, $^{3}J_{FH}$ = 10 Hz, $^{4}J_{FH}$ = 9 Hz), -138.63 (ddd, $^{3}J_{FF}$ = 21 Hz, $^{3}J_{FH}$ = 11 Hz, $^{4}J_{FH}$ = 9 Hz). HRMS: m/z; Calcd for $C_{16}H_{11}F_2NO_4$; 319.0656. Found: 319.0644 (M^+).

4h: Brown oil; ^{1}H NMR ($CDCl_3$) δ = 2.22 (s, 3H, CH_3), 3.99 (s, 2H, CH_2), 7.10 (dd,$^{3}J_{HF}$ = 11 Hz, $^{4}J_{HF}$ = 8 Hz, 1H, ArH), 7.24 (dd,$^{3}J_{HF}$ = 9 Hz, $^{4}J_{HF}$ = 8 Hz, 1H, ArH), 7.43 (t, *J* = 8 Hz, 1H, ArH), 7.58 (d, *J* = 8 Hz, 1H, ArH), 7.63 (d, *J* = 8 Hz, 1H, ArH), 7.77 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ = 30.3, 47.4, 120.0 (d, *J* = 18 Hz), 121.5 (d, *J* = 18 Hz), 128.6, 130.1, 130.2, 132.7 (dd, $^{1}J_{CF}$ = 3 Hz, $^{2}J_{CF}$ = 4 Hz), 133.4, 133.9 (dd, $^{1}J_{CF}$ = 2 Hz, $^{2}J_{CF}$ = 4 Hz), 135.1, 139.0, 148.9 (dd, $^{1}J_{CF}$ = 345 Hz, $^{2}J_{CF}$ = 13 Hz), 151.9 (dd, $^{1}J_{CF}$ = 350 Hz, $^{2}J_{CF}$ = 13 Hz), 197.8, 204.5. ^{19}F NMR ($CDCl_3$) δ = -139.07 (ddd, $^{3}J_{FF}$ = 21 Hz, $^{3}J_{FH}$ = 10 Hz, $^{4}J_{FH}$ = 9 Hz), -132.58 (ddd, $^{3}J_{FF}$ = 21.3 Hz, $^{3}J_{FH}$ = 10 Hz, $^{4}J_{FH}$ = 9 Hz);

HRMS: m/z Calcd for $C_{16}H_{11}ClF_2O_2$; 308.0416. Found; 308.0415 (M^+).

Reaction of triflate 2a with ethyl benzoylacetate

To a solution of ethyl benzoyl acetate **6a** (35 mg, 0.18 mmol) and CsF (136 mg, 0.90 mmol) in acetonitrile (3 mL) was added triflate **2a** (106 mg, 0.30 mmol) in acetonitrile (2 mL). After being stirred for 8 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 x 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 ethyl 2-benzoyl-4,5-dimethoxyphenylacetate **7a** (44 mg, 0.15 mmol). **7a**: colorless solid; mp 78-79ºC (Ref.[16] mp 78-79ºC). ^{1}H NMR ($CDCl_3$) δ= 1.15 (t, *J* = 7 Hz, 3H, CH_3), 3.79 (s, 3H, OMe), 3.82 (s, 2H, CH_2), 3.96 (s, 3H, OMe), 4.06 (q, *J* = 7 Hz, 2H, CH_2), 6.86 (s, 1H, ArH), 6.94 (s, 1H, ArH), 7.46 (t, *J* = 8 Hz, 2H, ArH), 7.57 (t, *J* = 8 Hz, 1H, ArH), 7.80 (d, *J* = 8 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ = 14.1, 38.7, 56.0, 56.1, 60.8, 113.9, 114.5, 128.2, 128.2, 130.2, 130.3, 132.6, 138.4, 146.9, 151.0, 171.4, 197.1. HRMS: calcd for $C_{19}H_{20}O_5$ *m/z* = 328.1311 (M^+). Found *m/z* = 328.1304 (M^+).

7b: yellow oil; ^{1}H NMR ($CDCl_3$) δ = 1.17 (t, *J* =7 Hz, 3H, CH_3), 3.80 (s, 3H, OMe), 3.82 (s, 2H, CH_2), 3.96 (s, 3H, OMe), 4.08 (q, *J* = 7 Hz, 2H, CH_2), 6.87 (s, 1H, ArH), 6.91 (s, 1H, ArH), 7.40 (t, *J* = 8 Hz, 1H, ArH), 7.54 (d, *J* = 8 Hz, 1H, ArH), 7.65 (d, *J* = 9 Hz, 1H, ArH), 7.66 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ = 14.1, 38.8, 56.1, 56.2, 60.8, 113.9, 114.7, 128.2, 128.5, 129.6, 129.6, 130.0, 132.5, 134.6, 140.1, 147.0, 151.3, 171.3, 195.7. HRMS: calcd for $C_{19}H_{19}ClO_5$ *m/z* = 36.09212 (M^+). Found *m/z* = 362.0925 (M^+).

7c: pale yellow oil; (Ref.[16] mp 113-114°C). ^{1}H NMR ($CDCl_3$) δ = 1.15 (t, *J* = 7 Hz, 3H, CH_3), 3.77 (s, 2H, CH_2), 3.82 (s, 2H, OMe), 3.93 (s, 3H, OMe), 3.95 (s, 3H, OMe), 3.95 (s, 3H, OMe), 4.06 (q, *J* = 7 Hz, 2H, CH_3), 6.86 (s, 1H, ArH), 6.87 (d, *J* = 9 Hz, 1H, ArH), 6.94 (s, 1H, ArH), 7.33 (d, *J* = 9 Hz, 1H, ArH), 7.49 (s, 1H,ArH). HRMS: Calcd for $C_{21}H_{24}O_7$ *m/z* = 388.1522 (M^+). Found *m/z* = 388.1520 (M^+).

7d: yellow oil; ^{1}H NMR ($CDCl_3$) δ = 1.11 (t, *J* = 7 Hz, 3H, CH_3), 3.88 (s, 2H, CH_2), 4.02 (q, *J* =7 Hz, 2H, OCH_2), 7.30-7.39 (m, 3H, ArH), 7.43-7.48 (m, 3H, ArH), 7.57 (t, *J* = 8 Hz, 1H, ArH), 7.81 (d, *J* =7 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ = 14.5 (CH_3), 39.3 (CH_2), C, 61.2 (CH_2), 126.7, 128.5, 130.2, 130.6, 131.0, 132.0, 133.1, 134.2, 138.0, 138.4 (Ar), 171.3 (C=O), 198.1 (C=O). HRMS: Calcd for $C_{17}H_{16}O_3$ *m/z* = 268.1099 (M^+). Found *m/z* = 268.1090 (M^+).

7e: Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ = 1.12 (t, *J* =8 Hz, 3H, CH_3), 3.82 (s, *2*H, CH_2), 3.93 (s, *3*H, OMe), 3.95 (s, *3*H, OMe), 4.02 (q, *J* = 8 Hz, 2H, OCH_2), 6.85 (d, *J* = 8 Hz, 1H, ArH), 7.30-7.40 (m, 4H, ArH), 7.46 (t, *J* = 8 Hz, 1H, ArH), 7.53 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ = 14.0 (CH_3), 38.7 (CH_2), 56.0 (OMe), 56.1 (OMe), 60.8 (CH_2), 109.7, 111.7, 126.1, 126.3, 129.3, 130.3, 130.6, 131.5, 133.5, 138.8, 149.0, 153.4, 171.2 (C=O), 196.7 (C=O). HRMS: Calcd for $C_{19}H_{20}O_5$ *m/z* = 328.1311 (M^+). Found *m/z* = 329.1320 (M^+).

7f : Colorles oil; ^{1}H NMR ($CDCl_3$) δ = 1.12 (t, *J* = 7 Hz, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.81 (s, 2H, CH_2), 4.03 (q, *J* = 7 Hz, 2H, OCH_2), 7.12 (s, 1H, ArH), 7.16 (s, 1H, ArH), 7.44 (t, *J* = 7 Hz, 2H, ArH), 7.56 (t, *J* = 7 Hz, 1H, ArH), 8.00 (d, *J* = 7 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ = 14.0 (CH_3), 19.2 (CH_3), 19.7 (CH_3), 38.5 (CH_2), 60.7 (CH_2), 128.4, 130.2, 131.5, 131.6, 132.5, 133.1, 134.7, 135.6, 138.2, 139.9, 171.6 (C=O), 198.1 (C=O). HRMS: Calcd for $C_{19}H_{20}O_3$ *m/z* = 296.1412 (M^+). Found *m/z* =

296.1421 (M^+).

7g: Colorles oil; ^{1}H NMR ($CDCl_3$) δ= 1.14 (t, *J* =8 Hz, 3H, CH_3), 2.25 (s, *3*H, CH_3), 2.32 (s, *3*H, CH_3), 3.82 (s, *2*H, CH_2), 4.04 (q, *J* = 8 Hz, 2H, CH_2), 7.13 (s, 1H, ArH), 7.14 (s, 1H, ArH), 7.39 (t, *J* = 8 Hz, 1H, ArH), 7.54 (d, *J* = 8 Hz, 1H, ArH), 7.66 (d, *J* = 8 Hz, 1H, ArH), 7.78 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ = 14.1, 19.3, 19.8, 38.5, 60.8, 128.4, 129.5, 130.0, 130.9, 131.6, 131.8, 132.5, 133.3, 133.6, 134.5, 134.9, 135.0, 140.0, 140.5, 171.5, 196.6. HRMS: Calcd for $C_{19}H_{19}ClO_3$ *m/z* = 330.1023 (M^+). Found *m/z* = 330.1020 (M^+).

7h: Colorless oil; ^{1}H NMR ($CDCl_3$) δ = 1.15 (t, *J* =7 Hz, 3H, CH_3), 3.79 (s, 2H, CH_2), 4.06 (q, *J* = 7 Hz, 2H, CH_2), 6.03 (s, 2H, OCH_2O), 6.84 (s, 1H, ArH), 6.88 (s, 1H, ArH), 7.45 (t, *J* =7 Hz, 2H, ArH), 7.56 (t, *J* = 8 Hz, 1H, ArH), 7.78 (d, *J* = 8 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ = 14.0 (CH_3), 38.9 (CH_2), 60.7 (CH_2), 101.7, 110.6, 111.9, 128.2, 129.8, 130.1, 131.7, 132.6, 138.1, 145.9, 149.6, 171.3 (C=O), 196.8 (C=O). HRMS: Calcd for $C_{18}H_{16}O_5$ *m/z* = 312.0998 (M^+). Found *m/z* = 312.1005 (M^+).

7i: Colorles oil; ^{1}H NMR ($CDCl_3$) δ= 1.17 (t, *J* =7 Hz, 3H, CH_3), 3.79 (s, 2H, CH_2), 4.08 (q, *J* = 7 Hz, 2H, CH_2), 6.05 (s, 2H, OCH_2O), 6.84 (s, 1H, ArH), 6.85 (s, 1H, ArH), 7.39 (t, *J* = 9 Hz, 1H, ArH), 7.54 (d, *J* = 7 Hz, 1H, ArH), 7.65 (d, *J* = 9 Hz, 1H, ArH), 7.75 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ = 14.6 (CH_3), 39.4 (CH_2), 61.3 (CH_2), 102.2, 110.8, 112.4, 128.5, 129.8, 130.2, 130.4, 131.2, 132.8, 134.7, 140.1, 146.2, 150.1, 171.3 (C=O), 195.4 (C=O). HRMS: Calcd for $C_{18}H_{15}ClO_5$ *m/z* = 346.0608 (M^+). Found *m/z* = 346.0610 (M^+).

7j: Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ= 1.14 (t, *J* = 7 Hz, 3H, CH_3), 3.82 (s, 2H, CH_2), 4.04 (q, *J* = 7 Hz, 2H, CH_2), 7.18-7.24 (m, 2H, ArH ×2), 7.48 (t, *J* = 8 Hz, 2H, ArH), 7.61 (t, *J* = 8 Hz, 1H, ArH), 7.78 (d, *J* = 8 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ = 14.0

(CH_3), 38.1 (CH_2), 61.1 (CH_2), 119.2 (d, J = 18 Hz), 120.8 (d, J = 18 Hz), 128.5, 130.2, 131.7 (dd, J = 3 and 4 Hz), 133.3, 134.8 (dd, J = 2 and 4 Hz), 137.1, 148.5 (dd, J = 290 and 12 Hz), 151.0 (d, J = 293 and 12 Hz), 170.4 (C=O), 195.6 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$) δ = -138.9 (d, $^3J_{FF}$ = 21 Hz), -133.3 (d, $^3J_{FF}$ = 21 Hz). HRMS: Calcd for $C_{17}H_{14}F_2O_3$ m/z =304.0911 (M^+). Found m/z = 304.0924 (M^+).

7k : Yellow oil; ^{1}H NMR ($CDCl_3$) δ = 1.16 (t, J = 7 Hz, 3H, CH_3), 3.84 (s, 2H, CH_2), 4.05 (q, J = 7 Hz, 2H, CH_2), 7.18-7.26 (m, 2H, ArH×2), 7.42 (t, J = 8 Hz, 1H, ArH), 7.57 (d, J = 8 Hz, 1H, ArH), 7.64 (d, J = 8 Hz, 1H, ArH), 7.77 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ = 14.5 (CH_3), 38.5 (CH_2), 61.4 (CH_2), 119.6 (d, J = 18 Hz), 121.3 (d, J = 18 Hz), 128.5, 130.0, 130.2, 132.2 (dd, J = 3 and 4 Hz), 133.4, 134.2 (dd, J = 2 and 4 Hz), 135.0, 138.9, 148.8 (dd, J = 308 and 13 Hz), 151.3 (dd, J = 312 and 13 Hz), 170.5 (C=O), 194.3 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$) δ = -138.4 (ddd, $^3J_{FF}$ = 18 Hz, $^3J_{FH}$ = 10 Hz, $^4J_{FH}$ = 8 Hz), -132.4 (ddd, $^3J_{FF}$ = 18 Hz, $^3J_{FH}$ = 11 Hz, $^4J_{FH}$ = 8 Hz). HRMS: Calcd for $C_{17}H_{13}ClF_2O_3$ m/z =338.0521 (M^+). Found m/z = 338.0531 (M^+).

Reaction of 4a with hydrazine hydrate

To a solution of **4a** (34 mg, 0.10 mmol) in EtOH (4.0 mL) was added a solution of hydrazine hydrate (50 mg, 1.0 mmol). After stirring at rt for 16h, the mixture was poured into water and extracted with dichloromethane. The separated dichloromethane solution was dried over magnesium sulfate, filtered, and evaporated to give pale orange oil, which was chromatographed over silica gel by elution with hexane-dichloromethane (1:1) to give 2,3-benzodiazepine **1a** (20 mg, 0.06 mmol).

1a: Colorless solid; mp 175-176°C. ^{1}H NMR ($CDCl_3$) δ = 2.18 (s, 3H, CH_3), 3.06 (d, J = 12 Hz, 1H, CH_2), 3.42 (d, J = 12 Hz, 1H, CH_2), 7.29 (d, J = 8 Hz, 1H, ArH), 7.34 (d, J = 8 Hz, 1H, ArH), 7.41 (t, J = 8 Hz, 1H, ArH), 7.58 (t, J = 8 Hz, 1H, ArH), 7.86 (d, J =

9 Hz, 2H, ArH), 8.26 (d, *J* = 9 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ = 23.0 (CH_3), 38.8 (CH_2), 123.4, 126.6, 127.3, 129.2, 129.8, 130.3, 132.1, 139.7, 144.6, 148.6, 155.2 (C=N), 157.1 (C=N). HRMS: Calcd for $C_{16}H_{13}N_3O_2$ *m/z* = 279.1008 (M^+). Found *m/z* = 279.1004 (M^+).

1b: Pale yellow solid; mp 141-142°C. ^{1}H NMR ($CDCl_3$) δ = 2.17 (s, 3H, CH_3), 3.08 (d, *J* = 12 Hz, 1H, CH_2), 3.38 (d, *J* = 12 Hz, 1H, CH_2), 7.29 - 7.38 (m, 4H, ArH), 7.40 (m, 2H, ArH), 7.54 (d, *J* = 8 Hz, 1H, ArH), 7.57 (d, *J* = 8 Hz, 1H, ArH), 7.66 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ = 23.3 (CH_3), 39.0 (CH_2), 126.6, 127.4, 127.9, 129.7, 129.7, 129.8, 130.0, 130.4, 132.0, 134.5, 139.8, 140.8, 155.6 (C=N), 158.0 (C=N). HRMS: Calcd for $C_{16}H_{13}ClN_2$ *m/z* = 268.0767 (M^+). Found *m/z* = 268.0765 (M^+).

1c: Yellow solid; mp 236-238°C (ref[4] mp 238-240°C). ^{1}H NMR ($CDCl_3$) δ = 2.18 (s, 3H, CH_3), 2.99 (d, *J* =12 Hz, 1H, CH_2), 3.34 (d, *J* = 12 Hz, 1H, CH_2), 3.75 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.70 (s, 1H, ArH), 6.76 (s, 1H, ArH), 7.89 (d, *J* = 8 Hz, 2H, ArH), 8.27 (d, *J* = 8 Hz, 2H, ArH). ^{13}C NMR (CD_3CN) δ = 23.0 (CH_3), 38.5 (CH_2), 56.2 (OMe), 56.2 (OMe), 108.8, 111.8, 121.5, 123.4, 130.3, 133.2, 144.9, 148.3, 148.6, 152.6, 154.6 (C=N), 156.6 (C=N).

1d: Pale yellow crystal; mp 172-173°C (ref.[4] mp 167-169°C). ^{1}H NMR ($CDCl_3$) δ = 2.16 (s, 3H, CH_3), 2.99 (d, *J* =12 Hz, 1H, CH_2), 3.28 (d, *J* = 12 Hz, 1H, CH_2), 3.76 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.74 (s, 1H, ArH), 6.76 (s, 1H, ArH), 7.34 (t, *J* = 8 Hz, 1H, ArH), 7.41 (d, *J* = 8 Hz, 1H, ArH), 7.58 (d, *J* = 8 Hz, 1H, ArH), 7.72 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ = 22.1 (CH_3), 37.4 (CH_2), 52.2 (OMe), 55.3 (OMe), 107.9, 111.2, 120.9, 126.9, 128.4, 128.6, 128.8, 132.3, 133.3, 139.9, 147.2, 151.4, 154.1 (C=N), 156.3 (C=N). HRMS: Calcd for $C_{18}H_{17}ClN_2O_2$ *m/z* (%)= 328.0979 (M^+, 100), 330.0949 (M^{+2}, 32). Found *m/z* = 328.0971 (M^+, 100), 330.0948 (M^{+2}, 32).

1e: Colorless solid; mp 188-189°C. ^{1}H NMR ($CDCl_3$) δ = 2.18 (s, 3H, CH_3), 2.93 (d, *J* = 12 Hz, 1H, CH_2), 3.30 (d, *J* = 12 Hz, 1H, CH_2), 6.03 (s, 1H, CH_2), 6.07 (s, 1H, CH_2), 6.68 (s, 1H, ArH), 6.78 (s, 1H, ArH), 7.87 (d, *J* = 7.9 Hz, 2H, ArH), 8.26 (d, *J* = 8.9 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ = 19.7 (CH_3), 20.1 (CH_3), 23.2 (CH_3), 38.5 (CH_2), 123.6, 127.0, 127.8, 130.5, 130.7, 136.3, 137.4, 141.9, 145.0, 148.7, 156.1 (C=N), 157.8 (C=N). HRMS: Calcd for $C_{18}H_{17}N_3O_2$; *m/z* = 307.1321 (M^+). Found: 307.1321 (M^+).

1f: Yellow crystals; mp 199-202°C (ref.[15] mp 200-203°C). ^{1}H NMR ($CDCl_3$) δ = 2.18 (s, 3H, CH_3), 2.93 (d, *J* = 12 Hz, 1H, CH_2), 3.30 (d, *J* = 12 Hz, 1H, CH_2), 6.03 (s, 1H, CH_2), 6.08 (s, 1H, CH_2), 6.67 (s, 1H, ArH), 6.78 (s, 1H, ArH), 7.87 (d, *J* = 8.4 Hz, 2H, ArH), 8.26 (d, *J* = 8.4 Hz, 2H, ArH).

Reduction of nitrobenzodiazepine 1c

To a suspension of **1c** (13 mg, 0.038 mmol) and iron powder (9 mg, 0.16 mmol) in ethanol-water (4:1, 5 mL) was added conc. HCl (0.02 mL, 0.18 mmol) at rt. After refluxing for 2h, resulting mixture was extracted with dichloromethane (3 ml x 3). Saturated sodium carbonate solution (1 mL) was added to the water layer, which was extracted with dichloromethane (2 mL x 3), dried over sodium sulfate, filtered, and evaporated to give almost pure Nerisopam **1c'** (9 mg, 0.025 mmol).

1c': Yellow crystals; mp 223-226°C (Ref[4] mp 225-227°C). ^{1}H NMR ($CDCl_3$) δ = 2.13 (s, 3H, CH_3), 3.04 (d, *J* = 12 Hz, 1H, CH_2), 3.22 (d, *J* = 12 Hz, 1H, CH_2), 3.76 (s, 3H, MeO), 3.97 (s, 3H, MeO), 6.55-6.75 (m, 3H, ArH), 6.85 (s, 1H, ArH), 7.52 (d, *J* = 8 Hz,2H, ArH).

One-pot synthesis of Tofisopam 1g

To a solution of 2-ethyl-1-(3,4-dimethoxyphenyl)butan-1,3-dione **3d** (50 mg, 0.20 mmol) and CsF (152 mg, 1.0 mmol) in acetonitrile (7 mL) was added triflate **2a** (122

mg, 0.34 mmol). After being stirred for 10 h at 60°C, the reaction mixture was evaporated to give pale yellow oil, which was added to a solution of hydrazine hydrate (50 mg, 1.0 mmol) in EtOH (7 mL). After atanding for 16h at rt, the reaction mixture was evaporated to give brown oil, which was chromatographed over silica gel by elution with hexane dichloromethane (1:1) to afford Tofisopam **1g** (34.4 mg, 0.09 mmol) and diketone **8** (17 mg, 0.044 mmol).

1g: Pale yellow crystals; mp 155-157°C (ref[4] mp 156-157°C). ^{1}H NMR ($CDCl_3$) δ = 0.55 (t, *J* = 8 Hz, 3H, CH_3), 1.97 (s, 3H, CH_3), 2.30 (m, 2H, CH_2), 3.74 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.35 (s, 1H, ArH), 6.70 (d, *J* = 8 Hz, 1H, ArH), 6.87 (s, 1H, ArH), 6.94 (d, *J* = 8 Hz, 1H, ArH), 7.55 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ = 7.8 (CH_3), 12.4 (CH_3), 25.5, 55.5 (OCH_3), 56.0 (OCH_3), 56.0 (OCH_3), 56.0 (OCH_3), 72.3 (CH), 108.9, 110.1, 110.6, 111.7, 117.9, 121.5, 122.7, 127.8, 149.0, 149.1, 149.8, 151.6, 179.8. HRMS: Calcd for $C_{22}H_{26}N_2O_4$; *m/z* = 382.1893. Found: 382.1896 (M^+).

8: pale yellow oil: ^{1}H NMR ($CDCl_3$) δ = 0.79 (t, 3H, *J* = 7 Hz, Me), 2.11 (s, 3H, Me), 2.24 (q, 1H, *J* = 7 Hz, C<u>H</u>H), 2.67 (q, 1H, *J* = 7 Hz, CH<u>H</u>), 3.81 (s, 6H, OMe), 3.86 (s, 3H, OMe), 3.88 (s, 3H, OMe), 6.69 (d, 1H, *J* = 9 Hz, 1H, Ar), 6.79 (d, 1H, *J* = 9 Hz, Ar), 6.95 (d, 1H, *J* = 9 Hz, Ar), 7.05 (s, 1H, Ar), 7.30 (d, 1H, *J* = 8 Hz, Ar), 7.44 (s, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ = 9.6 (CH_3), 28.3 (CH_3), 29.6 (CH_2), 56.0 (OCH_3), 56.0 (OCH_3), 56.2 (OCH_3), 56.2 (OCH_3), 72.3 (CH), 110.0, 111.1, 111.9, 112.3, 121.5, 125.1, 128.7, 131.6, 148.4, 148.7, 148.9, 153.2, 197.6 (C=O), 205.4 (C=O). HRMS: Calcd for $C_{22}H_{26}O_6$; *m/z* = 386.1729. Found: 386.1731 (M^+).

Reaction of ethyl 2-aroylphenylacetate with hydrazine hydrate.

To a solution of **7a** (34 mg, 0.20 mmol) in BuOH (4.0 mL) was added a solution of

hydrazine hydrate (50 mg, 1.0 mmol). After refluxing for 16h, the mixture was poured into water and extracted with dichloromethane (5 mL x 3). The separated dichloromethane solution was dried over magnesium sulfate, filtered, and evaporated to give pale orange oil, which was chromatographed over silica gel by elution with hexane-dichloromethane (1:1) to give 2,3-benzodiazepin-3-one **9a** (20 mg, 0.06 mmol).

9a: Colorless solid; mp 200-202ºC (ref.[17] mp 202-20 ºC). ^{1}H NMR ($CDCl_3$) δ = 3.51 (s, 2H, CH_2), 3.72 (s, 3H, OMe), 3.97 (s, 3H, OMe), 6.67 (s, 1H, ArH), 6.85 (s, 1H, ArH), 7.41-7.49 (m, 3H, ArH), 7.63 (d, *J* = 7 Hz, 2H, ArH), 8.49 (br, 1H, NH); GCMS: calcd for $C_{17}H_{16}N_2O_3$ *m/z* = 296 (M^+). Found *m/z* = 296 (M^+).

9b: Pale yellow solid; mp 263.5-265ºC (Ref.[18] no mp.) ^{1}H NMR ($CDCl_3$) δ = 3.50 (s, 2H, CH_2), 3.74 (s, 3H, OMe), 3.97 (s, 3H, OMe), 6.63 (s, 1H, ArH), 6.85 (s, 1H, ArH), 7.36 (t, *J* = 8 Hz, ArH), 7.44 (d, *J* = 8 Hz, 1H, ArH), 7.48 (d, 1H, 7.28 Hz, Ar), 7.67 (s, 1H, ArH), 8.73 (br, 1H, NH). ^{13}C NMR ($CDCl_3$) δ = 41.7 (CH_2), 56.1 (OCH_3), 56.2 (OCH_3), 110.4, 111.6, 123.0, 127.5, 129.2, 129.6, 129.7, 130.0, 134.6, 139.7, 147.8, 152.5, 160.1 (C=N), 170.7 (C=O). HRMS: Calcd for $C_{17}H_{15}ClN_2O_3$ *m/z* = 330.0771 (M^+). Found *m/z* = 330.0766 (M^+).

9c: Colorless oil; ^{1}H NMR ($CDCl_3$) δ= 3.58 (s, 2H, CH_2), 3.91 (s, 3H, OMe), 3.93 (s, 3H, OMe), 6.86 (d, *J* = 8 Hz, 1H, ArH), 7.00 (d, *J* = 8 Hz, 1H, ArH), 7.28-7.41 (m, 4H, ArH), 7.55 (t, *J* = 8 Hz, 1H, 8.34 (br, 1H, NH). ^{13}C NMR (CD_3CN) δ = 42.1, 56.0 (MeO×2), 110.3, 111.2, 123.4, 126.7, 128.0, 129.8, 130.4, 131.2, 131.9, 136.2, 149.0, 150.9, 161.9, 171.2. HRMS: Calcd for $C_{17}H_{16}N_2O_3$ *m/z* (%)= 296.1161 (M^+). Found *m/z* = 296.1158 (M^+).

9d: Colorless solid; mp 222.5-223.5ºC. ^{1}H NMR ($CDCl_3$) δ = 2.22 (s, 3H, CH_3), 2.33

(s, 3H, CH_3), 3.51 (s, 2H, CH_2), 6.94 (s, 1H, ArH), 7.16 (s, 1H, ArH), 7.35 (t, *J* = 8 Hz, 1H, ArH), 7.43 (d, *J* = 8 Hz, 1H, ArH), 7.46 (d, *J* = 8 Hz, 1H, ArH), 7.63 (s, 1H, ArH), 8.44 (br, 1H, NH). ^{13}C NMR (CD_3CN) δ = 19.5, 19.8, 41.6, 127.5, 128.4, 129.2, 129.2, 129.6, 129.9, 130.0, 133.6, 134.5, 135.7, 139.9, 141.7, 160.7, 171.1; HRMS: Calcd for $C_{17}H_{15}ClN_2O$ *m/z* (%) = 298.0873 (M^+). Found *m/z* = 298.0843 (M^+).

9e: Colorless solid; mp 180-181ºC (ref.[19] mp 181.5-182.5ºC). ^{1}H NMR ($CDCl_3$) δ = 3.46 (s, 2H, CH_2), 6.02 (s, 2H, -OCH_2O-), 6.62 (s, 1H, ArH), 6.83 (s, 1H, ArH), 7.40-7.48 (m, 3H, ArH), 7.59 (d, *J* = 8 Hz, 2H, ArH), 8.86 (br, 1H, NH); HRMS: calcd for $C_{16}H_{12}N_2O_3$ *m/z* = 280.0848 (M^+). Found *m/z* = 280.0841 (M^+).

9f: Colorless oil; ^{1}H NMR ($CDCl_3$) δ = 3.45 (s, 2H, CH_2), 6.05 (s, 2H, -OCH_2O-), 6.60 (s, 1H, ArH), 6.83 (s, 1H, ArH), 7.35 (t, *J* = 8 Hz, 1H, ArH), 7.43 (d, *J* = 8 Hz, 1H, ArH), 7.47 (d, *J* = 8 Hz, 1H, ArH), 7.61 (s, 1H, ArH), 8.63 (br, 1H, NH). ^{13}C NMR ($CDCl_3$) δ = 42.1 (CH_2), 102.3, 108.3, 108.9, 124.6, 127.7, 129.4, 129.9, 130.3, 131.2, 134.7, 139.8, 147.0, 151.2, 160.1, 170.7 (C=O). HRMS: calcd for $C_{16}H_{11}ClN_2O_3$ *m/z* = 314.0458 (M^+). Found *m/z* = 314.0445 (M^+).

9g: Colorless oil; ^{1}H NMR ($CDCl_3$) δ= 3.55 (s, 2H, CH_2), 7.07 (dd, $^3J_{HF}$ = 10 Hz, $^4J_{HF}$ = 8 Hz 1H, ArH), 7.22 (dd, $^3J_{HF}$ = 10 Hz,$^4J_{HF}$ = 8 Hz, 1H, ArH), 7.43-7.49 (m, 3H, ArH), 7.57 (d, *J* = 7 Hz, 2H, ArH), 8.50 (br, 1H, NH). ^{13}C NMR ($CDCl_3$) δ = 41.3, 116.9 (d, *J* = 18 Hz), 118.5 (d, *J* = 18 Hz), 128.0 (dd, $^1J_{CF}$ = 4 Hz, $^2J_{CF}$ = 3 Hz), 128.6, 129.1, 130.5, 133.0 (dd, $^1J_{CF}$ = 3 Hz, $^2J_{CF}$ = 4 Hz), 137.1, 149.4 (dd, $^2J_{CF}$ = 343 Hz, $^3J_{CF}$ = 13 Hz), 151.9 (dd, $^2J_{CF}$ =349 Hz, $^3J_{CF}$ = 13 Hz), 160.0, 170.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ= -137.8 (d, $^3J_{FF}$ = 23 Hz), -131.2 (d, $^3J_{FF}$ = 23 Hz); HRMS: calcd for $C_{15}H_{10}F_2N_2O$ m/z =272.0761 (M^+). Found m/z = 272.0765 (M^+).

Synthesis of 1-(p-nitrophenyl)-3-methyl-6,7-dimethylisoquinoline

To a solution of 2-ethyl-1-(p-nitrophenyl)butan-1,3-dione **2d** (50 mg, 0.20 mmol) and CsF (152 mg, 1.0 mmol) in acetonitrile (7 mL) was added triflate **2a** (122 mg, 0.34 mmol). After being stirred for 10 h at 60°C, the reaction mixture was evaporated to give pale yellow oil, which was added to a solution of ammonium hydroxide (50 mg, 1.0 mmol) in EtOH (7 mL). After standing for 16h at rt, the reaction mixture was evaporated to give brown oil, which was chromatographed over silica gel by elution with hexane dichloromethane (1:1) to afford 1-(p-nitrophenyl)-3-methyl-6,7-dimethylisoquinoline (17 mg, 0.044 mmol).

10a: Pale yellow solid; mp 251-251.8°C (ref.[20] mp 252°C). ^{1}H NMR ($CDCl_3$) δ= 2.71 (s, 3H, CH_2), 3.86 (s, 3H, OMe), 4.05 (s, 3H, OMe), 7.05 (s, 1H, ArH), 7.13 (s, 1H, ArH), 7.43 (s, 1H, ArH), 7.88 (d, *J* = 8 Hz, 2H, ArH), 8.39 (d, *J* = 8 Hz, 2H, ArH).

10b: Yellow solid; mp 161.5-162°C; ^{1}H NMR ($CDCl_3$) δ = 2.71 (s, 3H, CH_3), 3.86 (s, 3H, OMe), 4.04 (s, 3H, OMe), 7.05 (s, 1H, ArH), 7.21 (s, 1H, ArH), 7.38 (s, 1H, ArH), 7.45-7.46 (m, 2H, ArH), 7.57 (t, *J* = 5 Hz, 1H, ArH), 7.70 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ = 22.9 (Me), 54.9 (OMe), 55.1 (OMe), 103.5, 103.7, 116.8, 119.5, 126.8, 127.7, 128.7, 128.9, 133.5, 133.8, 140.1, 148.3, 148.8, 152.1, 154.9. HRMS: Calcd for $C_{18}H_{18}ClNO_2$ *m/z* (%) = 313.0870 (M^+), 315.0840 (M^{+2}). Found *m/z* = 313.0882 (M^+), 315.0845 (M^{+2}).

10c: Yellow solid; mp 168.2-169°C (ref.[21] mp 167-168°C). ^{1}H NMR ($CDCl_3$) δ= 2.76 (s, 3H, CH_3), 7.50 (t, *J* = 7 Hz, 1H, ArH), 7.57 (s, 1H, ArH), 7.68 (t, *J* = 8 Hz, 1H, ArH), 7.83-7.91 (m, 4H, ArH), 8.39 (d, *J* = 8.8 Hz, 2H, ArH).

10d: Yellow solid; mp 198-199 °C (ref.[15] mp 178-181°C). ^{1}H NMR ($CDCl_3$) δ = 2.69 (s, 3H, CH_3), 6.09 (s, 2H, -OCH_2O-), 7.08 (s, 1H, ArH), 7.12 (s, 1H, ArH), 7.41 (s, 1H,

ArH), 7.82 (d, *J* = 9 Hz, 2H, ArH), 8.38 (d, *J* = 9 Hz, 2H, ArH).

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Synthesis of 2,3-Benzodiazepines and 2,3-Benzodiazepin-4-ones from Arynes and β-Diketones

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2,3-Benzodiazepines were synthesized by the reaction of β–diketones or β-keto esters with 2-(trimethylsilyl)aryl triflates in the presence of CsF, followed by the addition of hydrazine hydrate.