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Facile Synthesis of 2,3-Benzodiazepines Using One-pot Two-step Phosphate-Assisted Acylation-Hydrazine Cyclization Reactions

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Abstract

Here, we report new methodology for synthesizing 2,3-benzodiazepines and their analogues by means of phosphate-assisted acylation reaction of 1-arylpropan-2-ones with a carboxylic acid followed by hydrazine cyclization in a one-pot two-step manner. An unprotected amino group is tolerated in this reaction. This method provides a direct access to 2,3-benzodiazepines containing aromatic 7,8-dimethoxy and 1-*p*-aminophenyl groups, which are generally considered important for bioactivity. The presence of 3,4-dimethoxy or 3-methoxy substitution on the benzene ring of the 1-arylpropan-2-one is important for high regioselectivity in the acylation reaction.

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Introduction

The 2,3-benzodiazepine skeleton is of interest to synthetic chemists and medicinal chemists as a core structure of compounds with various bioactivities, such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists, and consequently several new synthetic routes have recently been developed **(Figure 1**). Chang and co-workers reported a four-step synthesis of the 2,3-benzodiazepine skeleton **3**, employing Wacker oxidation reaction of **1** to generate diketone intermediate (**2**) (Figure 1 [a])[7]. Zhu and co-workers also reported a 2,3-benzodiazepine (**6**) synthesis via Rh(III)-catalyzed C-H functionalization of hydrazone **4** with diazoketoester **5** (Figure 1 [b]).[8] Okuma and co-workers synthesized the 2,3-benzodiazepine skeleton (**10**) from reactive benzyne generated from **7** and ketoester **8** (Figure 1 [c]).[9] Generation of benzo[c]pyrilium salt **13** from β-keto aromatic compound **11** and carboxylic acid chloride **12** through Friedel-Crafts acylation reaction was also reported (Figure 2 [d]).[10] The pyrilium salt **13** reacted smoothly with hydrazine to give the 2,3-benzodiazepine skeleton **14**.[11] A similar Friedel-Crafts acylation reaction of ketone **15** with *p*-nitrobenzonic acid **16** was also reported to give the diketone **17**, which was transformed into 2,3-benzodiazepine **18** (Figure 1 [e]).

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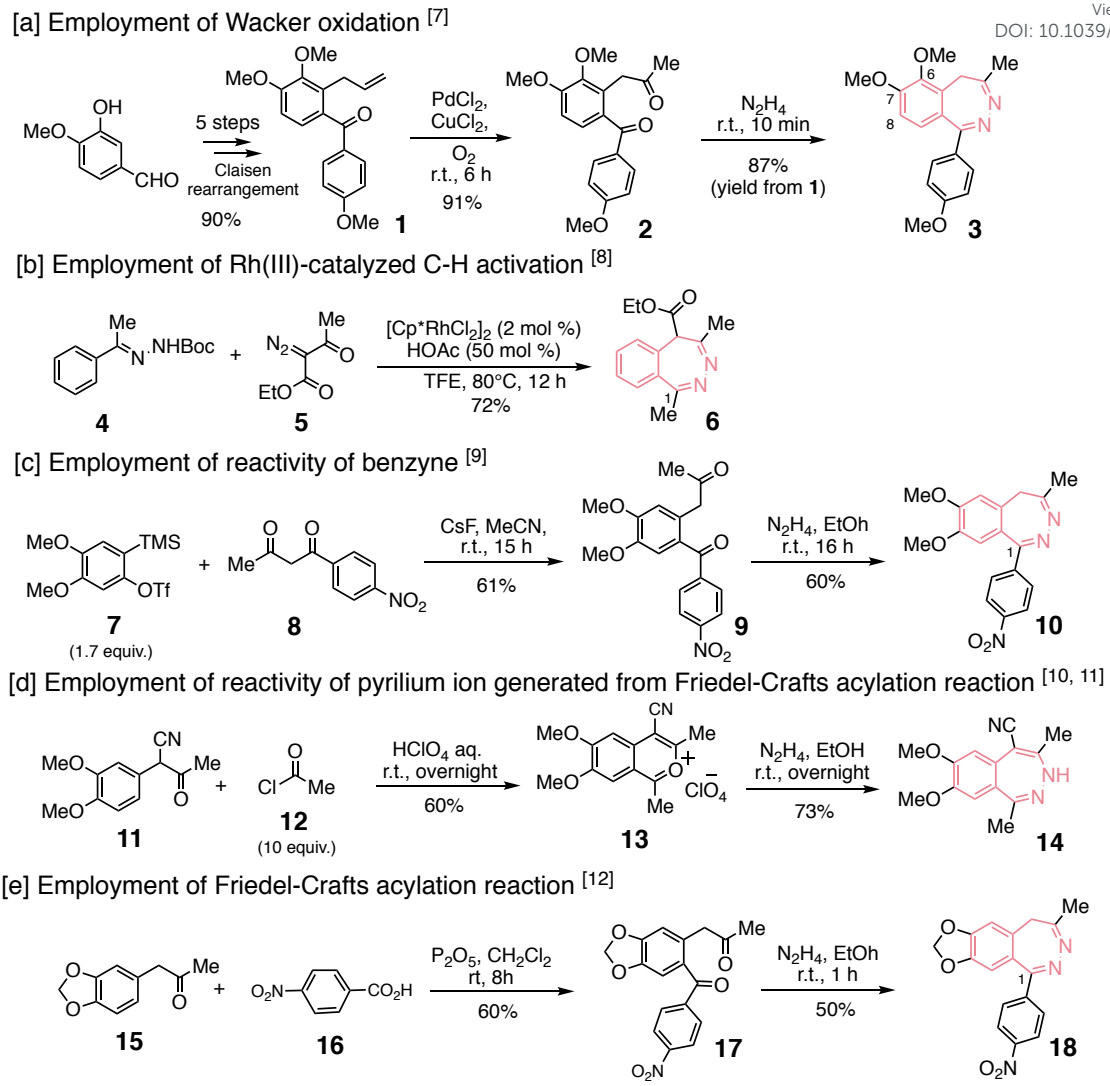

Figure 1. Representative synthetic routes leading to the 2,3-benzodiazepine skeleton.

However, these new methodologies (Figure 1) are not necessarily well suited for the synthesis of bioactive 2,3-benzodiazepine derivatives in which aromatic 7, 8-dimethoxy and substituted 1-phenyl groups are considered to be important, as exemplified by the compounds shown in **Figure 2**. Among these compounds, tofisopam **19a** is a highly active nonsedative, anxiolytic agent in humans.[5] Other 2,3-benzodiazepines such as girisopam **19b**, nerisopam **19c** and GYKI52466 **19d** also possess similar biological activities.[6] In the cases of nerisopam **19c** and GYKI52466

19d, the amine functionality is considered to be particularly important for AMPA receptor binding. [4c]

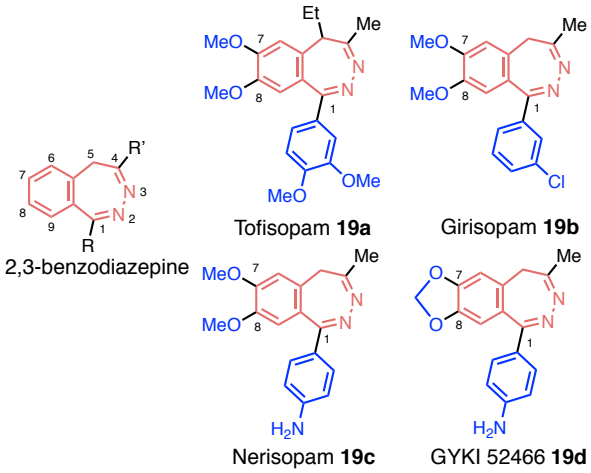

Figure 2. Representative bioactive 2,3-benzodiazepine derivatives.

But, such structures are not readily accessible via the methodologies shown in Figure 1. For example, in method [a], the Claisen rearrangement cannot afford 7,8-dimethoxy substitution instead of the 6,7-dimethoxy substitution seen in **3**. Method [b] gives poor regiocontrol if another aromatic substituent is present, since the regiochemistry of the hydroazone is crucial for ortho-directed insertion of the ketoester. In method [c], several aromatic substituents at the C1 position are compatible with the reaction, but the aromatic amino functionality found in **19c** and **19d** has to be obtained by hydrogenation of the corresponding nitro compound **10**, probably because the amino functionality can react with the putative benzyne intermediate. Method [d] is restricted to the formation of tautomeric 2,3-benzodiazepine **14**. Method [e] is the most straightforward route to 2,3-benzodiazepines, but the *p*-nitrobenzoic acid **16**, instead of *p*-aminobenzoic acid, is employed in this reaction. Thus, access to bioactive 2,3-benzodiazepine compounds is still inconvenient; for example, the synthesis of bioactive 2,3-benzodiazepines such as

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nerisopam (**19c**) requires multi-step reactions according to the relevant patents and methods (c) and (e) in Figure 1. Therefore, more direct and efficient methodology for synthesizing bioactive 2,3-benzodiazepines is still required.

Recently, we reported a phosphate-assisted acylation reaction of carboxylic acids (**Figure 3**).[13] The tailored phosphate ester **22** is activated under acidic conditions, and reacts with carboxylic acid **21** to form acyl phosphate **21a**. The acyl phosphate **21a** smoothly reacts with an aromatic compound to give the corresponding ketone **23** in high yield at room temperature after a short time. The phosphate-assisted acylation reaction can afford aromatic ketones containing a free amino functional group (Figure 3). Thus, this reaction should provide direct access to 2,3-benzodiazepines containing a free amino functional group, such as nerisopam (**19c**).

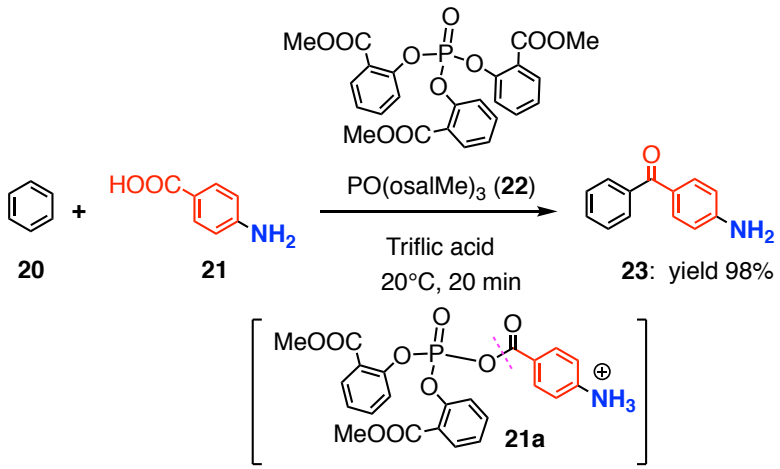

Figure 3. Phosphate-assisted acylation reaction.

We report herein a one-pot two-step synthesis of bioactive 2,3-benzodiazepines by means of phosphate-assisted acylation reaction followed by basic hydrazine cyclization, staring from 1-(3,4-dimethoxyphenyl)propan-2-one **24**. In this synthesis, an appropriate choice of commercially available carboxylic acids allows

various substituent groups to be introduced at the C1 position of 7,8-dimethoxy-2,3-benzodiazepine. 3,4-Dimethoxy substitution, or at minimum a 3-methoxy group, on the aromatic ring of the 1-arylpropan-2-one (**24**) is critical for high regioselectivity in the acylation reaction.

Results and Discussion

Development of one-pot two-step acylation and hydrazine cyclization reactions

To build the desired 2,3-benzodiazepines (**Figure 2**) by means of phosphate-assisted acylation reaction, we considered stepwise and one-pot two-step approaches **(Figure 4**). We attempted to isolate the di-ketone intermediate **25-1** or **25-2**, a precursor for hydrazine cyclization, through basic aqueous work-up, extraction and column-chromatography (see Experimental Sections) after phosphate-assisted acylation reaction of **24** with **21**, but the diketone **25** cannot be isolated. Instead, only the isomeric diketone (**26**) was obtained in a low yield (17% yield) (Figure 4, [a]). Because the related non-aminodiketone compounds such as **2**, **9** and **13** and **17** were inert and isolable in high yields (see Figure 1), the aniline-diketone compound **25-1** or the resultant pyrilium ion (**25-2**) were unstable upon neutralization due to the presence of two incompatible reactive functionalities, ketone and amino groups, resulting in the formation of polar polymeric substances in the work-up process. A similar situation was also encountered in the cases of reactions of various methoxy-substituted 1-phenylpropan-2-ones (see Figure 6).

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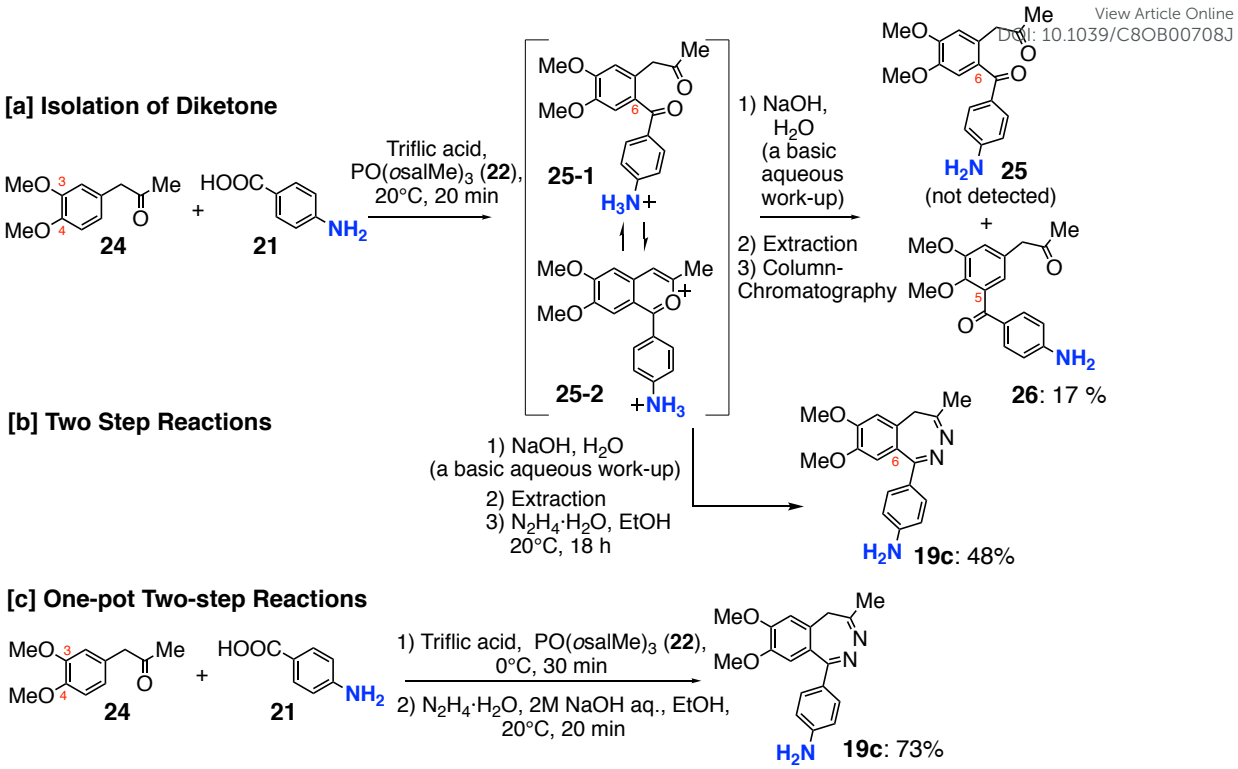

Figure 4. Optimization of reaction procedures

Thus, we applied the above base work-up procedure after the phosphate-assisted acylation reaction to neutralize the reaction mixture, and then added hydrazine to the crude diketone mixture **25** without purification with column chromatography. The desired 2,3-benzodiazepine, nerisopam **19c**, was formed (Figure 4, [b]), while the yield was still 48%, probably for the same reason as before (see Experimental Sections).[15] After treatment with hydrazine, it was difficult to identify the isomeric diketone **26**, probably hydrazine reacts with diketone **25** in multiple manners. Therefore, we tried one-pot two-step reactions. The acid reaction mixture for phosphate-assisted acylation of **24** was poured directly into an alkaline solution of hydrazine monohydrate and sodium hydroxide in water and ethanol, which basified the medium *in situ* (Figure 4, [c]). Ethanol was employed as a co-solvent to aid dissolution of the substrates. This *in situ* quenching procedure worked well, and the

yield of nerisopam **19c** was increased to 73% (Figure 4, [c]). The regioselectivity of acylation was approximately 81% (regioselectivity at the 6-position (**19c**)): 19% (regioselectivity at the 5-position (**26**)) (see Figure 6 and discussion of regioselectivities). Finally, we conducted detailed optimization of the reaction conditions of the hydrazine cyclization reaction in the one-pot two-step reaction, as follows.

Optimization of reaction conditions of hydrazine cyclization reaction

Using the optimal conditions of the acid-catalyzed acylation described above, we next focused on the hydrazine cyclization reaction in the one-pot two-step method (Figure 4, [c]). We examined several factors including (a) the amount of hydrazine (b) solvent (c) base (d) reaction time, and (e) reaction temperature (**Table 1**). When the amount of hydrazine monohydrate was increased to 20 equivalents, the yield of **19c** increased from 53% to 73% (Table 1, entries 1, 2), probably because the hydrazine monohydrate also worked as a base to neutralize triflic acid. On the other hand, when the amount of hydrazine monohydrate was further increased to 30 equivalents, the yield of the reaction did not change (74%, entry 3), so we considered that 20 equivalents of hydrazine monohydrate was sufficient. Moreover, cooling and a longer reaction time during the hydrazine cyclization reaction had no effect on the yield (71~77%, entries 3, 4 and 5). Also, cooling during the phosphate-assisted acylation reaction was ineffective (78%, entry 6). A heterogeneous condition using ethanol instead of water gave a comparable yield (79%, entry 7). Therefore, the conditions in entries 6 and 7 were concluded to be optimal for the hydrazine cyclization reaction. We applied these reaction conditions to another *p*-bromobenzonic acid **27a** and several aliphatic carboxylic acids (**27b**, **27c** and **27d**). Under either of the reaction

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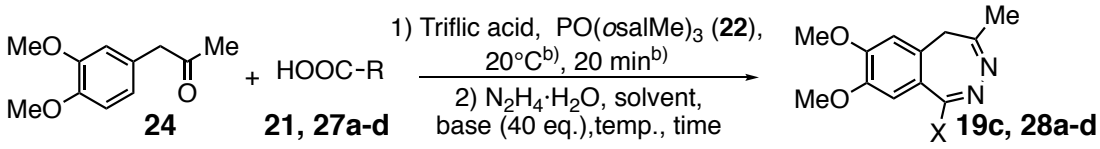
conditions (entries 6 and 7), we obtained the corresponding 2,3-benzodiazepines in good yields: (**28a**: 71%, (entry 8); **28b**: 80% (entry 9); **28c**: 74% (entry 10); **28d**: 72% (entry 11).

Table 1. Optimization of the one-pot two-step reaction.



Entry	R	$N_2H_4{\cdot}H_2O$	Solvent	Base	Temp.	Time	Yield (%)[a]
1[b]	*p*-NH_2Ph (**21**)	5 eq.	H_2O-EtOH	NaOH	0°C	20 min	**19c**: 53%
2[b]	*p*-NH_2Ph (**21**)	20 eq.	H_2O-EtOH	NaOH	0°C	20 min	**19c**: 73%
3[b]	*p*-NH_2Ph (**21**)	30 eq.	H_2O-EtOH	NaOH	0°C	20 min	**19c**: 74%
4[b]	*p*-NH_2Ph (**21**)	20 eq.	H_2O-EtOH	NaOH	20°C	20 min	**19c**: 77%
5[b]	*p*-NH_2Ph (**21**)	20 eq.	H_2O-EtOH	NaOH	20°C	1440 min	**19c**: 71%
6	*p*-NH_2Ph (**21**)	20 eq.	H_2O-EtOH	NaOH	20°C	20 min	**19c**: 78%
7	*p*-NH_2Ph (**21**)	20 eq.	EtOH	Na_2CO_3	20°C	10 min	**19c**: 79%
8	*p*-BrPh (**27a**)	20 eq.	EtOH	Na_2CO_3	20°C	10 min	**28a**: 71%
9	Me (**27b**)	20 eq.	H_2O-EtOH	NaOH	20°C	10 min	**28b**: 80%
10	Et (**27c**)	20 eq.	H_2O-EtOH	NaOH	20°C	10 min	**28c**: 74%
11	$C_{18}H_{37}$ (**27d**)	20 eq.	EtOH	Na_2CO_3	20°C	10 min	**28d**: 72%

a) Isolation yields, calculated on the basis of the amount of carboxylic acids.
b) For the phosphate-assisted acylation reaction, the reaction temperature was 0°C, and the reaction time was 30 minutes.

Scope of the present acylation reaction

Using the optimized one-pot two-step reaction, *m*-chlorobenzonic acid **27e** and 1-(3,4-dimethoxyphenyl)propan-2-one **24** successfully afforded girisopam **19b** in 73% yield **(Figure 5**). We also attempted the synthesis of GYKI52466 **19d** starting from

24-acetal and *p*-aminobenzoic acid **21**, but the reaction became complex, probably because the acetal unit of **24-acetal** decomposed under the acid conditions (Figure 5).

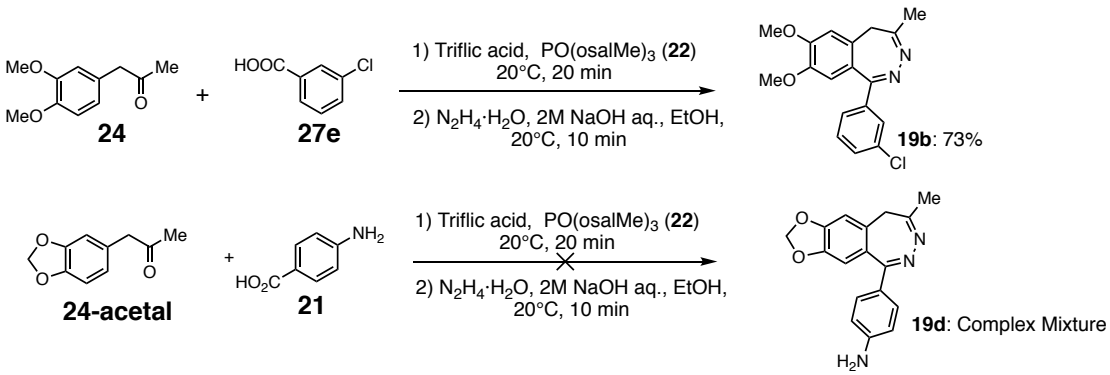


Figure 5. Synthesis of 19b and attempted synthesis of 19d

We found that the position of electron-donating methoxy groups on the benzene ring of **29** was crucial for high regio-selective *in situ* acylation of **29** (**Figure 6**). Under the optimal reaction conditions, aromatic acylation of unsubstituted 1-phenyl-3-methyl-butan-2-one **29a** with *p*-aminobenzoic acid **21** in the presence of triflic acid and phosphate **22** did not proceed, and instead only two esters were formed (**30a**: 68% yield; **31**: 28% yield) (Figure 6 (a)). Furthermore, when 1-(4-methoxyphenyl)propan-2-one **29b** and *p*-aminobenzoic acid **21** were used, the acylation occurred at the 3-position of the benzene ring with high regioselectivity and the di-ketone **30b** was isolated in 75% yield (Figure 6 (b)). This di-ketone **30b** was sufficiently stable because it cannot cyclize to afford the pyrilium ion (such as **25**, see **Figure 4**). When the one-pot two-step reaction was applied to 1-(3-methoxyphenyl)propan-2-one **29c** and *p*-aminobenzoic acid **21**, the corresponding 2,3-benzodiazepine **30c** was obtained in 66% yield (Figure 6(c)). Therefore, the acylation reaction of *p*-aminobenzoic acid **21** was significantly influenced by the

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electron-donating substituent at the 3-position of the aromatic ring of **29c**. Furthermore, when 1-(2-methoxyphenyl)propan-2-one **29d** and *p*-aminobenzoic acid

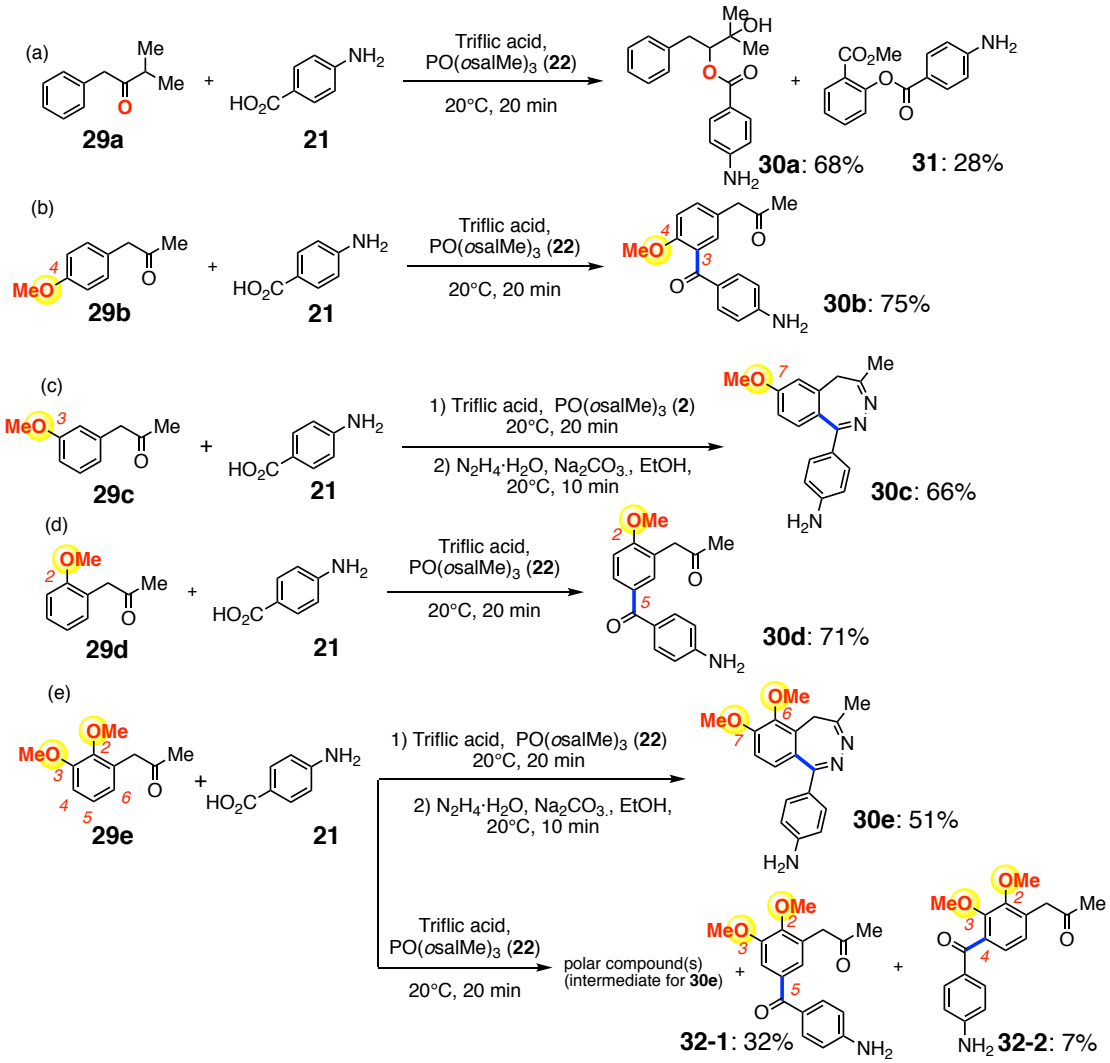

Figure 6. Predominat regioselectivities of methoxy-substituted 1-phenylpropan-2-ones

21 were used, the acylation occurred at the 5-position of the benzene ring with high selectivity and the di-ketone **30d** was isolated in 71% yield (Figure 6(d)). Finally, 1-(2,3-methoxyphenyl)propan-2-one **29e** and *p*-aminobenzoic acid **21** afforded the corresponding 2,3-benzodiazepine **30e** in 51% yield under the one-pot two-step reaction conditions. When the same reagents were subject to acylation reaction

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without hydrazine cyclization, the acylation occurred at the 4- and 5-positions as well as the 6-position of the benzene ring, affording a mixture of the di-ketones **32-1** and **32-2** in 32%, and 7% yields, respectively, while the 6-substituted compound decomposed to polar products during the isolation. Therefore, the aromatic 3,4-dimethoxy groups, or at a minimum the 3-methoxy group, on the benzene ring are crucial for highly regioselective acylation leading to the generation of 2,3-benzodiazepines (the regioselectivity of acylation was approximately 81% (regioselectivity at the 6-position (**19c**)): 19% (regioselectivity at the 5-position (**26**)), see Figure 4). The 4-methoxy group favored ortho-directed acylation (Figure 6 (b)) while the 3-methoxy group favored para-directed acylation (Figure 6 (c)). In the case of 2,3-dimethoxy substitution (Figure 6 (e)), acylation at the para position with respect to the 3-methoxy group was favored (57% regioselectivity), but acylation at the 4 and 5-positions also occurred (43% regioselectivity). On the other hand, in the case of 3,4-dimethoxy substitution (Figure 4 (c)), acylation at the para-position with respect to the 3-methoxy group was predominant (at least more than 80% regioselectivity). This difference of regioselectivity between the 2,3-dimethoxy (**29e**) and 3,4-dimethoxy (**24**) substrates may be due to steric interactions of the methoxy group(s).

Moreover, the steric effect at the α-position of the β-keto aromatic compound greatly affected the efficiency of the hydrazine cyclization reaction (**Figure 7**). When a methyl group was introduced at the α-position of the β-keto aromatic compound **33**, the one-pot two-step reaction became complex, although the formation of **34** was detected. Moreover, when two methyl groups were introduced at the α-position of the β-keto aromatic compound **35**, the desired 2,3-benzodiazepine skeleton **36** was not

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formed. These results are consistent with the idea that the initial addition of hydrazine occurs at the aliphatic ketone rather than the aromatic ketone; that is, steric hindrance at the β-keto moiety hampers the addition of hydrazine, inhibiting hydrazine cyclization. This in turn suggests that benzoic acid derivatives bearing an *o*-substituent would be challenging substrates in this Friedel-Crafts acylation process. Indeed, less sterically demanding *o*-substituents such as halogen atoms were found to be compatible (see Table 2). These data suggested that the present method would not provide access to tofisopam **19a** from a ketone starting material similar to **33**.

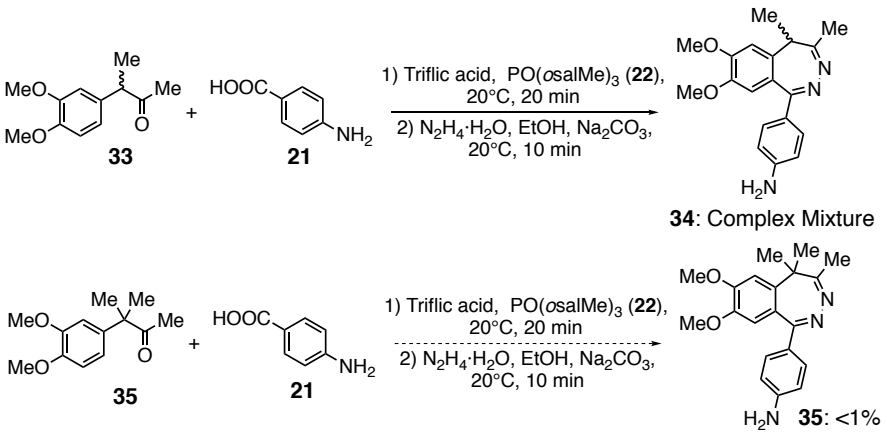

Figure 7. Effect of steric hindrance on the acylation reaction.

Scope of the synthesis for 7,8-dimethoxy-2,3-benzodiazepine derivatives

With the optimized conditions in hand, we examined the substrate generality of this sequential reaction (**Table 2**). Among aromatic carboxylic acids, benzoic acid **27d**, toluic acid (**27g**, **27h**, **27i**), halogen-substituted benzoic acid (**27a**, **27e**, **27j**, **27k**, **27l**, **27m**),[19] and aminobenzoic acid (**21**, **27n**) could be used in the one-pot two-step phosphate-assisted acylation and ring formation. Interestingly, *o*-substituted benzoic acids (**27i**, **27k**, **27l**, **27m**) afforded high yields. The presence of an aromatic ring substituted at the C1 position on the 2,3-benzodiazepine ring is suggested to be crucial for interaction with the AMPA receptor.[4c,20] However, the one-pot two-step

reaction from *o*-substituted aminobenzoic acid failed (**27n**) (recovery **24**: 52%). This inertness of **24** may be due to charge-charge repulsion between protonated **24** and the *o*-substituted ammonium-acylium dication. As for heteroaromatic carboxylic acids, thiophene 2-carboxylic acid **27p** and quinoline 6-carboxylic acid **27q** gave the desired 2,3-benzodiazepines in high or moderate yields. This one-pot two-step reaction also afforded 2,3-benzodiazepines from conjugated carboxylic acid or aliphatic carboxylic acid. As for the conjugated carboxylic acids (**27r**, **27t**, **27u**), β-keto aromatic compound **24** reacted with these conjugated carboxylic acids only in the Friedel-Crafts acylation mode, and side products derived from 1,4-addition reaction (i.e. Michel addition reaction) were not observed.[21] When an electron-rich functional group was introduced into the conjugated carboxylic acid (**27s**), the desired 2,3-benzodiazepine skeleton was not formed. Probably the electron-rich conjugated system would be activated under the acidic condition to promote polymerization.[22] Among aliphatic carboxylic acids, both small molecules such as acetic acid (**27b**) and large molecules such as nonadecanoic acid (**27d**) were suitable for the one-pot two-step reaction. Also, secondary carboxylic acid (**27v**), carboxylic acid containing ethyl ester (**27w**),[23] and benzylacetic acid (**27x**) were tolerated in the one-pot two-step reaction. A protection-free aliphatic secondary amino group (**27y**) was also tolerated, and the desired 2,3-benzodiazepine skeleton was obtained in good yield.

In all the examples in Table 2, no significant amount of other regioisomers was detected, confirming that the aromatic 3,4-dimethoxy groups are crucial for high regioselectivity in the Friedel-Crafts acylation.

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Table 2. Substrate generality in one-pot two-step build-up of the 2,3-benzodiazepine skeleton.[a)]

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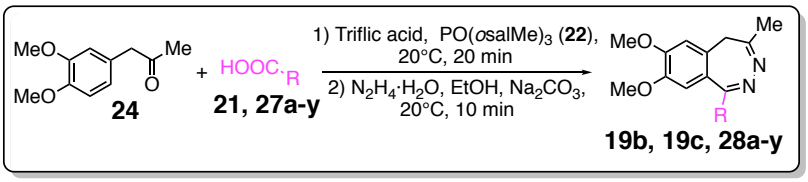

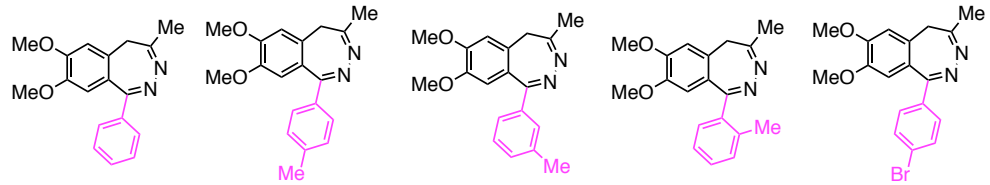

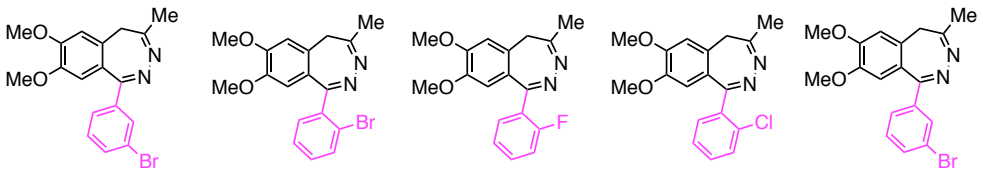

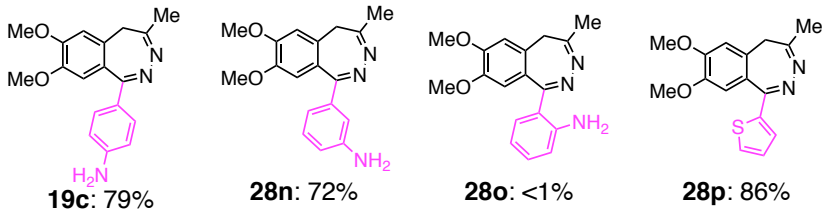

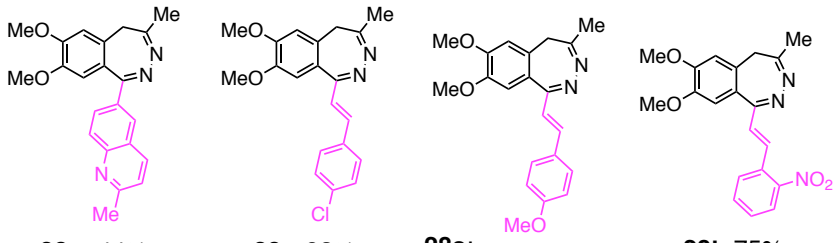

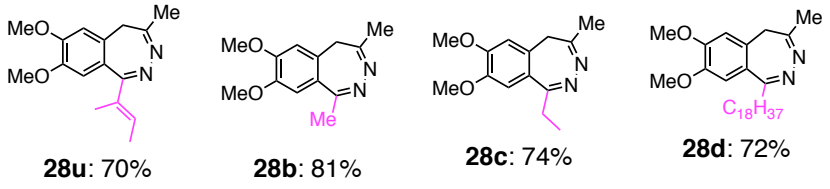

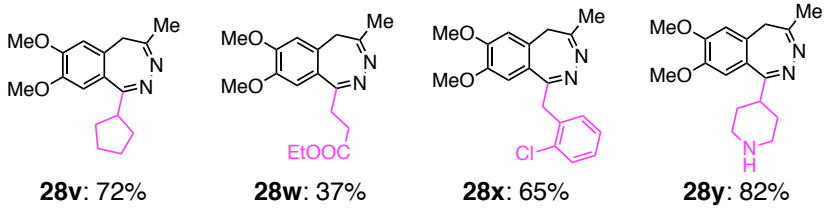

a) Isolation yields, calculated on the basis of carboxylic acids are shown.

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Conclusion

We have developed a straightforward synthesis of bioactive 2,3-benzodiazepines by means of phosphate-assisted acylation and hydrazine cyclization reactions using one-pot two-step methodology. This methodology was also applicable to aromatic and aliphatic carboxylic acids and a β-keto aromatic compound **24**. A free amino functional group was tolerated under the reaction conditions. We found that the 3,4-dimethoxy groups of 1-phenylpropan-2-one are crucial for high regioselectivity in the Friedel-Crafts acylation. Thus, bioactive 2,3-benzodiazepines such as girisopam **19b** and nerisopam **19c** can be directly synthesized in the present reaction from commercially available compounds at room temperature within a short reaction time. However, further work will be needed to achieve direct access to other bioactive 2,3-benzodiazepines.

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Experimental Section

General Procedures

Melting points were determined with a Yanaco micro melting point apparatus without correction. ^{1}H-NMR (400 MHz), ^{13}C-NMR spectra (100 MHz) and ^{31}P-NMR spectra (162 MHz) were recorded on a Bruker Avance400. Chemical shifts are given in ppm (δ) values, and coupling constants are shown in hertz (Hz). Chemical shifts were calibrated with internal tetramethylsilane or with the solvent peak for the ^{1}H NMR and ^{13}C NMR spectra, and with 85% H_3PO_4 in a sealed capillary used as an external

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standard for ^{31}P NMR spectra. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, ddd = double double doublet, dt = double triplet, td = triple doublet, qd = quarto doublet, qt = quarto triplet m = multiplet, and brs = broad singlet. Electron spray ionization time-of-flight mass spectra (ESI-TOF MS) were recorded on a Bruker micrOTOF-05 to obtain high-resolution mass spectra (HRMS). All of the reactions were performed in heat-gun-dried or oven-dried glassware. Trifluoromethanesulfonic acid (triflic acid) was treated with trifluoromethanesulfonic anhydride (Tf_2O) before distillation, and purified prior to use by distillation under reduced pressure. Other commercially available compounds and solvents were used as received.

Preparation of tris(methylsalicylate) phosphate ester 22

To a mixture of methyl salicylate (11976.5 mg, 78.7 mmol), *N*,*N*-diisopropylethylamine (15.0 mL) in CH_2Cl_2 (10.0 mL), phosphoryl trichloride (2.5 mL, 26.7 mmol) was added slowly at 0°C. The whole was stirred at 20°C for 22 hours and then evaporated to give a residue, which was column-chromatographed on silica gel (eluent: EtOAc : n-hexane = 1 : 1) to afford tris(methylsalicylate) phosphate ester **22** (11781.3 mg, 23.5 mmol, 90%) as a colorless solid.

Mp. 74.2-75.1°C (colorless plates, recrystallized from Et_2O/n-hexane). ^{1}H-NMR ($CDCl_3$, 400 MHz) : δ (ppm): 7.901 (3H, d, J = 7.6 Hz), 7.557-5.479 (6H, m), 7.273 (3H, dd, J = 7.2, 7.2 Hz), 3.696 (9H, s). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 165.85, 149.68 (d, J^{CP} = 7 Hz), 134.13, 132.50, 126.02, 123.82 (d, J^{CP} = 7 Hz), 122.38 (d, J^{CP} = 3 Hz), 52.74. ^{31}P-NMR ($CDCl_3$, 162 MHz) δ (ppm): -19.95. HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{24}H_{21}NaO_{10}P^+$: 523.0765. Found: 523.0765. Anal. Calcd. for $C_{24}H_{21}O_{10}P$: C, 57.61; H, 4.23. Found: C, 57.47; H, 4.30.

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Typical procedure for the phosphate-assisted acylation reaction and hydrazine cyclization reaction under one-pot two-step conditions. – Synthesis of Nerizopam 19c

Triflic acid (2.0 mL) was added to a mixture of 1-(3,4-dimethoxyphenyl)propan-2-one (**24**) (197.6 mg, 1.02 mmol), 4-aminobenzoic acid **21** (137.6 mg, 1.00 mmol), and tris(methylsalicylate) phosphate ester **22** (501.8 mg, 1.00 mmol) at 20°C. The reaction mixture was stirred for 20 minutes at 20°C. The crude mixture was added to a mixture of hydrazine monohydrate (1.0 mL, 20.6 mmol), EtOH (20.0 mL), and sodium carbonate (4221.9 mg, 39.83 mmol) at 0°C. The whole was stirred for 10 minutes at 20°C, and then $CHCl_3$ (50 mL) and water (50 mL) were added. The reaction mixture was extracted with $CHCl_3$ (50 mL x 3). The organic phase was washed with brine (40 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give a residue, which was column-chromatographed on silica gel (eluent : EtOAc : MeOH = 10 : 1) to afford 4-(7,8-dimethoxy-4-methyl-5*H*-benzo[*d*][1,2]diazepin-1-yl)aniline **19c** (243.3 mg, 0.79 mmol, 79%) as a yellow solid.

Mp. 120.1-122.2°C (colorless plates, recrystallized from EtOH). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.504 (2H, d, J = 8.8 Hz), 6.837 (1H, s), 6.715 (1H, s), 6.680 (2H, d, J = 8.4 Hz), 3.960 (3H, s), 3.746 (3H, s), 3.220 (1H, d, J = 12.0 Hz), 3.031 (1H, d, J = 12.0 Hz), 2.126 (3H, s). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 158.72, 155.62, 152.30, 148.79, 148.32, 133.45, 131.51, 129.54, 123.11, 114.93, 113.38, 108.93, 56.67, 56.61, 38.85, 23.56. HRMS (ESI-TOF, $[M+H]^+$): Calcd. for $C_{13}H_{12}NO^+$: 310.1550. Found: 310.1545. Anal.: Calcd. for $C_{13}H_{11}NO$ + 0.46 EtOH: C, 67.06; H, 6.75; N, 12.40. Found: C, 66.68; H, 6.82; N, 12.21.

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