An Improved Method for Synthesis of 4,4-Dimethylpyrazolone and Application to Dihydropyridazinone Ring Formation

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An improved method for 4,4-dimethylpyrazolone synthesis with *t*-butylcarbazate was described. The applicability of this method to dihydropyridazinone formation was demonstrated. This method is useful for suppressing the side reaction caused by the high nucleophilicity of hydrazine.

Key words 4,4-dimethylpyrazolone; *t*-butylcarbazate; dihydropyridazinone

We have been searching for dual phosphodiesterase (PDE) 3/4 inhibitors and found that dihydropyridazinone derivative **3a** has unique biological activity.[1,2] On the other hand, pyrazolone is also known as an attractive structure in medicinal chemistry.[3,4] We therefore attempted to synthesize 4,4-dimethylpyrazolone derivative **5**, in which a 4,4-dimethylpyrazolone ring was introduced instead of a dihydropyridazinone ring.[5] However, **5** was obtained in an insufficient yield under the same conditions as for dihydropyridazinone ring formation, because a nucleophilic attack of hydrazine to the 7-position of pyrazolo[1,5-*a*]pyridine occurred, generating mainly undesired byproduct **5′** (Chart 1). In the case of dihydropyridazinone ring formation, no such side reaction was observed, even in the synthesis of dimethyldihydropyridazinone derivative **3b**. The difference in yield between **3a** and **b** can be explained by steric hindrance at the α-position of a ketone. But we cannot explain why the yield of **5** is very low. Calculation of the lowest unoccupied molecular orbitals (LUMOs) of **2a**, **b**, and **4** suggested that the 7-position of pyrazolo[1,5-*a*]pyridine can be more reactive for a nucleophile than a ketone in 4,4-dimethylpyrazolone formation. However, in dihydropyridazinone formation, a ketone is more reactive, even in the case of **2b**.[6] Therefore, it was presumed that hydrazine attacked the 7-position of pyrazolo[1,5-*a*]pyridine prior to a ketone.

By considering the result of calculation of the LUMOs, it was supposed that 4,4-dimethylpyrazolone formation from **4** with hydrazine was very difficult, and we attempted to apply the other method. Kobayashi *et al.* reported that $Sc(OTf)_3$ catalyzed a Mannich-type reaction of acylhydrazones with silyl enolates followed by cyclization to give pyrazolone derivatives in an excellent yield.[7—9] We utilized Kobayashi's method for the synthesis of **5** (Chart 2). Contrary to our expectation, 4,4-dimethylpyrazolone precursor **9** was obtained in a low yield even if excess amounts of **8** or $Sc(OTf)_3$ were employed, the reaction temperature was increased, or the solvent was changed.

Application of Kobayashi's method to the synthesis of our target compound was a failure, however, it was found that benzoylhydrazone **7** was obtained without the occurrence of a nucleophilic attack of $BzNHNH_2$ to the 7-position of pyrazolo[1,5-*a*]pyridine. This shows that some acylhydrazines might have a potential to attack a ketone selectively. Based on this finding, we carefully examined the formation of hydrazone, which was a pyrazolone precursor, without inducing a side reaction (Table 1). We selected *t*-butylcarbazate ($BocNHNH_2$) as a hydrazine source because the Boc group could be easily removed under acidic conditions after dimethylpyrazolone formation. As a result, an undesired side reaction, nucleophilic substitution at the 7-position, was suppressed (Entry 1). However, the desired compound **10** was not obtained under this condition. Although the reaction temperature was increased by changing the solvent from EtOH to toluene, **10** was not observed (Entry 2). Surprisingly, when 0.1 eq of pyridinium *p*-toluenesulfonate (PPTS) was added under

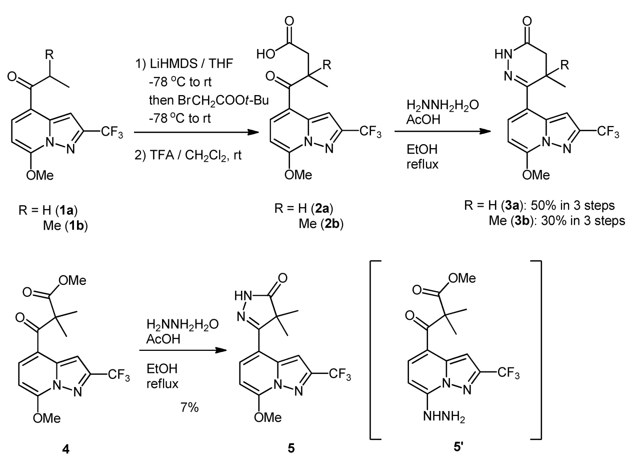

Chart 1. Syntheses of Dihydropyridazinone and 4,4-Dimethylpyrazolone in the General Method

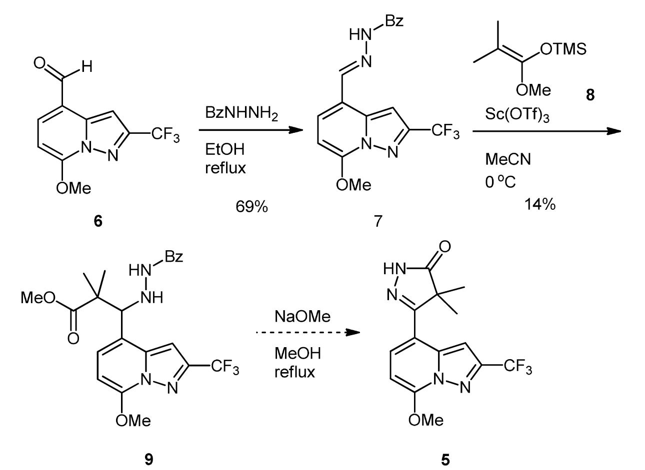

Chart 2. 4,4-Dimethylpyrazolone Formation under Kobayashi's Condition

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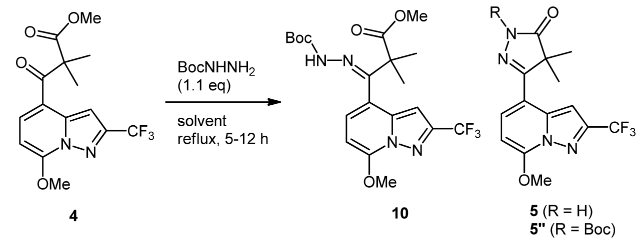
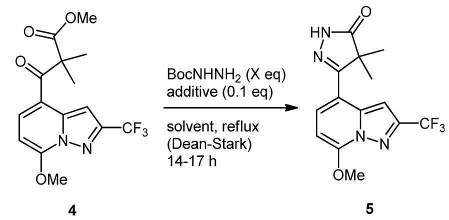
Table 1. Hydrazone Formation with *t*-Butylcarbazate



Entry	Solvent	Additive	Yield of **10** (%)[a]	Yield of **5″** (%)[a]	Yield of **5** (%)[a]
1	EtOH	None	NR[b]	NR[b]	NR[b]
2	Toluene	None	NR[b]	NR[b]	NR[b]
3[c]	Toluene	PPTS[d]	0	15	Trace

a) Isolated yield. *b*) NR=no reaction. *c*) Dean–Stark trap was used to remove water. *d*) 0.1 eq of PPTS was used.

Table 2. Optimization of Reaction Conditions



Entry	X (eq)	Solvent	Additive	Yield of **5** (%)[a]
1	1.1	Xylene	PPTS	37
2	3	Xylene	PPTS	46
3	3	Xylene	PTSA	41
4	10	Xylene	PPTS	51
5[b]	3	EtOH	PPTS	Trace

a) Isolated yield. *b*) Molecular sieves 3A (powder) was added to the reaction mixture instead of using the Dean–Stark trap.

dehydration conditions with a Dean-Stark trap, we obtained 4,4-dimethylpyrazolone **5″** in a low yield, not hydrazone **10**. In addition, we observed a trace amount of **5**. Thus, since we could produce the desired pyrazolone **5** directly from ketoester **4**, the reaction conditions for the synthesis of **5** were further optimized (Table 2).

When the solvent was changed from toluene to xylene and the reaction temperature was increased, the yield of **5** improved (Entry 1). Treatment of **4** with 3 eq of $BocNHNH_2$ gave **5** in 46% yield (Entry 2). The yield of **5** was not influenced by the change of the acid (*p*-toluenesulfonic acid (PTSA) instead of PPTS) (Entry 3). Moreover, when 10 eq of $BocNHNH_2$ was employed, the yield of **5** was slightly increased to give the best result (Entry 4). On the other hand, the use of a polar solvent such as EtOH, which was reacted under general conditions, was ineffective even under dehydration conditions by the addition of molecular sieves (Entry 5). It was presumed that the reaction between a sterically hindered ketone **4** and $BocNHNH_2$, which is less nucleophilic than hydrazine, required a high temperature, and that the cyclization of the resultant hydrazone **10** was very fast. In addition, it seems that the Boc group is thermally removed after the construction of the 4,4-dimethylpyrazolone ring. As mentioned above, we have found the reaction conditions for 4,4-dimethylpyrazolone synthesis without an undesired side reaction.

At around the same time, we faced another problem on the dual PDE3/4 inhibitor project. In the case of the synthesis of 2-trifluoromethyl-benzoxazole derivative **14**, the nucleophilic attack of hydrazine to the 2-position of the benzoxazole core as well as dihydropyridazinone ring formation was observed under the same conditions as the synthesis of **3**, and we could not obtain the desired **14** (Chart 3). Then, we applied the optimized condition for 4,4-dimethylpyrazolone synthesis to the formation of a dihydropyridazinone ring. As expected, the desired compound **14** was obtained in a moderate yield without an undesired side reaction. We demonstrated that the optimized condition for 4,4-dimethylpyrazolone synthesis was applicable to dihydropyridazinone ring formation.

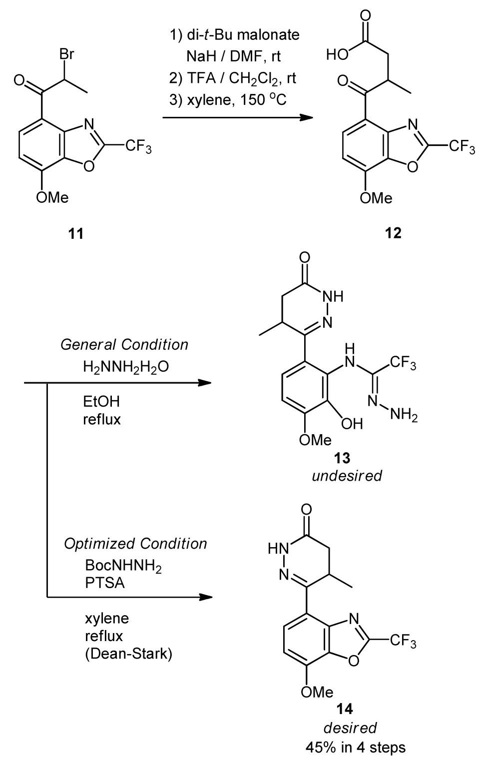


Chart. 3. Application to Dihydropyridazinone Formation

In conclusion, we have found an improved method for synthesis of 4,4-dimethylpyrazolone with $BocNHNH_2$ and for dramatically increasing the yield of **5**, from 7 to 51%. In addition, we demonstrated the applicability of this method to the formation of the dihydropyridazinone ring. This method is useful for suppressing the side reaction caused by the high nucleophilicity of hydrazine.

Experimental

General ^{1}H-NMR spectra were measured with a JEOL JNM-ECA-400 or -ECX-400 (400 MHz) spectrometer. The chemical shifts are expressed in parts per million (δ value) downfield from tetramethylsilane, using tetramethylsilane (δ=0) and/or residual solvents such as chloroform (δ=7.26) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet. Measurements of mass spectra were performed with a JEOL JMS-SX102X mass spectrometer. Data for elemental analyses are within ±0.3% of the theoretical values, and were determined by a Yanaco CHN-corder MT-6. The melting points were determined on a TOKYO INSTRUMENTS, INC., Japan, OptiMelt Automated Melting Point System and are uncorrected. Unless otherwise noted, all the experiments were carried out using anhydrous solvents under an atmosphere of argon. Throughout this study, Merck precoated TLC plates (Silica gel 60 F_{254}, 0.25 mm) were used for thin layer chromatographic (TLC) analysis, and all of the spots were visualized using UV light followed by coloring with phosphomolybdic acid or anisaldehyde. Silica gel 60N (40—50 μm, neutral; Kanto Chemical Co., Inc., Tokyo, Japan) or Chromatorex® NH DM2035 (200—350 mesh; Fuji Silysia Chemical, Ltd., Aichi, Japan) was used for the flash column chromatography.

Preparation of 5 To a stirred solution of **4** (1.15 g, 3.34 mmol) in xylene (30.0 mL) were added *t*-butylcarbazete (1.32 g, 10.0 mmol) and PPTS (100 mg, 0.398 mmol), and the reaction mixture was stirred for 16 h under reflux conditions with a Dean–Stark trap. The resultant solution was directly purified by silica gel column chromatography (*n*-hexane : EtOAc=1 : 1) to give **5** (501 mg, 1.54 mmol, 46%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 1.59 (6H, s), 4.24 (3H, s), 6.30 (1H, d, J=8.0 Hz), 7.58 (1H, d, J=8.0 Hz), 7.68 (1H, s), 8.89 (1H, brs). *Anal.* Calcd for $C_{14}H_{13}F_3N_4O_2$: C, 51.54; H, 4.02; N, 17.17. Found: C, 51.33; H, 4.10; N, 17.10. mp >170°C (decomp.).

Preparation of 7 To a stirred solution of **6** (500 mg, 2.05 mmol) was added $BzNHNH_2$ (279 mg, 2.05 mmol). After stirring for 3.5 h under reflux conditions, solvent was removed under reduced pressure. The resultant solid was triturated with diisopropyl ether, filtered, and recrystallized from MeCN to give **7** (513 mg, 1.42 mmol, 69%) as a white solid. ^{1}H-NMR (DMSO-d_6) δ: 4.20 (3H, s), 6.74 (1H, d, J=8.0 Hz), 7.53—7.61 (3H, m), 7.75 (1H, d, J=8.0 Hz), 7.81 (1H, s), 7.94—7.95 (2H, m), 8.55 (1H, s), 12.00 (1H, s). Electron ionization-high resolution-mass spectra (EI-HR-MS) *m/z*: 362.0997 (Calcd for $C_{17}H_{13}F_3N_4O_2$: 362.0991). *Anal.* Calcd for $C_{17}H_{13}F_3N_4O_2$: C, 56.36; H, 3.62; N, 15.46. Found: C, 56.26; H, 3.71; N, 15.32. mp 273—274°C.

Preparation of 9 To a stirred solution of **7** (50.0 mg, 0.138 mmol) in MeCN (3 mL) were added $Sc(OTf)_3$ (6.80 mg, 13.8 μmol) and **8** (42.0 mL, 0.207 mmol) at 0°C. After stirring for 1.5 h at 0°C, the reaction was quenched with sat. $NaHCO_3$ aq. and the resultant mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative thin-layer chromatography (*n*-hexane : EtOAc=1 : 1) to give **9** (9.20 mg, 19.8 μmol, 14%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, s), 1.36 (3H, s), 4.18 (3H, s), 4.75 (1H, brs), 5.52 (1H, brs), 6.27 (1H, d, J=7.3 Hz), 7.06 (1H, brs), 7.28—7.53 (7H, m). FAB-MS *m/z*: 465 ($M+H^+$).

Preparation of 14 To a stirred solution of *t*-butyl malonate (1.08 g, 4.99 mmol) in *N*,*N*-dimethylformamide (DMF) (20 mL) was added NaH (60% in oil, 150 mg, 3.75 mmol) at 0°C. After stirring for 0.5 h at room temperature, a solution of **11** (684 mg, 1.94 mmol) in DMF (5 mL) was added and the reaction mixture was stirred for 1 h. The reaction was quenched with sat. NH_4Cl aq. and the resultant mixture was extracted with EtOAc. The organic layer was washed with H_2O, brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane : EtOAc=4 : 1) to give diester (793 mg). The resultant diester (793 mg) was dissolved in CH_2Cl_2 (10 mL) and treated with trifluoroacetic acid (TFA) (5 mL). After stirring for 0.5 h at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in xylene (30 mL) and the mixture was stirred for 2 h at 150°C. *t*-Butylcarbazate (646 mg, 4.89 mmol) and *p*-toluenesulfonic acid monohydrate (310 mg, 1.63 mmol) were added, and the reaction mixture was stirred for 2 h under reflux conditions with a Dean–Stark trap. The resultant mixture was directly purified by silica gel column chromatography (*n*-hexane : EtOAc=2 : 3) to give **14** (285 mg, 0.871 mmol, 45% in 4 steps) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, J=7.3 Hz), 2.53 (1H, dd, J=17.1, 1.2 Hz), 2.82 (1H, dd, J=17.1, 7.3 Hz), 4.06—4.16 (1H, m), 4.09 (3H, s), 7.06 (1H, d, J=8.6 Hz), 7.91 (1H, d, J=8.6 Hz), 8.65 (1H, s). EI-MS *m/z*: 327 (M^+). *Anal.* Calcd for $C_{14}H_{12}F_3N_3O$: C, 51.38; H, 3.70; N, 12.84. Found: C, 51.54; H, 3.65; N, 12.88. mp 155—156°C.

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References and Notes

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