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Intramolecular Cyclization of Alkynyl α-Ketoanilide Utilizing [1,2]-Phospha-Brook Rearrangement Catalyzed by Phosphazene Base

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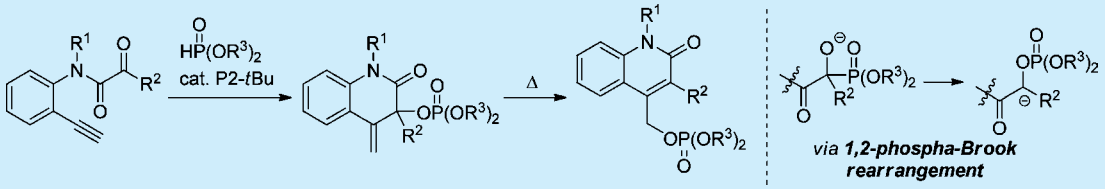
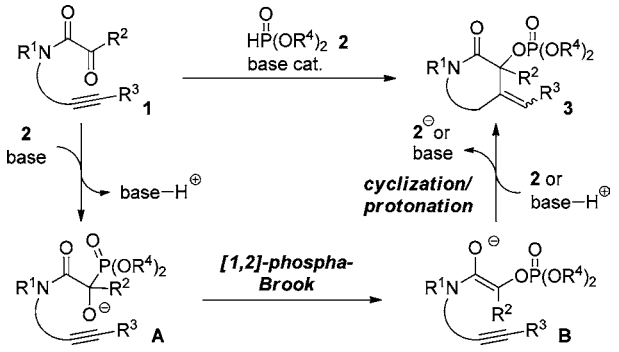
Supporting Information



ABSTRACT: A novel catalytic cyclization reaction of alkynyl α-ketoanilide was developed by utilizing the [1,2]-phospha-Brook rearrangement. This reaction involves the generation of an amide enolate via the umpolung process, that is the addition of dialkyl phosphite to a keto moiety followed by the [1,2]-phospha-Brook rearrangement, and the subsequent intramolecular addition of the enolate to an alkyne to afford 3,4-dihydro-2-quinolone derivatives. Under high-temperature reaction conditions, further rearrangement of the allylic phosphate moiety occurs to provide 2-quinolone derivatives.

The [1,2]-phosphonate−phosphate rearrangement, the so-called [1,2]-phospha-Brook rearrangement, involves the migration of a dialkoxyphosphoryl moiety of an α-hydroxy phosphonate from carbon to oxygen under the influence of a Brønsted base to generate an α-oxygenated carbanion.[1,2] The resulting carbanion, which requires several steps to generate by other methods, is potentially useful for new bond formation. However, the carbon−carbon bond-forming reactions that utilize this rearrangement are limited to the benzoin-type condensation of acyl phosphonates[3] and the aldol-type reaction of α-hydroxy phosphonates.[4] Meanwhile, the intramolecular addition of enols or enolates to alkynes is a useful method for the construction of cyclic frameworks.[5] In this transformation, the substrates are mainly limited to compounds possessing relatively high acidity at the nucleophilic site, such as 1,3-dicarbonyl compounds, which facilitate the generation of enols and enolates[6,7] or silyl enol ethers generated by a cumbersome prefunctionalization of carbonyl compounds.[8] On the other hand, reactions involving the direct generation of enolates of the substrates having a less acidic nucleophilic site are rare.[9] In this context, during the course of our studies of novel reactions utilizing the [1,2]-phospha-Brook rearrangement[10] as well as the intramolecular cyclization reactions of substrates bearing less acidic pro-nucleophiles,[9] we designed a novel intramolecular cyclization reaction of alkynyl α-ketoamide with dialkyl phosphite under Brønsted base catalysis. We envisioned that an amide enolate would be directly generated from an α-ketoamide via the *umpolung process*, that is, the addition of a dialkyl phosphite to a keto moiety followed by the [1,2]-phospha-Brook rearrangement under the influence of a Brønsted base catalyst, and the amide enolate would be utilized for intramolecular cyclization. Our proposed reaction system is shown in Scheme 1. At first, the deprotonation of dialkyl phosphite **2** by a Brønsted base and the following chemoselective addition of the resulting anion to a keto moiety of α-ketoamide **1** provide alkoxide **A**. Subsequently, the [1,2]-phospha-Brook rearrangement proceeds to generate amide enolate **B**. Finally, the addition of the enolate to an alkyne followed by protonation by the conjugated acid of the Brønsted base or dialkyl phosphite affords product **3** along with the regeneration of the Brønsted base or the anion of **2**. The key to the success of this tandem reaction is the addition of amide enolate **B** to an alkyne in preference to the protonation of enolate **B**, which is a competing side reaction arising from the basicity of **B**. Once **B** is protonated to form the corresponding acyclic amide, re-entering the catalytic cycle, or regeneration of **B**, would be difficult because of the low acidity of the amide. We were able to resolve this challenging issue and report herein the phosphazene base-catalyzed

Scheme 1. Proposed Catalytic System



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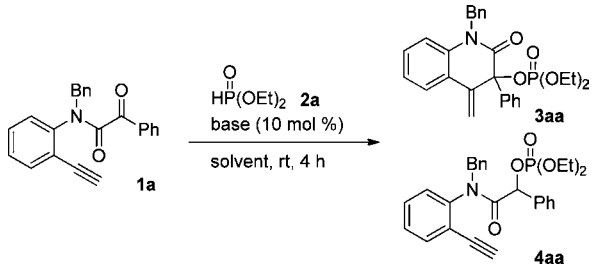
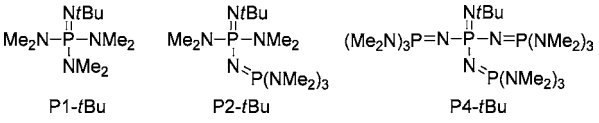
cyclization reaction of alkynyl α-ketoanilide with dialkyl phosphite to provide 3,4-dihydro-2-quinolone derivatives.

Table 1. Initial Screening of Reaction Conditions[a]



entry	base	solvent	yield of **3aa**[b] (%)	yield of **4aa**[b] (%)
1	DBU	DMSO	0	90
2	TBD	DMSO	0	98
3	P1-*t*-Bu	DMSO	52	35
4	P2-*t*-Bu	DMSO	88[c]	3
5	P4-*t*-Bu	DMSO	81	11
6	*t*-BuOK	DMSO	79	11
7	Cs_2CO_3	DMSO	49	36
8	P2-*t*-Bu	DMF	86	9
9	P2-*t*-Bu	CH_3CN	79	12
10	P2-*t*-Bu	THF	30	68
11	P2-*t*-Bu	CH_2Cl_2	69	25
12	P2-*t*-Bu	toluene	8	89
13	P2-*t*-Bu	EtOH	0	62

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), base (0.025 mmol), solvent (1.0 mL), rt, 4 h. [b]NMR yields. Bn_2O was used as the internal standard. [c]Determined by ^1H NMR measurement after column chromatography. See the Supporting Information for details.



To ascertain the viability of the proposed tandem reaction system, we started our investigation by screening for the reaction conditions using alkynyl α-ketoanilide **1a** as the primary substrate (Table 1). First, **1a** was treated with diethyl phosphite (**2a**) in the presence of a number of organic bases in DMSO at room temperature (entries 1−5). DBU (pK_{BH^+} = 13.9 in DMSO)[11] and TBD[12] provided only amide **4aa**, which was formed via the expected side reaction, namely, the protonation of the amide enolate generated by the [1,2]-phospha-Brook rearrangement (entries 1 and 2). In contrast, phosphazene P1-*t*-Bu (pK_{BH^+} = 15.7), to our delight, afforded the desired product **3aa** as the major product (entry 3).[13] Two stronger phosphazene bases, P2-*t*-Bu (pK_{BH^+} = 21.5) and P4-*t*-Bu (pK_{BH^+} = 30.3), dramatically improved the yield of **3aa**, and P2-*t*-Bu gave the best among the organic bases tested, affording the product in 88% yield (entries 4 and 5). For comparison, such inorganic bases as *t*-BuOK and Cs_2CO_3 were also examined (entries 6 and 7). However, they were less effective than P2-*t*-Bu and provided **3aa** in 79% and 49% yield, respectively. Next, several solvents were screened (entries 8−13). The results showed that the solvent effect was also significant, and aprotic polar solvents, such as DMSO and DMF, were the solvents of choice (entries 4 and 8). In order to clarify whether amide **4aa** was the appropriate intermediate to form **3aa**, **4aa** was treated with P2-*t*-Bu in DMSO at room temperature (eq 1). Low conversion of **4aa** was observed even after 16 h, which indicated that the cyclization occurred directly from the enolate generated via the [1,2]-phospha-Brook rearrangement. Considering that the acidity of dialkyl phosphite lies between that of the conjugated acid of P1-*t*-Bu and that of P2-*t*-Bu (dimethyl phosphite, pK_a = 18.4 in DMSO, estimated),[14] the results of the initial study implied that the acidity of a proton source in the reaction system, as well as the basicity of a Brønsted base catalyst, strongly affected the outcome, that is, the ratio of **3aa** to **4aa**.

With the optimum reaction conditions in hand, the scope of alkynyl α-ketoanilide **1** and phosphite **2** was investigated (Table 2). At first, some phosphites were tested (entries 1 and 2). Bulky diisopropyl phosphite (**2b**) provided the corresponding product **3ab** in good yield. In contrast, diphenyl phosphite (**2c**) did not provide any products, and **1a** was recovered. Next, a variety of alkynyl α-ketoanilides were subjected to the reaction conditions. In this reaction, an alkyl substituent on nitrogen was crucial. Whereas methyl-substituted **1b** provided the product in good yield, *N*-H **1c** afforded not **3ca** but **4ca** as the main product.[15] Various substituents on a keto moiety were then investigated. In regard to aryl substituents, an electron-donating group as well as an electron-withdrawing group at the para or meta position was favorable for this reaction, and the corresponding products were obtained in good yields (entries 5−8).[16] In contrast, the reaction of an ortho-substituted substrate, such as **1h**, was sluggish, and cyclized product **3ha** was obtained in low yield (entry 9). In the case of **1i** and **1j**, which are substrates possessing an alkyl substituent on a keto moiety, the desired products **3** were formed in moderate yields along with considerable amounts of side products **4** (entries 10 and 12). Decreasing of the concentration of **1** and **2** from 0.25 to 0.05 M improved the yield of **3**, and **3ia** and **3ja** were obtained in 59 and 82% yield, respectively (entries 11 and 13). The presence of a bromo group on the benzene ring of an anilide moiety did not affect the reaction, and the product was obtained in high yield (entry 14). The halo moieties allow for the further transformation of **3ea** and **3ka**. Then, substrates bearing an internal alkyne moiety were also examined (eqs 2 and 3). Interestingly, phenyl-substituted **1l** provided tricyclic product **5** as a diastereo mixture, which should be formed by the nucleophilic attack of a vinyl anion on the phosphorus center and the concomitant elimination of one of the ethoxides on the phosphorus after the cyclization.[17] On the other hand, alkyl-substituted **1m** did not provide any cyclized products, and **4ma** was obtained in high yield.

In the course of investigations of this reaction, we found that 2-quinolone derivatives **6** were formed when the reaction was conducted at elevated temperatures (Scheme 2). Specifically, when the reaction of **1a** with diethyl phosphite was carried out in DMSO at 90 °C, **6aa** was obtained in 82% isolated yield (Scheme 2a). As a control experiment, **3aa** was heated in DMSO at 90 °C. As a result, **3aa** was completely converted into **6aa**, which clearly indicated that **6aa** was formed via the thermal rearrangement of the allylic phosphate moiety of **3aa** (Scheme 2c).[18] Other aryl-substituted substrates having an electron-donating group as well as an electron-withdrawing group were also subjected to the high-temperature reaction conditions to afford the correspond-

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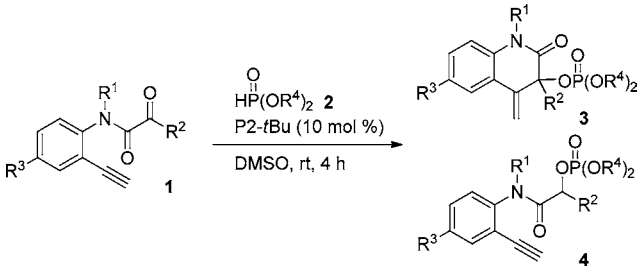
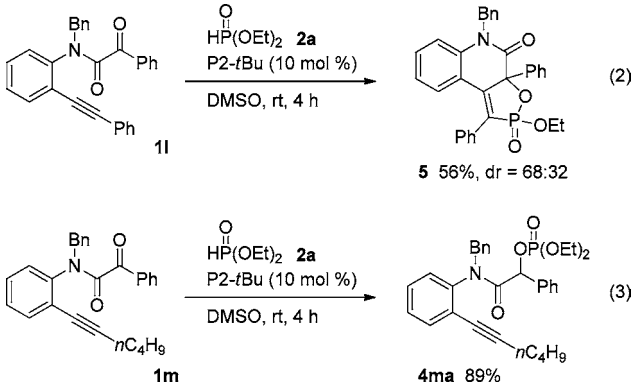
Table 2. Scope of Alkynyl α-Ketoanilide 1 and Phosphite 2[a]



entry	R^1	R^2	R^3	1	R^4	2	yield of 3[b] (%)		yield of 4[b] (%)	
1	Bn	Ph	H	**1a**	*i*Pr	**2b**	**3ab**	88[c]	**4ab**	5[d]
2	Bn	Ph	H	**1a**	Ph	**2c**	**3ac**	0	**4ac**	0
3	Me	Ph	H	**1b**	Et	**2a**	**3ba**	83	**4ba**	3
4	H	Ph	H	**1c**	Et	**2a**	**3ca**	0	**4ca**	88[c]
5	Bn	4-MeO-C_6H_4	H	**1d**	Et	**2a**	**3da**	85[d]	**4da**	7[d]
6	Bn	4-Cl-C_6H_4	H	**1e**	Et	**2a**	**3ea**	78	**4ea**	10
7	Bn	4-F-C_6H_4	H	**1f**	Et	**2a**	**3fa**	72	**4fa**	14
8	Bn	3-MeO-C_6H_4	H	**1g**	Et	**2a**	**3ga**	85	**4ga**	5
9	Bn	2-Me-C_6H_4	H	**1h**	Et	**2a**	**3ha**	28	**4ha**	15
10	Bn	*n*-C_5H_{11}	H	**1i**	Et	**2a**	**3ia**	31	**4ia**	59
11[e]	Bn	*n*-C_5H_{11}	H	**1i**	Et	**2a**	**3ia**	59	**4ia**	35
12	Bn	*c*-C_6H_{11}	H	**1j**	Et	**2a**	**3ja**	68	**4ja**	24
13[e]	Bn	*c*-C_6H_{11}	H	**1j**	Et	**2a**	**3ja**	82	**4ja**	15
14	Bn	Ph	Br	**1k**	Et	**2a**	**3ka**	84[c]	**4ka**	0

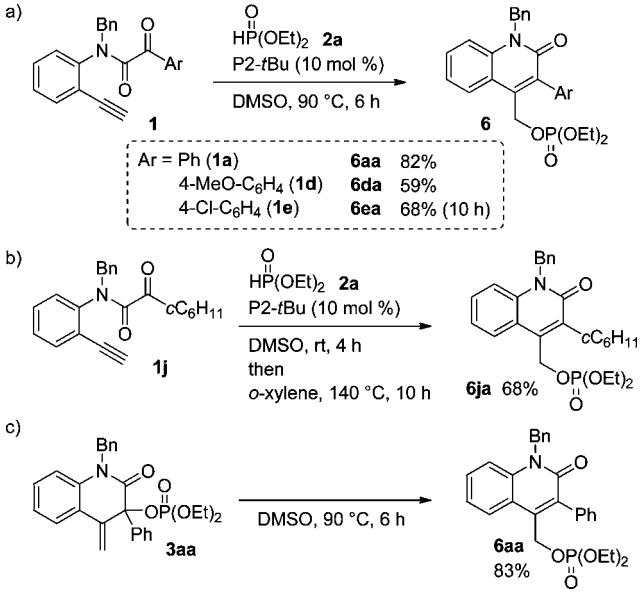
[a]Reaction conditions: **1** (0.25 mmol), **2** (0.25 mmol), P2-*t*-Bu (0.025 mmol), DMSO (1.0 mL), rt, 4 h. [b]Determined by ^{1}H NMR measurement after column chromatography unless otherwise noted. See the Supporting Information for details. [c]Isolated yields. [d]Determined by ^{1}H NMR analysis of crude mixture. Bn_2O was used as the internal standard. [e]The reaction was conducted in DMSO (5.0 mL).



ing 2-quinolone derivatives in moderate to good yields. In contrast, the rearrangement of alkyl-substituted **3ja** did not proceed at 90 °C, and further elevation of the reaction temperature in DMSO resulted in the decomposition of the product. Thus, a two-step operation was conducted: After treatment of **1j** with **2a** in DMSO at room temperature for 4 h, the crude product was then heated in *o*-xylene at 140 °C for 10 h to afford **6ja** in 68% yield (Scheme 2b).[19]

The product of this reaction possesses an allylic phosphate moiety, which makes further manipulation possible (Scheme 3). For example, treatment of **3aa** with sodium ethoxide in ethanol provided corresponding alcohol **7** quantitatively. Compound **6aa** was also converted into the corresponding hydroxy-2-quinolone in excellent yield under the same reaction conditions. On the other hand, treatment of **3aa** with a heteroatom nucleophile, such as dodecanethiol, as well as a carbon nucleophile, such as lithium diphenylcuprate, resulted in an S_N2' type substitution reaction to provide 2-quinolone derivatives **9** and **10**,

Scheme 2. Reactions under High-Temperature Conditions



respectively, where a diethoxyphosphoryloxy group served as the leaving group.

In conclusion, a novel catalytic cyclization reaction of alkynyl α-ketoanilide was developed by utilizing the [1,2]-phospha-Brook rearrangement. This reaction involves the generation of an amide enolate via the umpolung process followed by the intramolecular addition of the enolate to an alkyne to construct a 3,4-dihydro-2-quinolone skeleton bearing a handle for further manipulation. In addition, the reaction system in combination with the thermal rearrangement of the allylic phosphate moiety

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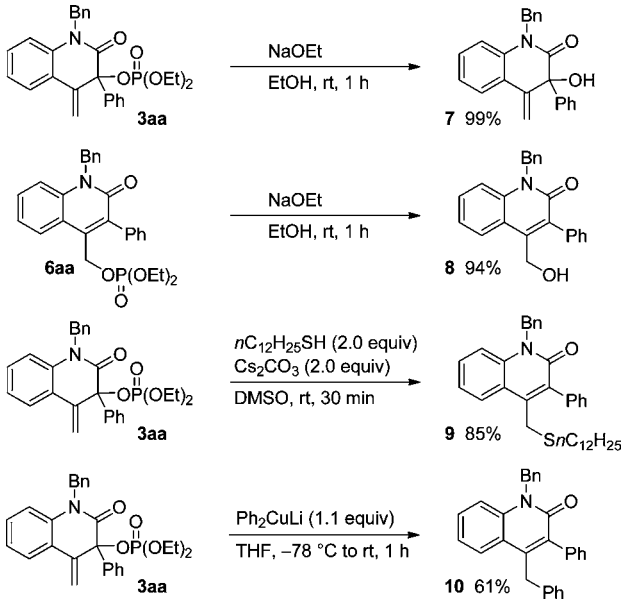
Scheme 3. Transformation of 3 and 6



was also established, which provided 2-quinolone derivatives. Further application of this concept to other substrates as well as exploration of novel carbon−carbon bond forming reactions utilizing the [1,2]-phospha-Brook rearrangement are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) The basicity of TBD seems to lie between those of DBU and P1-*t*-Bu in DMSO. The pK_{BH^+} values of those bases in CH_3CN are 24.34 (DBU), 26.03 (TBD), and 26.98 (P1-*t*-Bu), respectively. See ref 11.

(13) The structure of **3** was confirmed by single-crystal X-ray diffraction analysis of **3ka** (CCDC no. 989787). See the Supporting Information.

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(15) A small amount of an indole derivative was detected along with **4ca**, which was formed by the intramolecular addition to an alkyne at the nitrogen center.

(16) **3da** was unstable, and the attempted purification by silica gel column chromatography resulted in complete decomposition.

(17) The structure of **5** was determined by NMR analysis, HRMS, and single-crystal X-ray diffraction analysis of one of the diastereomers of the analogue of **5** obtained by the reaction of **1l** with **2b** (CCDC no. 989788). See the Supporting Information.

(18) For an example of thermal rearrangement of allylic phosphates, see: Mita, T.; Fukuda, N.; Roca, F. X.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 259 and references cited therein.

(19) See the Supporting Information for details.