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Preparation of Allenephosphoramide and Its Utility in the Preparation of 4,9-Dihydro-2*H*-benzo[*f*]isoindoles

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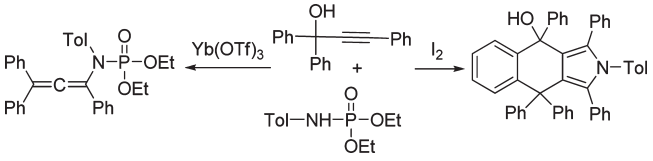
ABSTRACT



Allenephosphoramides were prepared from propargyl alcohols and diethyl arylphosphoramides using $Yb(OTf)_3$ as catalyst. In the presence of iodine, 4,9-dihydro-2*H*-benzo[*f*]isoindole derivatives could be efficiently constructed from the same two starting materials in a single step.

Allene has been widely investigated because of its high reactivity in a number of reaction patterns and its applications as the key building block in constructing various compounds with multifunctionalities.[1] Allenamine,[2] in which a terminal carbon of allene is substituted by a nitrogen atom, enriches the electron density of the C=C bond and makes the chemistry of allene more prosperous. However, for the same reason, allenamine is unstable and cannot easily be handled and isolated, which has largely limited its utility in organic synthesis. In order to overcome this drawback, allenamide as a more stable allenamine equivalent has been derived and applied in the construction of complicated molecules. For example, epoxidation of allenamide led to the formation of nitrogen-stabilized oxyallyl cation, which could be used as a 1,3-dipolar substituent in [4 + 3] cycloaddition.[3] It could also function as dienophile in [4 + 2] cycloaddition.[4] Furthermore, one of the C=C bonds of allenamide could be nucleophilically attacked to afford enamide under a gold catalyst.[5] Traditionally, allenamide was prepared by base-catalyzed isomerization of propargylic amide,[6] Claisen rearrangement,[7] and aminocyclization.[8] It was also reported that copper-catalyzed coupling of allenyl halide with amide could afford allenamide.[9]

(1) For a compendium on the chemistry of allenes, see: Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004; Vols. 1 and 2.

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(9) (a) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117. (b) Shen, L.; Hsung, R. P.; Zhang, Y.; Antoline, J. E.; Zhang, X. *Org. Lett.* **2005**, *7*, 3081. (c) Persson, A. K. Å.; Johnston, E. V.; Bäckvall, J. -E. *Org. Lett.* **2009**, *1*, 3814.

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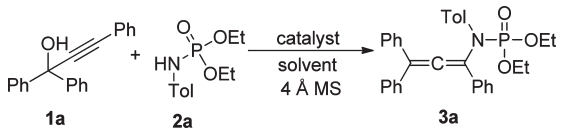
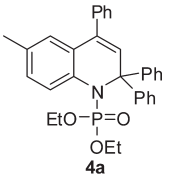
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent	temp (°C)	yield[b] (%)
1	$Yb(OTf)_3$	DCE	rt	62
2	$Yb(OTf)_3$	DCE	50	75
3	$Yb(OTf)_3$	DCE	80	61[c]
4	$Yb(OTf)_3$	DCM	0	54
5	AgOTf	DCE	50	63
6	$Zn(OTf)_2$	DCE	50	53
7	$Cu(OTf)_2$	DCE	50	56
8	$BF_3 \cdot Et_2O$	DCE	50	32
9	$AlCl_3$	DCE	50	n.d.
10	$FeCl_3$	DCE	50	trace
11	$Yb(OTf)_3$	THF	50	trace
12	$Yb(OTf)_3$	CH_3CN	50	n.d.
13	$Yb(OTf)_3$	DMF	50	n.d.
14	$Yb(OTf)_3$	toluene	50	n.d.
15	$Yb(OTf)_3$[d]	DCE	50	75
16	$Yb(OTf)_3$[e]	DCE	80	trace
17	$Yb(OTf)_3$[e]	DCE	50	13
18	$Yb(OTf)_3$[f]	DCE	50	63

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), $Yb(OTf)_3$ (0.025 mmol), 4 Å MS (200 mg), DCE (3 mL), 12 h. [b] Isolated yields. [c] **4a** was isolated in 10%. [d] 10% catalyst. [e] Without 4 Å MS. [f] 8 h.

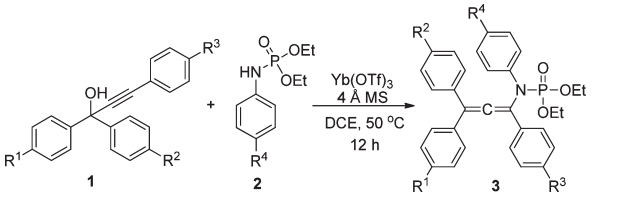


Although allenamide has attracted considerable attention in recent years, allenesulfonamide[10] and allenephosphoramide[11] have seldom been reported. Typically, as in the case of allenephosphoramide and its related chemistry, it is a comparatively virgin territory relative to the well-known allenamide. Enlightened by the chemistry of allenamide, we report a facile preparation of allenephosphoramide and its extension to 4,9-dihydro-2*H*-benzo[*f*]isoindole derivatives.

As we predicted, propargyl alcohol **1a** could be transferred to propargylic carbocation under acidic conditions, which would possess a resonance structure of allenic carbocation.[12] Therefore, we first treated **1a** with diethyl benzylphosphoramidate in 1,2-dichloroethane (DCE) using $Yb(OTf)_3$ as catalyst and isolated the anticipated allenephosphoramide in 10% yield. To our delight, when phosphoramidate **2a** was used as substrate instead of diethyl benzylphosphoramidate, we obtained allenephosphoramide **3a**[13] in 62% yield.

Encouraged by this result, we optimized the reaction conditions (Table 1). The yield of **3a** was increased when the reaction temperature was raised to 50 °C (Table 1, entry 2). However, higher temperature (80 °C) led to a decrease in yield and the formation of byproduct **4a**[14] (Table 1, entry 3). Lowering the temperature would decrease the yield as well (Table 1, entry 4). AgOTf, $Zn(OTf)_2$, $Cu(OTf)_2$, and trifluoroborane also catalyzed the reaction, but with relatively lower yields (Table 1, entries 5−8). Neither aluminum trichloride nor iron trichloride allowed this reaction to proceed (Table 1, entries 9 and 10). The desired product was not detected (n.d.) or only formed in a trace amount if the solvent was changed to THF, acetonitrile, DMF, or toluene (Table 1, entries 11−14). A 5 mol % ratio of catalyst to propargylic alcohol was enough (Table 1, entries 2 and 15). Without 4 Å molecular sieves, the reaction was not effective (Table 1, entries 2, 16, and 17). Shortening the reaction time reduced the yield (Table 1, entry 18).

Table 2. Substrate Diversity of the Transformation[a]



entry	**1** (R^1 / R^2/ R^3)	**2** (R^4)	yield[b] (%)
1	**1a** (H/H/H)	**2a** (CH_3)	**3a**/75
2	**1a**	**2b** (H)	**3b**/62
3	**1a**	**2c** (OCH_3)	**3c**/82
4	**1a**	**2d** (Br)	**3d**/62
5	**1a**	**2e** (Cl)	**3e**/60
6	**1b** (H/H/F)	**2a**	**3f**/62
7	**1c** (H/H/C_2H_5)	**2a**	**3g**/77
8	**1c**	**2c**	**3h**/82
9[c]	**1d** (CH_3O/CH_3O/H)	**2a**	**3i**/81
10[c]	**1d**	**2c**	**3j**/84
11	**1e** (Cl/Cl/H)	**2c**	**3k**/41
12	**1f** (Cl/CH_3O/H)	**2a**	**3l**/69

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $Yb(OTf)_3$ (0.025 mmol), 4 Å MS (200 mg), DCE (3 mL), 50 °C, 12 h. [b] Isolated yield. [c] Room temperature.

With the optimized reaction conditions in hand, we subsequently tested the substrate diversity (Table 2). The substrates bearing an electron-donating group on the *para* position of the aryl of **2** gave higher yields than those

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(11) (a) Corbel, B.; Paugam, J.-P.; Dreux, M.; Savignac, P. *Tetrahedron Lett.* **1976**, *17*, 835. (b) Danowitz, A. M.; Taylor, C. E.; Shrikian, T. M.; Mapp, A. K. *Org. Lett.* **2010**, *12*, 2574.

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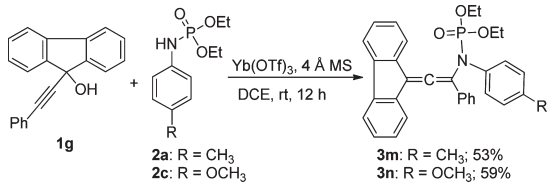
(13) CCDC 800666 contains the crystallographic data of **3a**. It can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(14) CCDC 800667 contains the crystallographic data of **4a**.

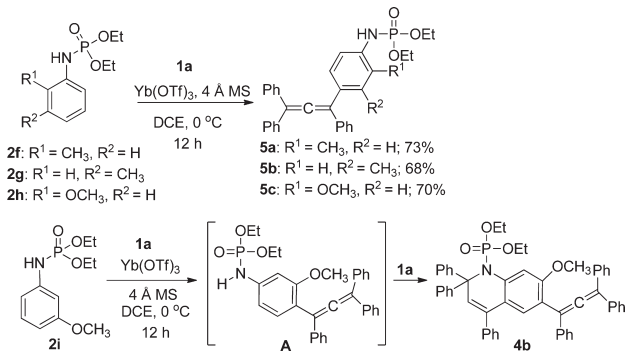
substrates with an electron-withdrawing group on the *para* position of the aryl of **2** (Table 2, entries 1−5). A similar electronic effect was observed for the aryl of propargyl alcohols (Table 2, entries 6 and 7). With methoxy groups on both the phosphoramide and propargyl alcohol sides, the highest yield was reached (Table 2, entry 10). Compound **1f**, derived from unsymmetrical ketone precusor, afforded **3l** successfully (Table 2, entry 12). However, an acetophenone-derived propargyl alcohol did not work for this transformation. It means that two aryl groups connected to the carbon substituted by a hydroxy group in propargyl alcohols are necessary to trigger the formation of propargylic carbocation and proceed with the subsequent steps in the reaction.

Scheme 1. Formation of **3m** and **3n**



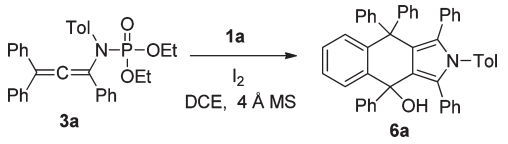
When **1g** was used as the precursor of allenic carbocation, **3m** was formed as the major product, as we expected. A similar situation was observed for the reaction between **1g** and **2c** (Scheme 1).

Scheme 2. Formation of **5** and **4b**



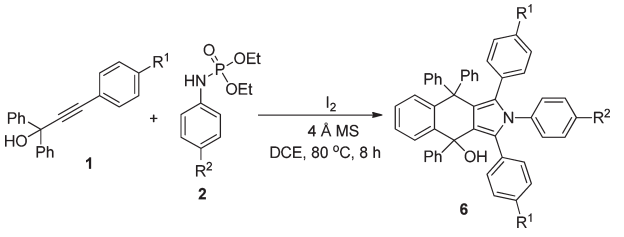
Interestingly, when the *ortho* or *meta* position of the aryl of phosphoramidate was altered by a methyl group (**2f** or **2g**), the allenic system could still be approached, but with four aryls attached (**5a** and **5b**) (Scheme 2). A similar situation was observed for **2h**, which afforded **5c**[15] in 70% yield. In these cases, the *para* position of the aryl of phosphoramidate (**2f**, **2g**, and **2h**) was electron rich enough to trap the allenic carbocation directly. To our surprise, when **2i** was used as the substrate, **4b**[16] was isolated in 32% yield. When the molar ratio of **1a** to **2i** was adjusted to 2:1, the yield of **4b** was increased to 60%. The electron density of the *para* position of the aryl group of **2i** was enriched by both nitrogen and oxygen, and thus it trapped allenic carbocation directly. Compound **A** was generated in situ, similar to the formation of **5**. In the structure of **A**, the electron density of the *ortho* position of the aryl of phosphoramide was doubly enriched. In cooperation with the nitrogen atom, this carbon trapped one more allenic carbocation. Finally, **4b** was constructed. The reaction was a three-component reaction, and **1a** was used as substrate twice.

Scheme 3. Formation of **6a** from **3a** and **1a**



The chemistry of allenephosphoramide is immature and has not been widely explored since 1976.[12] All synthesized allenephosphoramides **3a**−**n** are sensitive to moisture and should be stored in the refrigerator. Hydrolysis of **3a** under acid conditions afforded 1,3,3-triphenylprop-2-en-1-one[17] accordingly. It was also found that **3a** could react with **1a** in the presence of iodine to give **6a**[18] (Scheme 3). Since **3a** was indeed prepared from **1a** and **2a** with $Yb(OTf)_3$ as catalyst, we directly combined **1a** and **2a** in a 1:0.6 ratio and used 2 molar equiv of iodine against **1a** to trigger the reaction. As

Table 3. Substrate Diversity of Three-Component Synthesis of **6**[a]



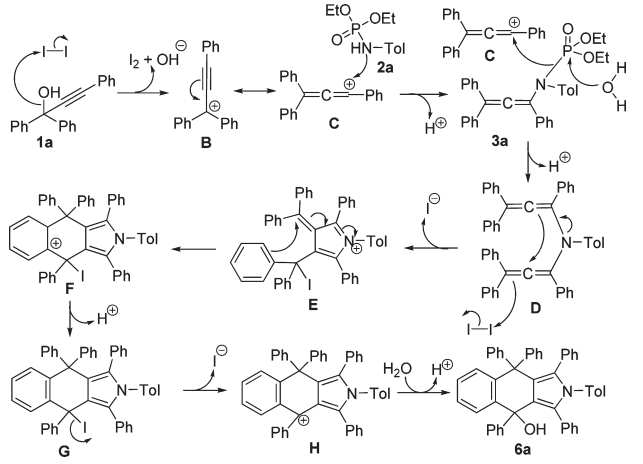
entry	**1** (R^1)	**2** (R^2)	yield[b] (%)
1	**1a** (H)	**2a** (CH_3)	**6a**/63
2	**1a**	**2b** (H)	**6b**/54
3	**1a**	**2c** (OCH_3)	**6c**/68
4	**1a**	**2d** (Br)	**6d**/61
5	**1a**	**2e** (Cl)	**6e**/60
6	**1h** (CH_3)	**2a**	**6f**/67
7	**1h**	**2c**	**6g**/71
8	**1i** (Br)	**2a**	**6h**/72
9	**1i**	**2c**	**6i**/84

[a] Reaction conditions: **1** (1 mmol), **2** (0.6 mmol), iodine (2 mmol), 4 Å MS (400 mg), DCE (3 mL), 80 °C, 8 h. [b] Isolated yield.

(15) CCDC 800668 contains the crystallographic data of **5c**.
(16) CCDC 800670 contains the crystallographic data of **4b**.
(17) Katritzky, A. R.; Denisenko, S. N.; Oniciu, D. C.; Ghiviriga, I. *J. Org. Chem.* **1998**, *63*, 3450.
(18) CCDC 800669 contains the crystallographic data of **6a**.

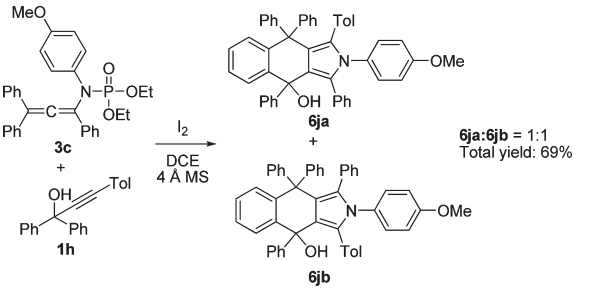
expected, **6a** was obtained in 63% yield after the mixture was heated at 80 °C for 8 h. The yield was slightly increased when the iodine was fed in 2.5 molar equiv to **1a**, while it was decreased when the temperature lowered to 50 °C. The substitution effect of **1** and **2** was further explored, and the results are summerized in Table 3. No significant electronic effect was seen in these cases. The best yield was obtained when **1i** reacted with **2c** (Table 3, entry 9). However, substrates **1d**, **1f**, and **1g** did not allow this three-component reaction to proceed, although all of these starting materials disappeared on the basis of the TLC tracking.

Scheme 4. Postulated Mechanism of Formation of **3a** and **6a**



On the basis of these results, we postulated a mechanism for the formation of **3a** and **6a** (Scheme 4). In the presence of iodine, **1a** is converted to **B**, which possesses another resonance structure **C**.[12] The nitrogen of **2a** nucleophilically attacks **C**,[19] followed by deprotonation, to give **3a**. However, **3a** is unstable and can be hydrolyzed very easily. If enough **C** exists in the solution, **C** can be trapped by the hydrolyzed product of **3a**. Diallenamine **D** is thus formed in situ. Isolation of **D** was a futile effort because of its unstability. Compound **D** immediately underwent the first cyclization to form **E**. Subsequently, the phenyl ring of **E** intramolecularly attacked α,β-unsaturated iminium and the second cyclization casually happened.[20,21] Aromatization of the resulting **F** formed **G**, which was hydrated to afford **6a**.

Scheme 5. Equivalent Formation of **6ja** and **6jb**



In order to support the postulated mechanism, we carried out the reaction of **3c** with **1h**. As we anticipated, a mixture of **6ja** and **6jb** was isolated in a 1:1 ratio (Scheme 5). This result demonstrated that the process from **D** to **E** (Scheme 4) might have two comparable opportunities when **1h** was used as the substrate, and the regioselectivity was then lost.

In conclusion, we have demonstrated that allenephosphoramides could be directly synthesized from phosphoramides and propargyl alcohols using $Yb(OTf)_3$ as catalyst. By elaborately adjusting the electron density of the aryl of phosphoramides via various substituents, 1,2-hydroquinolines and tetraaryl allenes could be successfully synthesized. More significantly, 4,9-dihydro-2*H*-benzo[*f*]isoindoles could be efficiently constructed from propargyl alcohols and phosphoramides in the presence of iodine in a single step. Further investigations on the chemistry of allenephosphoramides are ongoing.

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Supporting Information Available. Experimental procedures, full spectroscopic data for all new compounds, and crystallographic information files (CIF) for compounds **3a**, **4a**,**b**, **5c**, and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org

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(21) Navarro-Vázquez, A.; Rodríguez, D.; Martínez-Esperón, M. F.; García, A.; Saá, C.; Domínguez, D. *Tetrahedron Lett.* **2007**, *48*, 2741.