ORGANIC LETTERS

2002
Vol. 4, No. 26
4677−4679

Tandem Reactions to Construct Heterocycles via Phosphine-Catalyzed Umpolung Addition and Intramolecular Conjugate Addition

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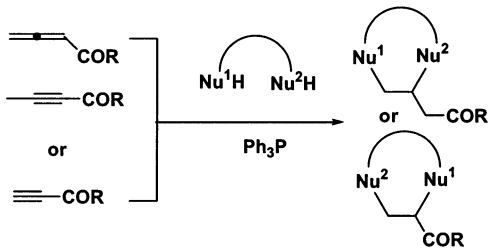
Received October 10, 2002

ABSTRACT



A highly efficient method for constructing heterocycles was achieved by phosphine-catalyzed tandem umpolung addition and intramolecular conjugate addition. This strategy offers a simple and promising method for constructing synthetically useful heterocycles under neutral conditions with high atom economy.

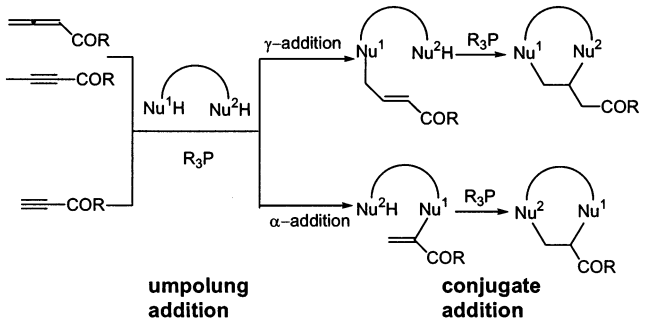
Heterocycles are of broad interest for both synthetic and pharmaceutical chemists.[1] Among the well-documented synthetic methods, tandem reactions are always chosen to construct heterocycles with high efficiency.[2] However, efficient and applicable approaches to form heterocycles via tandem nucleophilic additions still remain rare. Tandem nucleophilic additions can be achieved by adding a bifunctional nucleophile to an electron-deficient multiple bond (a bifunctional electrophile, e.g., an allene or an alkyne) and intramolecular trapping of the intermediary monofunctional nucleophile with the properly located electrophilic center formed from the preceding addition reaction. With this in mind, our attention was turned to the phosphine-catalyzed umpolung (α- or γ-) addition reaction.[3,4] If a bifunctional nucleophile was used in the addition reaction with an electron-deficient alkyne or allene, the resulting umpolung adduct would have not only a nucleophilic center but also an electrophilic center (the electron-deficient double bond) required for an intramolecular conjugate addition. Although there were some reports concerning this strategy, a general approach to construct heterocycles on the basis of this strategy still needs to be developed.[5] Furthermore, conjugate

(1) Newkome, G. R.; Paudler, W. W. *Contemporary Heterocyclic Chemistry: Syntheses, Reactions and Application*; Wiley: New York, 1982.
(2) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992.
(3) (a) Trost, B. M.; Li, C. J. *J. Am. Chem. Soc.* **1994**, *116*, 3167. (b) Trost, B. M.; Li, C. J. *J. Am. Chem. Soc.* **1994**, *116*, 10819. (c) Trost, B. M.; Dake, G. R. *J. Org. Chem.* **1997**, *62*, 5670. (d) Dake, G. R.; Trost, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 7595. (e) Zhang, C.; Lu, X. *Synlett* **1995**, 645. (f) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (g) Alvarez-Ibarra, C.; Csáky, A. G.; de la Oliva, C. G. *Tetrahedron Lett.* **1999**, *40*, 8465.
(4) For recent reports on phosphine-catalyzed reactions, see: (a) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402. (b) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404.
(5) (a) Trost et al. reported that the ring-opening product of the γ-adduct of Meldrum's acid and alkynone was sufficiently active to effect cyclization to afford γ-butyrolactone; see ref 3a. (b) Liu et al. reported a phosphine-catalyzed annulation of thioamides and 2-alkynoates or 2,3-dienoates for constructing substituted thiazolines; see: Liu, B.; Davis, R.; Joshi, B.; Reynolds, D. W. *J. Org. Chem.* **2002**, *67*, 4595.

10.1021/ol0270733 CCC: $22.00
Published on Web 11/23/2002

addition can also be catalyzed by a tertiary phosphine,[6] implying that the heterocycles could be formed by the phosphine-catalyzed tandem reactions (Scheme 1). In this

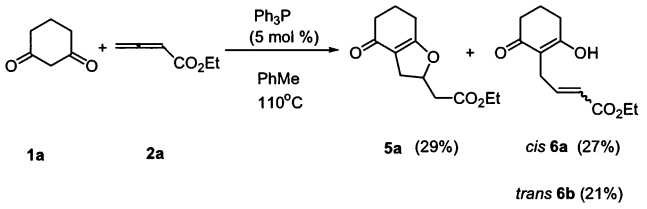
Scheme 1



regard, we report herein tandem reactions involving umpolung addition and conjugate addition of a bifunctional nucleophile to an electron-deficient alkyne or allene catalyzed by triphenylphosphine.[7]

Initial efforts focused on the tandem γ- and β-additions. Heating a mixture of cyclohexan-1,3-dione (a carbonucleophile as well as an oxygenucleophile) with ethyl 2,3-butadienoate in toluene at 110 °C using 5 mol % triphenylphosphine as the catalyst gave 29% yield of the expected cyclized product **5a** and 48% yield of the γ-adducts **6a** and **6b** (Scheme 2). Using other phosphines such as

Scheme 2



tributylphosphine, dppe, a more polar solvent (THF, CH_3CN) or a buffer system (HOAc, NaOAc) did not give satisfactory results. In view of the fact that conjugate addition can also be catalyzed by tertiary phosphines,[6] the catalyst loading was enhanced. To our delight, 68% yield of **5a** was obtained when 20 mol % triphenylphosphine was used (Table 1, entry 1).

With the preliminarily optimized condition in hand, the scope of the phosphine-catalyzed tandem reactions was tested

(6) For phosphine-catalyzed conjugate addition to electron-deficient alkenes, see: (a) White, D. A.; Baizer, M. M. *Tetrahedron Lett.* **1973**, 3597. (b) Yoshida, T.; Saito, S. *Chem. Lett.* **1982**, 1587. (c) Gómez-Bengoa, E.; Cueva, J. M.; Mateo, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 8553. (d) Lumbierres, M.; Marchi, C.; Moreno-Manãs, M.; Sebastián, R. M.; Vallribera, A.; Lago, E.; Molins, E. *Eur. J. Org. Chem.* **2001**, 2321.

(7) For stoichiometric multistep additions on vinyl-triphenylphosphonium salt to afford heterocycles, see: Cristau, H. J.; Fonte, M.; Torreiles, E. *Synthesis* **1989**, 301 and references therein.

Table 1. Phosphine-Catalyzed Tandem Nucleophilic Additions[8,a]

entry	NuH	allenes or alkynes	T(°C)/ T (h)	product	yield (%)[b]
1	**1a**	R=OEt **2a**	110/24	**5a**	68
2[c]	**1a**	**2b** R=Me	70/2	**5b**	84
3[c]	**1a**	**2c** R=Ph	70/5	**5c**	70
4[c]	**1b** R^1=Me	**2b**	70/5	**5d**	66[d]
5[c]	**1c** R^1=OEt	**2b**	70/5	**5e**	77[d]
6	**1a**	R=OBn **3d**	110/48	**5f**	71
7	**1a**	**3e** R=Cy	110/48	**5g**	92
8[e]	**1d** X=NTs	**3b** R=Me	80/24	**5h**	93
9[e]	**1d**	**3c** R=Ph	80/24	**5i**	81[g]
10[e]	**1d**	**3e** R=Cy	80/24	**5j**	96
11[e]	**1e** X=O	**3b**	80/24	**5k**	66[g]
12[e]	**1e**	**3e**	80/24	**5l**	66[e]
13[f]	**1d**	**4a** R=OEt	80/24	**5m**	86
14[f]	**1d**	**4f** R=^{n}Pr	80/24	**5n**	83[g]
15[f]	**1f**	**4a**	80/72	**5o**	88

[a] Reaction conditions: a solution of bifunctional nucleophile (0.5 mmol), allene or alkyne (0.5 mmol), and Ph_3P (0.1 mmol) were heated at the indicated temperature. For details of the reaction conditions, see ref 8. [b] Isolated yield. [c] Used 0.025 mmol of Ph_3P. [d] Solution of 1 equiv of allenone in toluene was added dropwise to the solution of 5 equiv of 1,3-dicarbonyl compound in toluene, and the yields were based on the allenone. [e] CH_3CN was used as solvent. [f] Toluene−CH_3CN(v:v = 4:1) was used as a solvent. [g] Alkynone (1.1 equiv) in toluene or CH_3CN was added dropwise.

by the reaction of a number of 1,3-dicarbonyl compounds as well as other bifunctional nucleophiles with electron-deficient allenes or alkynes, and the results are summarized in Table 1.

Reaction of 1,3-dicarbonyl compounds with electron-deficient allenes catalyzed by triphenylphosphine afforded dihydrofuran derivatives with good yields (entries 1−5). Switching the electron-withdrawing group from an ester group to a ketone group (entries 2−5) resulted in lower catalyst loading (5 mol %) and more smooth conversion to the cyclized product, indicating that tandem nucleophilic additions were favored by a stronger electron-withdrawing group.

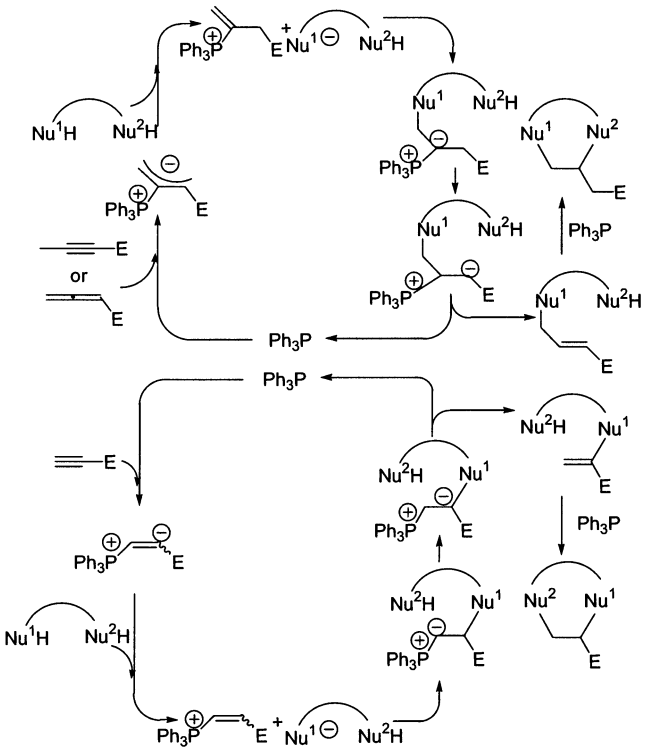
Electron-deficient alkynes, synthetically equivalent to the electron-deficient allenes in the phosphine-catalyzed um-

polung addition reactions,[3] were subject to similar reaction conditions and gave cyclized products in good to excellent yield (entries 6 and 7).

Reaction of bifunctional nitrogen−nucleophile 1,2-bis(*p*-toluenesulfonylamino) ethane with electron-deficient alkynes afforded piperazine derivatives in good to excellent yields (entries 8−10). When the nitrogen−oxygen bifunctional nucleophile 2-(*p*-toluenesulfonylamino) ethanol was used, morpholine derivatives were obtained in moderate yields (entries 11 and 12).[9] Encouraged by the above results, tandem α- and *β*-additions were also realized by the reaction of 1-hexyn-3-one or ethyl propiolate with the bifunctional nucleophile **1d** (entries 13 and 14). It is noteworthy that the seven-membered heterocycle, a diazepane derivative, was also obtained in high yield (entry 15). Moreover, the synthetic utility of the tandem reactions was exemplified by the synthesis of piperazine-2-carboxylic acid,[10] a precursor for the synthesis of CPP[10b,11] and Crixivan.[12] Detosylation and hydrolysis of the ester group of **5m** in one pot using 48% HBr gave piperazine-2-carboxylic acid dihydrobromide in 71% yield.

A possible mechanism was illustrated in Scheme 3. The reaction was triggered by nucleophilic addition of a triphenylphosphine to the electron-deficient multiple bond. Then, the zwitterionic intermediate deprotonated the pronucleophile, which facilitated the umpolung addition. Proton transfer and elimination of the triphenylphosphine from the resulting zwitterionic intermediate gave the corresponding umpolung adduct (*γ*- or α-adduct). Finally, the umpolung adduct effected intramolecular conjugate addition reaction in the presence of the triphenylphosphine. Although a detailed mechanistic study was not undertaken, preliminary results concerning the role of phosphine in the intramolecular

Scheme 3



conjugate addition step were given by the control experiment. Heating cis-*γ*-adduct **6a** in toluene at 110 °C in the presence of 20 mol % triphenylphosphine gave 92% yield of the cyclized product **5a**, while a disordered result was obtained in the absence of triphenylphosphine. Similar results for α-adduct **6c** were obtained (see Supporting Information).

In summary, we have developed a highly efficient method for constructing heterocycles via phosphine-catalyzed umpolung addition and intramolecular conjugate addition. This strategy offers a simple and promising method for constructing heterocycles under neutral conditions with high atom economy.

Acknowledgment. We thank the Major State Basic Research Program (Grant G20000077502-A). We also thank the National Natural Sciences Foundation of China and Chinese Academy of Sciences for financial support.

Supporting Information Available: Spectroscopic data, analytical data, and copies of ^{1}H NMR and ^{13}C NMR for new compounds **5a**−**l**,**n**,**o** and **6a**−**c**, copies of ^{1}H NMR and ^{13}C NMR for **5m**, and X-ray crystallography of **5l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Typical reaction conditions: to a solution of a bifunctional nucleophile (0.5 mmol) and triphenylphosphine (0.1 mol) in toluene (1.5 mL) at the indicated temperature under nitrogen was added a solution of an electron-deficient allene or alkyne (0.5 mmol) in toluene (1 mL).

(9) Structure of compound **5l** was confirmed by X-ray crystallography, indicating that the tandem nucleophilic addition reactions of oxygen−nitrogen bifunctional nucleophile with electron-deficient alkyne started from the nitrogen nucleophilic center.

(10) For synthesis of piperazine-2-carboxylic acid, see: (a) Mérour, J. Y.; Coadou, J. Y. *Tetrahedron Lett.* **1991**, *32*, 2469. (b) Bigge, C. F.; Hays, S. J.; Novak, P. M.; Drummond, J. T.; Johnson, G.; Bobovski, T. P. *Tetrahedron Lett*. **1989**, *30*, 5193.

(11) CPP is a high-affinity competitive antagonist of the NMDA subtype of the glutamate receptor. For references, see: (a) Davis, J.; Evans, R.; Herrling, P. L.; Jones, A. W.; Olverman, H. J.; Pook, P.; Watkins, J. C. *Brain Res.* **1986**, *382*, 169. (b) Hays, S. J.; Bigge, C. F.; Novak, P. M.; Drummond, J. T.; Bobovski, T. P.; Rice, M. J.; Johnson, G.; Brachce, L. J.; Coughenour, L. L. *J. Med. Chem*. **1990**, *10*, 2916.

(12) An HIV protease inhibitor indinavir; for references, see: (a) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I. W.; Holloway, M. K.; Fizgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem*. **1994**, *37*, 3443. (b) Hamner, S. M.; Squires, K. E.; Huges, M. D.; Grimes, J. M.; Demeter, L. M.; Currier, J. S.; Eron, J. J.; Fienberg, J. E.; Balfour, H. H.; Deyton, L. R.; Chodakewitz, J. A.; Fischl, M. A. *N. Engl. J. Med.* **1997**, *337*, 725.