Published in final edited form as:

Org Lett. 2010 March 5; 12(5): 1084–1087. doi:10.1021/ol100078w.

Diphosphine-Catalyzed Mixed Double-Michael Reaction: A Unified Synthesis of Indolines, Dihydropyrrolopyridines, Benzimidazolines, Tetrahydroquinolines, Tetrahydroisoquinolines, Dihydrobenzo-1,4-oxazines, and Dihydrobenzo-3,1-oxazines

Vardhineedi Sriramurthy and Ohyun Kwon*

Department of Chemistry and Biochemistry, University of California, Los Angeles, 607, Charles E. Young Drive East, Los Angeles, California 90095-1569

Abstract

Seven different types of benzannulated *N*-heterocycles—indolines, dihydropyrrolopyridines, benzimidazolines, dihydrobenzo-3,1-oxazines, benzomorpholines, tetrahydroquinolines, and tetrahydroisoquinolines—can be obtained from simple dinucleophiles and electron-deficient acetylenes in one synthetic step. This powerful methodology was made possible through the use of diphenylphosphinopropane (DPPP) as the catalyst, with acetic acid and sodium acetate used as additives in some cases. The benzannulated *N*-heterocycles were isolated in excellent yields under mild metal-free conditions; they were purified without the need for aqueous work-ups.

Functionalized saturated benzannulated *N*-heterocycles (e.g., indoline, dihydropyrrolopyridine, benzimidazoline, tetrahydroquinoline, tetrahydroisoquinoline, dihydrobenzo-1,4-oxazine, dihydrobenzo-3,1-oxazine) have been of interest to chemists for over a century because of their seemingly ubiquitous presence in natural products¹ and pharmaceutical drugs.² Not surprisingly, several useful strategies are available for the synthesis of these heterocycles, with the majority of them typically generating one or two of the compounds mentioned above.³ Based on our recent finding of a diphosphine-catalyzed mixed double-Michael reaction that proceeds through a [4 + 1] annulation, in this paper we report a unified protocol for the synthesis of the title heterocycles under robust metal-free reaction conditions (Scheme 1).⁴ Our approach is highly modular and particularly well suited for the preparation of substituted saturated benzannulated *N*-heterocycles. The requisite dinucleophiles are readily assembled from commercially available starting materials.⁵ Given the common occurrence of the title heterocycles in a large number of bioactive molecules, this

ohyun@chem.ucla.edu.

Supporting Information Available Representative experimental procedures and spectral data for all new compounds (PDF). Crystallographic data for **3a**, **3f**, **3g**, **3h**, **3j**, and **3m** (CIF). This information is available free of charge via the Internet at <http://pubs.acs.org>.

methodology should provide new avenues toward the preparation of compounds relevant to the development of human medicines.

As a test case for the construction of aniline-containing benzannulated heterocycles, we subjected the nucleophile **1a** and acetylacetylene (**2a**) to our previously reported mixed double-Michael reaction conditions: i.e., 20 mol % diphenylphosphinopropane (DPPP) in CH₃CN (Table 1, entry 1). The desired indoline **3a** was obtained in 79% yield.⁶ Although this yield is acceptable synthetically, the reaction efficiency was markedly poorer than that for pyrrolidine formation from a corresponding aliphatic amine-derived nucleophile (91% vs. 79%). To improve the reaction efficiency, we tested Brønsted acid additives that are known to be compatible with nucleophilic phosphine catalysis.⁷ To our delight, addition of 50 mol % AcOH provided a reaction efficiency comparable with that of aliphatic amine-derived nucleophiles (entry 5; 92% yield).⁸ The combination of a Brønsted acid and its conjugate base performed even better; we obtained indoline **3a** in 99% yield in the presence of AcOH and NaOAc (50 mol % each).⁹ Indeed, for several common Brønsted acid additives, pairs of acids and bases, rather than the acids or bases alone, consistently provided higher product yields (entries 5–11).¹⁰ Although there was no clear correlation between the pK_a of the Brønsted acid and the reaction efficiency, additives of low pK_a completely shut down the reaction, presumably through quenching of the reactive zwitterionic intermediates (entries 2–4).¹¹ Notably, one inorganic acid/base pair (NaHCO₃/CO₃²⁻) improved the reaction yield by 8%, whereas another (H₂O/NaOH) did not (entries 8 and 11).¹² The added acid/base pair presumably facilitated the proton transfer steps involved in the double-Michael process.

The combination of DPPP catalyst and AcOH/NaOAc additives provided a variety of aniline-containing heterocycles efficiently (Table 2).¹³ With the phenylmalonate nucleophile **1a**, both benzoylacetylene and methyl propiolate were suitable Michael acceptors (entries 1 and 2). A variety of substituents on the benzene ring (cf. entries 6 and 12) as well as heteroaromatic rings were compatible with the reaction. For instance, the pyridylmalonate **1d** provided the dihydropyrrolopyridines **3d** and **3e** in excellent yields at elevated temperature (entries 3 and 4). The 1,2-benzenediamine-derived nucleophile **1f** also underwent the double-Michael reaction to provide the benzimidazoline **3f** (entry 5). This result is in stark contrast with Lu's report of the tandem umpolung addition/Michael reactions of 1,2-di(*p*-toluenesulfonamido)ethane onto acetylenes.¹⁴ Benzimidazolines are not only important biologically—they are used as sources of organic hydrides and hydrogen storage materials.¹⁵

Next, we extended this chemistry to 1,5- dinucleophiles for the synthesis of six-membered ring-fused benzannulated heterocycles via [5 + 1] annulation. The benzyl alcohol **1g** reacted well under the optimized reaction conditions, providing the dihydrobenzo-3,1-oxazine **3g** in 88% isolated yield (entry 6). A notable extension of this methodology is represented by the annulations of the related nitrogen–carbon dinucleophile **1h** to give the benzomorpholines **3h** and **3i** (entries 7 and 8), which slowly decomposed in the presence of AcOH and NaOAc in refluxing CH₃CN; we found, however, that catalytic DPPP alone provided slightly better product yields.¹⁶ Dihydrobenzo-1,4- and -3,1-oxazines have long been recognized for their wide range of medicinal activities (e.g., antibacterial, neuroprotectant, cardiovascular, antitumor).¹⁷

We further extended this [5 + 1] annulation to the synthesis of tetrahydroquinolines and tetrahydroisoquinolines (Table 2, entries 9–12). The benzylmalonate **1j**, when mixed with electron-deficient acetylenes and catalytic DPPP, generated the tetrahydroquinolines **3j** and **3k** in excellent yields (entries 9 and 10). The tetrahydroisoquinolines **3l** and **3m** were formed from the corresponding benzylamine-derived pronucleophiles **1l** and **1m** (entries 11 and 12). Tetrahydroquinolines and -isoquinolines are present in many natural products and exhibit a wide range of pharmacological activities.¹⁸

To summarize, seven different types of bicyclic heterocycles—indoline, dihydropyrrolopyridine, benzimidazoline, dihydrobenzo-3,1-oxazine, dihydrobenzo-1,4-oxazine, tetrahydroquinoline, and tetrahydroisoquinoline—can be synthesized in one step, in excellent yields, from simple dinucleophiles and electron-deficient acetylenes. The Michael reaction is one of the most important fundamental organic reactions; our study highlights the power of the Michael reaction when applied to the right combination of starting materials under suitable reaction conditions. This versatile catalysis was mediated by DPPP with, in some cases, AcOH/NaOAc additives. This DPPP-catalyzed mixed double-Michael reaction should be further expandable to the assembly of other heterocycles—one goal for our future endeavors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support was provided by the NIH (R01GM071779 and P41GM081282). We thank Dr. Saeed Khan (Department of Chemistry and Biochemistry, UCLA) for performing the crystallographic analyses.

References

1. Bonjoch J, Sole D. Chem Rev 2000;100:3455. [PubMed: 11777429]
2. The Chemical Abstracts Service (CAS) database provided the following numbers of references for each heterocycle: indoline, 3374 patents, 102 reviews; benzimidazoline, 1085 patents, 19 reviews; tetrahydroquinoline, 2020 patents, 38 reviews; tetrahydroisoquinoline, 2165 patents, 361 reviews; dihydrobenzoxazines, 928 patents, 25 reviews.
3. For reviews on their synthesis, see: (a) Katritzky AR, Rachwal S, Rachwal B. Tetrahedron 1996;52:15031. (b) Achari B, Mandal SB, Dutta PK, Chowdhury C. Synlett 2004:2449. (c) Ilas J, Anderluh PS, Dolenc MS, Kikelj D. Tetrahedron 2005;61:7325. (d) Chrzanowska M, Rozwadowska MD. Chem Rev 2004;104:3341. [PubMed: 15250744] For selected examples, see: (e) Mei TS, Wang X, Yu JQ. J Am Chem Soc 2009;131:10806. [PubMed: 19606861] (f) Liu XY, Che CM. Angew Chem, Int Ed 2009;48:2367.
4. Sriramurthy V, Barcan GA, Kwon O. J Am Chem Soc 2007;129:12928. [PubMed: 17924625]
5. See the Supporting Information for the preparation of the starting materials.
6. With 20 mol% of the monodentate tertiary phosphines PPh₃ and PEtPh₂, we obtained **3a** in 18 and 23% yields, respectively.
7. For selected examples, see: (a) Takashina N, Price CC. J Am Chem Soc 1962;84:489. (b) Oda R, Kawabata T, Tanimoto S. Tetrahedron Lett 1964;5:1653. (c) McClure JD. J Org Chem 1970;35:3045. (d) Rychnovsky SD, Kim J. J Org Chem 1994;59:2659. (e) Thalji RK, Roush WR. J Am Chem Soc 2005;127:16778. [PubMed: 16316211] (f) Xia Y, Liang Y, Chen Y, Wang M, Jiao L, Huang F, Liu S, Li Y, Yu ZX. J Am Chem Soc 2007;129:3470. [PubMed: 17319666] (g) Mercier E, Fonovic B, Henry C, Kwon O, Dudding T. Tetrahedron Lett 2007;48:3613.
8. Trost BM, Kazmaier U. J Am Chem Soc 1992;114:7933.
9. Trost BM, Dake GR. J Am Chem Soc 1997;119:7595.
10. See the Supporting Information for a list of all of the additives tested.
11. Virieux D, Guillouzie AF, Cristau HJ. Tetrahedron 2006;62:3710.
12. For Brønsted acid/phosphine bifunctional catalysis, see: (a) Shi M, Chen LH, Li CQ. J Am Chem Soc 2005;127:3790. [PubMed: 15771513] (b) Cowen BJ, Miller SJ. J Am Chem Soc 2007;129:10988. [PubMed: 17711278] (c) Fang YQ, Jacobsen E. J Am Chem Soc 2008;130:5660. [PubMed: 18393504] (d) Meng X, Huang Y, Chen R. Org Lett 2009;11:3498. and references therein. [PubMed: 19580297]
13. The structures of **3a**, **3f**, **3g**, **3h**, **3j**, and **3m** were confirmed through X-ray crystallographic analysis. See the Supporting Information for details.
14. Lu C, Lu X. Org Lett 2002;4:4677. [PubMed: 12489959]

15. (a) Smith JG, Ho I. *Tetrahedron Lett* 1971;38:3541. (b) Prakash GKS, Mathew T, Panja C, Vaghoo H, Venkataraman K, Olah GA. *Org Lett* 2007;9:179. and references therein. [PubMed: 17217259]
16. See the Supporting Information for details.
17. (a) Gromachevskaya EV, Kvitkovskii FV, Kosulina TP, Kul'nevich VG. *Chem Heterocycl Comp* 2003;39:137. (b) Liu Z, Chen Y. *Tetrahedron Lett* 2009;50:3790. and references therein.
18. (a) Balasubramanian, M.; Keay, JG. *Comprehensive Heterocyclic Chemistry II*. McKillop, A., editor. Vol. 5. Pergamon Press; Oxford: 1996. p. 245-300. Chapter 5 (b) Scott JD, Williams RM. *Chem Rev* 2002;102:1669. [PubMed: 11996547]

Scheme 1.
Formation of Benzannulated Heterocycles

Table 1

Evaluation of Conditions for the Formation of Indoline **3a**^a

entry	acid	pK _a ^b	conjugate base	yield (%) ^c
1	none		none	79
2	CF ₃ CO ₂ H	-0.25 ^d	CF ₃ CO ₂ Na	0
3	H ₃ PO ₄	2.1 ^d	N/A	0
4	2,4-dinitrophenol	5.1	N/A	0
5	CH ₃ CO ₂ H	12.6	CH ₃ CO ₂ Na	92
6	bi(2-naphthol)	16.2	+ <i>n</i> -BuLi	81
7	thiourea	21.0	+ <i>n</i> -BuLi	57
8	NaHCO ₃	10.2 ^d	Na ₂ CO ₃	80
9	CF ₃ CH ₂ OH	23.5	CF ₃ CH ₂ ONa	91
10	urea	26.9	+ <i>n</i> -BuLi	82
11	H ₂ O	31.4	NaOH	67
				with acid/base
				N/D
				0
				N/D
				N/D
				99
				94
				68
				87
				93
				85
				75

^a All reactions were performed using 1.0 mmol of **1a**, 1.1 mmol of acetylacetylene (**2a**), 20 mol % of DPPP, and 0.50 mmol of the additive(s).

^b pK_a in DMSO.

^c Isolated yield.

^d pK_a in H₂O.

Table 2Syntheses of Benzannulated N-Heterocycles^a

entry	nucleophile
1	1a
2	1a

entry

nucleophile

3^c 4^c**1d**

entry

nucleophile

5^c

1f

entry

nucleophile

 6^c

1g

 7^d

1h

entry	nucleophile
-------	-------------

8^d

1h

9^d

10^d

1j

entry

nucleophile

11^e

11

entry

nucleophile

12^e

1m

^a Performed using 1.0 mmol of the nucleophile, 1.1 mmol of the acetylene, 20 mol % of DPPP, and 0.50 mmol of AcOH and NaOAc in CH₃CN at rt, unless otherwise noted.

^b Isolated yields after chromatographic purification.

^c Reactions were performed under reflux.

^d Reactions were run in the absence of AcOH/NaOAc in CH₃CN under reflux.

^e In the absence of AcOH/NaOAc in CH₃CN at rt.