

An efficient palladium-catalyzed coupling reaction of lithium alkynyltriisopropoxyborates with acid chlorides: a new access to synthesis of conjugated ynones

Chang Ho Oh* and V. Raghava Reddy

Department of Chemistry, Hanyang University, Sungdong-Gu, Seoul 133-791, South Korea

Received 18 July 2004; revised 15 September 2004; accepted 16 September 2004

Abstract—An efficient palladium-catalyzed protocol for the synthesis of ynones from lithium alkynyltriisopropoxyborates with acid chlorides under mild neutral conditions.

© 2004 Elsevier Ltd. All rights reserved.

The Suzuki–Miyaura coupling reaction between organoboron compounds and organic electrophiles provides a powerful method for the formation of carbon–carbon bonds.¹ Recently this method has been extended to synthesis of ketones from the corresponding acid chlorides and anhydrides.² Conjugated ynones have been prominently utilized as equivalents of valuable intermediates in organic synthesis as well as various functional groups in natural product,³ heterocycles,⁴ and acetylenic scaffolds.⁵ This has encouraged the development of a number of traditional approaches for the synthesis of ynones and ynoates. Among most frequently employed methods to access ynones,⁶ the use of organometallic reagents such as organosilanes,⁷ organoantimony,⁸ and organotin⁹ have attracted much attention. However these organometallic reagents and their byproducts are highly toxic and difficult to remove.¹⁰ We imagined that the coupling reaction of acid chlorides with alkynylborate salts might be an interesting alternative toward the synthesis of ynones.

Alkynylborates have long been known to useful synthetic intermediates.¹¹ Utility of these reagents in metal catalyzed reactions have become the subject of intense interest due to their enhanced reactivity and stability, and successful transformations now include Suzuki–Miyaura cross coupling,¹² conjugated addition to enones,¹³ allylic additions to allylic carbonates,¹⁴ and

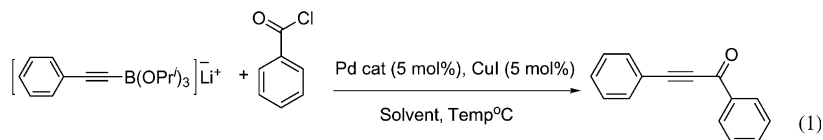
Mannich reaction.¹⁵ On the basis of these promising potentialities, our efforts have been made in developing new synthetic methodologies using organoboron compounds.¹⁶ Herein we wish to report an efficient protocol for the synthesis of ynones from cross-coupling reaction of acyl halides with lithium alkynylboronate salts. Initial studies were directed toward finding a general set of reaction conditions that could be applied to a wide variety of acid chlorides and alkynylborates. The reaction was optimized by using phenylacetylene borate (**1a**) with benzoyl chloride (**1b**) as standard substrates. These results are summarized in Table 1.

Both the Pd(0) and Pd(II) complexes catalyzed the reaction smoothly. When the reaction was screened with a catalytic amount of PdCl₂(PPh₃)₂ and CuI in various solvents such as DME, acetonitrile, 1,4-dioxane, THF, and toluene. The reaction worked in DMF, toluene and 1,4-dioxane albeit in low yields. The reaction in THF afforded the coupling product in 54% yield along with the homocoupled product. Gratifyingly, the use of PdCl₂(PPh₃)₂ (5 mol%) in acetonitrile at 60 °C for 10 h resulted in **3aa** in 91% yield.¹⁷ It is noteworthy that the present catalytic system does not require any added base or additives. Also various palladium compounds such as Pd(OAc)₂, Pd(OAc)₂/DPEPhos, Pd(OAc)₂/PPh₃, Pd(PPh₃)₄, and Pd₂(dba)₃ in acetonitrile were tested for this selected cross coupling.

To expand this approach further, we have applied the method on cross coupling of alkynylborates with acyl halides in the presence of optimized catalyst system in acetonitrile. The reaction did not proceed without

Keywords: Alkynyl borate; Acid chlorides; Cross coupling; Pd; Ynones.

* Corresponding author. Tel.: +82 2 2299 0932; fax: +82 2 2299 0762; e-mail: changho@hanyang.ac.kr

Table 1. Optimization of cross-coupling reaction of phenyl acetylene borate (**1a**) with benzoyl chloride (**2a**)

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	% Yield ^a
1	PdCl ₂ (PPh ₃) ₂	DMF	120	14	32
2 ^b	PdCl ₂ (PPh ₃) ₂	THF	60	10	54
3	PdCl ₂ (PPh ₃) ₂	1,4-Dioxane	80	12	46
4	PdCl ₂ (PPh ₃) ₂	CH ₃ CN	60	10	91
5	PdCl ₂ (PPh ₃) ₂	Toluene	100	12	54
6	Pd(PPh ₃) ₄	CH ₃ CN	60	14	73
7 ^c	Pd(OAc) ₂ /DPEPhos	CH ₃ CN	60	10	58
8	Pd(OAc) ₂	CH ₃ CN	60	15	32
9	Pd(OAc) ₂ /PPh ₃	CH ₃ CN	60	16	45
10 ^d	Pd ₂ (dba) ₃	CH ₃ CN	60	17	—

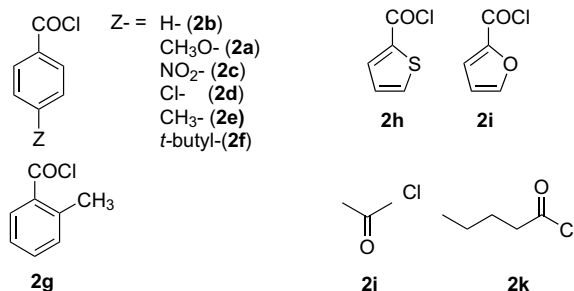
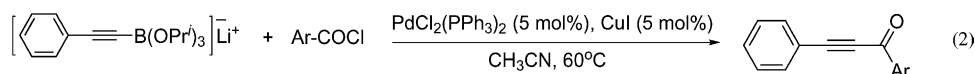
^a Isolated yields.^b Homocoupled product (diphenyl-1,3-butadiyne) was observed.^c Bis(diphenylphosphino ether).^d Undesired product was observed.

adding CuI, though its role in the reaction was unknown. Performing a similar transformation with CuI but without Pd(II) catalyst resulted in no reaction, consistent with the need for a Pd catalyst.¹⁸

With the optimized conditions for the facile cross coupling of **1a** and **2a** in hand, we further explored the tolerance of this process toward a range of acid chlorides (Table 2). Both the electron donating and withdrawing substituted aryl chlorides (**2b–f**) performed well, and

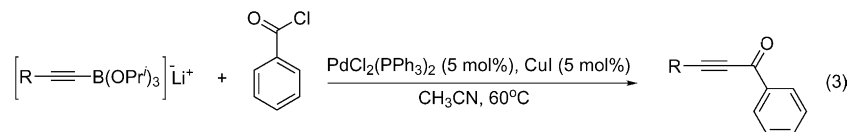
provided the cross-coupled products in 76–84% yields (entries 1–5).

However, the *ortho*-substituted aryl chloride (**2g**) displayed poor reactivity, presumably because of steric factors (entry 6). The use of heterocyclic aryl chlorides were tolerated well, with 2-thiophenoyl (**2h**), 2-furoyl (**2i**) chlorides providing the coupled products **3af** and **3ai** in 72% and 74% yields, respectively. The reaction also performed well with alkylic acid chlorides such

Table 2. Palladium catalyzed cross-coupling reaction of phenyl acetylene borate (**1a**) with various acid chlorides (**2b–k**)

Entry	Substrates	Time (h)	Products	% Yield ^a
1	2b	8	3ab	84
2	2c	12	3ac	78
3	2d	8	3ad	82
4	2e	10	3ae	78
5	2f	10	3af	76
6	2g	14	3ag	61
7	2h	13	3ah	72
8	2i	12	3ai	74
9	2j	14	3aj	65
10	2k	15	3ak	68

^a Isolated yields.

Table 3. Palladium catalyzed cross-coupling reaction of benzoyl chloride (**2a**) with a various lithium alkynylborates (**1b–m**)

Entry	Substrates	Time (h)	Products	% Yield
1		10	3ba	83
2		8	3ca	81
3		8	3da	78
4		8	3ea	76
5		10	3fa	68
6		8	3ga	78
7		10	3ha	76
8		10	3ia	74
9		12	3ja	72
10		10	3ka	76
11		10	3la	68
12		10	3ma	64

as methyl (**2j**) and *n*-butyl (**2k**) provided the corresponding ynones **3aj** and **3ak** in moderate yields (entries 9 and 10).

To extend the general applicability of this coupling reaction, we initiated to test the reaction of several alkynylborates with benzoyl chloride (**2a**) under the above optimized conditions. To this end we have prepared a series of alkynylborates from the commercially available triisopropoxyborate with alkynyllithium, which was in situ prepared from the corresponding terminal alkynes with the *n*-BuLi at -78°C in ether.¹⁹

In most cases, good to excellent yields of the corresponding coupling products were observed (Table 3). At first, arylacetylene borates bearing both an electron-deficient group (**1b**) and an electron-rich group (**1c**) worked smoothly under these conditions to afford **3ba** and **3ca** in 83% and 81% yields, respectively. Alkyl-substituted acetylene borates such *tert*-butyl (**1d**) and *n*-butyl (**1e**) gave the even more promising results. The TMS protected alkynylboronate (**1f**) underwent cross coupling with aroyl chloride (**2a**) to afford the product **3fa** in 68% yield.

We next employed a series of terminal alkynes bearing an oxy-functionality. The reaction of TBDMS ether **1g** of propargyl alcohol provided the corresponding ynone **3ga** in good yield. Similarly, the reaction with TBDMS ethers **1h** of 1-butynol afforded the product **3ha** in 76%

yield. Benzyl ether **1i** of 1-hexynol was also effective to furnish the product **3ia** in 74% yield.

Finally, the substrates **1j** and **1k** underwent smooth couplings to give the products **3ja** and **3ka** in 72% and 76% yields, respectively. Without significant loss of yields, two more alkynyl substrates **1l** and **1m** were also effectively coupled with benzoyl chloride (**2a**) to furnish the products **3la** and **3ma** in 68% and 64% yields, respectively.

The overall process displays a good generality as well as good functional group compatibility toward acid chlorides and alkyne components as well.

In summary, we have demonstrated a new and efficient palladium-catalyzed coupling reaction of acid chlorides with lithium alkynyltriisopropoxyborates leading to ynones. Furthermore, the reaction proceeded under mild conditions and employed a stable, nontoxic, and functional group tolerant boronates. Extension of this strategy to the synthesis of functionalized amines is being pursued.

Acknowledgements

We wish to acknowledge the financial support of the Centre of Molecular Design and Synthesis (CMDs), V.R.R. is grateful for a graduate fellowship supported by the BK21 project.

References and notes

- (a) Miyaura, N.; Yamada, Y.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437; for reviews see: (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 2457; (c) Suzuki, A. *Pure. Appl. Chem.* **1994**, *66*, 213; (d) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178; (e) Oh-e, T.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1990**, 221.
- (a) Haddach, M.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 3057; (b) Bumagin, N. A.; Korolev, D. N. *Tetrahedron Lett.* **1999**, *40*, 3057; (c) Gooben, L. J.; Ghosh, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3458; (d) Gooben, L. J.; Winkel, L.; Dohring, A.; Ghosh, K.; Paetzold, J. *Synlett* **2002**, *8*, 1237; (e) Urawa, Y.; Ogura, K. *Tetrahedron Lett.* **2003**, *44*, 271.
- (a) Perollier, C.; Sorokin, A. B. *Chem. Commun.* **2002**, 1548; (b) Basak, A.; Bdour, H. M.; Shain, J. C.; Mandal, S.; Rudra, K. R.; Nag, S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1321; (c) Chowdary, C.; Kundu, N. G. *Tetrahedron* **1999**, *55*, 7011; (d) Adlington, R. M.; Baldwin, J. E.; Pritchard, G. J.; Spencer, K. *Tetrahedron Lett.* **2000**, *41*, 575; (e) Aoki, S.; Matsui, K.; Wei, H.; Murakami, N.; Kobayashi, M. *Tetrahedron* **2000**, *58*, 5417; (f) Baldwin, J. E.; Pritchard, G. J.; Rathmell, R. E. *J. Chem. Soc., Perkin. Trans. 1* **2001**, 1682.
- (a) Li, P.; Fong, W. M.; Chao, L. C. F.; Fung, S. H. C.; Williams, I. D. *J. Org. Chem.* **2001**, *66*, 4087; (b) Wang, X.; Tan, J.; Zhang, L. *Org. Lett.* **2000**, *2*, 3107; (c) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974; (d) Bagley, M. C.; Hughes, D. D.; Taylor, P. H. *Synlett* **2003**, *2*, 3107; (e) Savarin, C. G.; Murry, J. A.; Dormer, P. G. *Org. Lett.* **2002**, *4*, 2071.
- Livingstone, R.; Cox, L. R.; Odermatt, S.; Diederich, F. *Hel. Chim. Acta* **2002**, *85*, 3052.
- (a) Davis, R. B.; Scheiber, D. H. *J. Am. Chem. Soc.* **1956**, *78*, 1675; (b) Normat, J. F. *Synthesis* **1972**, 63; (c) Chowdary, C.; Kundu, N. *Tetrahedron* **1999**, *55*, 7011; (d) Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc.* **1988**, *110*, 2301; (e) Thoda, Y.; Sonogoshira, K.; Hagihara, N. *Synthesis* **1977**, 777; (f) Alonoso, D. A.; Najera, C.; Pacheco, M. C. *J. Org. Chem.* **2004**, *69*, 1615, and also see for Lithium acetylides; (a) Goldstein, J.; Orlek, B. S. *Synth. Commun.* **1993**, *23*, 487; (b) Brown, H. C.; Racherla, U. S.; Singh, S. M. *Tetrahedron Lett.* **1984**, *25*, 2411; (c) Yamaguchi, M.; Shibata, K.; Fujiwara, S.; Hirao, I. *Synthesis* **1986**, 421; Magnesium acetylide: Kroeger, J. W.; Nieuwland, J. A. *J. Am. Chem. Soc.* **1936**, *58*, 1861.
- (a) Ito, H.; Arimoto, K.; Sensui, H.; Hosomi, A. *Tetrahedron Lett.* **1997**, *38*, 3977; (b) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S. *Synlett* **2003**, 1722.
- Kakusuwa, N.; Yamaguchi, K.; Kurita, J.; Tsuchiya, T. *Tetrahedron Lett.* **2000**, *41*, 4143.
- Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549.
- For toxicology studies see: (a) Chau, Y. K.; Wong, P. T. S. *Some Environmental Aspects of Organo-arsenic, Lead and Tin*; NBS Special Publication: US, 1981; Vol. 618, p 65; (b) Sandhu, G. K. *J. Chem. Sci.* **1983**, *9*, 36; (c) Barnes, J. M.; Magos, L. *Organomet. Chem. Rev.* **1968**, *3*(2), 137.
- (a) Suzuki, A. *Pure. Appl. Chem.* **1991**, *63*, 419; (b) Colberg, J. C.; Rane, A.; Vaquer, J.; Soderquist, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 6065; (c) Soderquist, J. A.; Matos, K.; Rane, A.; Ramos, J. *Tetrahedron Lett.* **1995**, *36*, 2401; (d) Furstner, A.; Seidel, G. *Tetrahedron* **1995**, *51*, 1165; (e) Furstner, A.; Seidel, G. *Synlett* **1997**, 161.
- (a) Oh, C. H.; Jung, S. H. *Tetrahedron Lett.* **2000**, *41*, 8513; (b) Molander, G. A.; Katona, B. W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416; (c) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393; (d) Molander, G. A.; Reviro, M. R. *Org. Lett.* **2002**, *4*, 107; (e) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867; (f) Batey, A. B.; Quatch, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099; (g) Fang, G.-H.; Zeng-Jun, Y.; Deng, M.-Z. *Org. Lett.* **2004**, *6*, 357; (h) Zou, G.; Flack, J. R. *Tetrahedron Lett.* **2001**, *42*, 5817.
- (a) Chong, M. J.; Shen, L.; Nicholas, J. T. *J. Am. Chem. Soc.* **2000**, *122*, 1822; (b) Battey, A. R.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683; (c) Brown, C. D.; Chong, J. M.; Shen, L. *Tetrahedron* **1999**, *55*, 14233.
- (a) Chen, H.; Deng, M.-Z. *J. Organomet. Chem.* **2000**, *603*, 189; (b) Kobayashi, Y.; Mizojiri, R.; Ikeda, E. *J. Org. Chem.* **1996**, *61*, 5391.
- Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2004**, *45*, 729.
- (a) Oh, C. H.; Jung, H. H.; Kim, K. S. *Angew. Chem. Int., Ed.* **2003**, *42*, 805; (b) Oh, C. H.; Ahn, T. W. R.; Reddy, V. *Chem. Commun.* **2003**, 2622; (c) Kim, N.; Kim, K. S.; Gupta, A. K.; Oh, C. H. *Chem. Commun.* **2004**, 618; (d) Oh, C. H.; Ryu, J. H. *Bull. Korean Chem. Soc.* **2004**, *24*, 1563; (e) Oh, C. H.; Reddy, R. V. *Tetrahedron Lett.* **2004**, *45*, 5221.
- Representative procedure: To a mixture of lithium alkynyltriisopropoxyborate (**1a**) (0.20 mmol) and benzoyl chloride (**2a**) (0.24 mmol), PdCl₂(PPh₃)₂ (0.0050 mmol, 5 mol%), CuI (0.005 mmol, 5 mol%), CH₃CN (2 mL) was added under argon atmosphere in a round bottomed flask. The resulting suspension was stirred at 60 °C. After heating for the time specified, the reaction mixture was allowed to cool to room temperature. The product was extracted into diethyl ether (3 × 10 mL), the solvent was removed by rotary evaporation, and the residue was purified by silica gel chromatography.
- A transition metal-free intermolecular alkyl transfer reaction of tetraorganoborate complexes with acyl halides has also been reported Negishi, E.; Chiu, K.-W.; Yosida, T. *J. Org. Chem.* **1975**, *40*, 1676.
- (a) Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316; (b) Brown, H. C.; Bhatt, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631.