ORGANIC
LETTERS

2004
Vol. 6, No. 13
2209−2212

Sonogashira Cross-Couplings of Ynamides. Syntheses of Urethane- and Sulfonamide-Terminated Conjugated Phenylacetylenic Systems

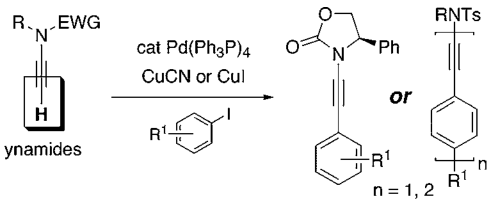
Michael R. Tracey, Yanshi Zhang, Michael O. Frederick, Jason A. Mulder, and Richard P. Hsung*

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

hsung@chem.umn.edu

Received April 13, 2004

ABSTRACT



The first successful Sonogashira coupling of ynamides with aryl and vinyl iodides is described here. This study resolves the problem of the competing pathway involving homocoupling of ynamides and provides a practical entry to novel urethane- or sulfonamide-terminated conjugated acetylenic systems. An interesting tandem hydrohalogenation and Sonogashira coupling was also observed to give an en-ynamide.

Ynamides have become useful synthons in organic synthesis.[1,2] Our efforts[3] have led to the development of a Cu-catalyzed *N*-alkynylation as a practical synthesis of ynamides **3**.[4] These endeavors[5] have provided access to terminally unsubstituted ynamides **4**, thereby allowing various explorations of functionalization of this unique terminal acetylenic carbon. Thus far, the only uncovered reactivities have involved additions of electrophiles such as MeI to the lithiated ynamide **4** reported by our group[4b] and addition of BuBr reported by Witulski[2i] and, recently, a Glaser-type coupling reported by Saá.[2a] We recognized that a potentially more important reaction would be the utility of ynamides **4** in transition metal-mediated cross-coupling reactions such as Sonogashira coupling,[6,7] which has not been reported,

---

(1) For reviews on ynamides, see: (a) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. For the first preparations of ynamides, see: (c) Janousek, Z.; Collard, J.; Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 917.

(2) For recent efforts in synthesis and applications of ynamides, see: (a) Rodríguez, D.; Castedo, L.; Saá, C. *Synlett* **2004**, 377. (b) Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, *6*, 727. (c) Klein, M.; König, B. *Tetrahedron* **2004**, *60*, 1087. (d) Marion, F.; Courillon, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 5095. (e) Witulski, B.; Alayrac, C.; Tevzaadze-Saeftel, L. *Angew. Chem., Int. Ed.* **2003**, *43*, 4392. (f) Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* **2003**, *5*, 67. (g) Witulski, B.; Lumtscher, J.; Bergsträsser, U. *Synlett* **2003**, 708. (h) Naud, S.; Cintrat, J.-C. *Synthesis* **2003**, 1391. (i) Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281. (j) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803. (k) Timbart, J.-C.; Cintrat. J.-C. *Chem. Eur. J.* **2002**, *8*, 1637. (l) Minière, S.; Cintrat. J.-C. *Synthesis* **2001**, 705. (m) Minière, S.; Cintrat. J.-C. *J. Org. Chem.* **2001**, *66*, 7385. (n) Hoffmann, R. W.; Brückner, D. *New. J. Chem.* **2001**, *25*, 369. (o) For citations appearing before 2001, see ref 1a,b.

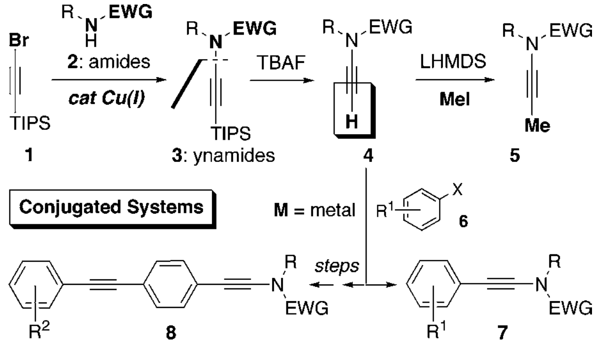
(3) For our recent applications of ynamides, see: (a) Shen, L.; Hsung, R. P. *Tetrahedron Lett.* **2003**, *44*, 9353. (b) Frederick, M. O.; Hsung, R. P.; Lambeth, R. H.; Mulder, J. A. Tracey, M. R. *Org. Lett.* **2003**, *5*, 2663. (c) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H. A.; Frederick, M. O.; Shen, L.; Zificsak, C. A. *Org. Lett.* **2003**, *5*, 1547. (d) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar. C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417. (e) Mulder, J. A.; Hsung, R. P.; Frederick, M. O.; Tracey, M. R.; Zificsak, C. A. *Org. Lett.* **2002**, *4*, 1383. (f) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459.

(4) For our syntheses of ynamides using copper-catalyzed amidations of alkynyl bromides, see: (a) Zhang, Y.; Hsung R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151. (b) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368.

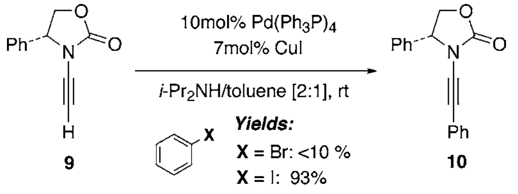
(5) For two related accounts involving synthesis of ynamides using copper metal, see: (a) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011. (b) Also see ref 2b for CuI-catalyzed *N*-alkynylations reported by Urabe and Sato.

10.1021/ol0493251 CCC: $27.50

Scheme 1



Scheme 2

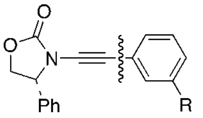
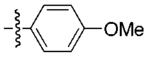
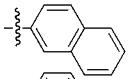
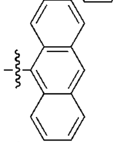
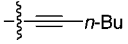


except two independent documentations of unsuccessful attempts.[2c,8] As an alternative, Saá[8] did report recently the use of zinc sulfonamido-acetylides, generated in situ from β,β'-dichloro-enamides, in Negishi-type couplings. However, the Sonogashira protocol still represents the most efficient and straightforward cross-couplings of any terminal alkynes.[6,7] These cross-coupling reactions should lead to the preparation of conjugated systems[9] such as **7** and **8** that can be useful in developing new materials given the significance of conjugated rigid rods molecular electronics[9,10] and self-assembly.[11−13] In addition, although the copper-catalyzed amidation of alkynyl iodides[4,5] is a viable approach for constructing these ynamides, a successful Sonogashira coupling would provide not only a complimentary protocol but also, more importantly, an entry that is more versatile and practical when one intends to design and synthesize a library of ynamides that differ only in the C-terminal substituents. We report here findings using ynamides **4** in Sonogashira couplings as an approach to conjugated phenylacetylenic systems.

The feasibility of Sonogashira coupling was readily established as shown in Scheme 2. We did not observe here homocoupling of ynamide **9**, which is an urethane-based ynamide, as reported in the literature for sulfonyl-substituted ynamides.[2c,8] The coupling reaction of ynamide **9** with iodobenzene using 10 mol % of $Pd(Ph_3P)_4$ and 7 mol % of CuI in i-Pr_2NH/toluene (2:1) at room temperature led to the formation of the desired phenyl-substituted ynamide **10**[14] in 93% yield (Scheme 2). Although both CuCN and CuI appear to be feasible for the Sonogashira coupling, as expected, iodobenzene coupled much faster than bromobenzene.[15]

The generality of this Sonogashira coupling with various aryl iodides is displayed in Table 1. The main features are as follows: (1) $PdCl_2(Ph_3P)_2$ was less effective in catalyzing these couplings than $Pd(Ph_3P)_4$ (respectively, entry 1 versus entries 2 and 3 (or see Scheme 2), and entries 7 versus 8), and thus only $Pd(Ph_3P)_4$ was used throughout this study. (2)

Table 1.

entry	coupling products[a]		copper	temp	yield[b]
1		**10**: R = H	CuCN[c]	rt	20%[c]
2		**10**: R = H	CuCN	rt	57
3		**10**: R = H	*vs.* CuI	rt	[93][d]
4		**11**: R = Me	CuCN	rt	64
5		**12**	CuCN	rt	65
6		**12**	*vs.* CuI	rt	54
7		**13**	CuCN[c]	rt	18[c]
8		**13**	*vs.* CuI	rt	92
9		**14**	CuCN	rt	59
10		**14**	*vs.* CuI	rt	20
11		**15**	CuI[e]	rt	58[e]

[a] Reactions were carried out using 10 mol % $Pd(Ph_3P)_4$ and 7 mol % copper salt in i-Pr_2NH/toluene (2:1) except for entries 1 and 7. [b] Isolated yields. [c] In entries 1 and 7, 10 mol % $PdCl_2(Ph_3P)_2$ was used. [d] The same result as in Scheme 2. [e] 1-Bromo-1-hexyne was used.

---

(6) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. For reviews on Heck couplings, see: (b) Hegedus, L. S. *Tetrahedron* **1984**, *40*, 2415.

(7) For reviews, see: (a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. In *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987. (b) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002; Vol I, p 7. (c) Sonogashira, K. Cross-coupling reactions to sp carbon atoms. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCh: New York, 1998; pp 203−229.

(8) During our pursuit of Sonogashira couplings, Saá reported an alternative Negishi coupling of sulfonyl ynamides and also documented the lack of feasibility in related Sonogashira coupling. See: Rodríguez, D.; Castedo, L.; Saá, C. *Synlett* **2004**, 783.

(9) For reviews, see: (a) Ahmed, H. *J. Vac. Sci. Technol., B* **1997**, *15*, 2101. (b) Petty, M. C.; Bryce, M. R.; Bloor, D. *Introduction to Molecular Electronics;* Oxford University Press: New York, 1995. (c) *Molecular Electronics and Molecular Electronic Devices*; Sienicki, K., Ed.; CRC Press: Boca Raton, 1992; Vols. I−III. (d) Mirkin, C. A.; Ratner, M. A. Molecular electronics. *Annu. Rev. Phys. Chem.* 1992, *43*, 719.

(10) Also see: (a) Wada, Y. *Surf. Sci.* **1997**,*386*. 265. (b) Reimers, J. R.; Lu, T. X.; Crossley, M. J.; Hush, N. S. *Nanotechnology* **1996**, *7*, 424. (c) *Conjugated Conducting Polymers*; Springer Series in Solid-State Sciences, no. 102; Kiess H., Ed.; Springer-Verlag: Berlin, 1992.

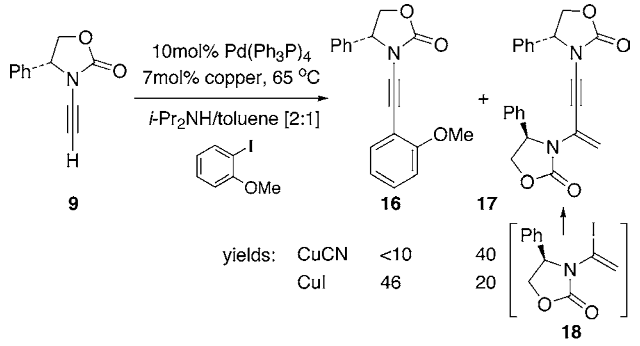
(11) (a) Dubois, L. H.; Nuzzo, R. G. *Annu. Rev. Phys. Chem.* **1992**, *43*, 437. (b) Ulman, A. *Chem. Rev.* **1996**, *96*, 1533.

(12) For some recent examples, see: (a) Zhang, J.: Pesak, D. J.; Ludwick, J. L.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 4227. (b) Scherf, U.; Müllen, K. *Synthesis* **1992**, 23. (c) Tour, J. M.; Jones, L., II; Pearson, D. L.; Lamba, J. J. S.; Burgin, T. P.; Whitesides, G. V.; Allara, D. L.; Parikh, A. N.; Atre, S. V. *J. Am. Chem. Soc.* **1995**, *117*, 9529.

(13) (a) Dhirani, A.-A.; Zehner, W. R.; Hsung, R. P.; Guyot-Sionnest, P.; Sita, L. R. *J. Am. Chem. Soc.* **1996**, *118*, 3319. (b) Sandra, S. B.; Dudek, S. P.; Hsung, R. P.; Sita, L. R.; Smalley, J. F.; Newton, M. D.; Feldberg, S. W.; Chidsey, C. E. D. *J. Am. Chem. Soc.* **1997**, *119*, 10563. (c) Zehner, R. W.; Parsons, B. F.; Hsung, R. P.; Sita, L. R. *Langmuir* **1999**, *15*, 1121.

(14) Relevant procedures for new compounds and their characterizations are in Supporting Information.

Scheme 3



CuCN and CuI did not always provide comparable outcome (entries 2 versus 3, entries 5 versus 6, and entries 9 versus 10), and we are not exactly sure as to the reason for this inconsistency. In addition, a cross-Glaser-type coupling[16] could be readily achieved using 1-bromo-1-hexyne (entry 11).

More interestingly, when using an *ortho*-substituted aryl iodide such as *o*-iodo-anisole, the rate of coupling was slowed, requiring the reaction temperature to be raised to afford the desired product **16** (Scheme 3). We obtained an X-ray structure of ynamide **16** (Figure 1), which represents the first crystal structure obtained for an ynamide.[17] Although the desired coupling product **16** was isolated in 46% yield using CuI, we also found 20% of en-ynamide **17**, which was found to be the major product when using CuCN.

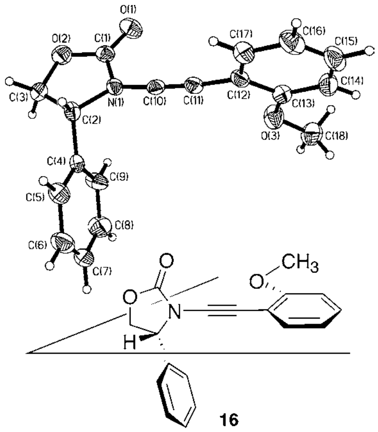
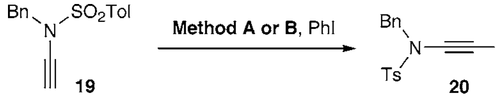


Figure 1.

Scheme 4



Method A. Yield: 20%
10mol% Pd(Ph$_3$P)$_4$, 7mol% of CuI;
Solvent: *i*-Pr$_2$NH/toluene [2:1]; *Temp*: rt.

Method B. Yield: 60%
3.3mol% Pd(Ph$_3$P)$_4$, and 1.5mol% CuI
was added *5-20 min* after mixing **19** and PhI with
Pd. *Solvent*: Et$_3$N/toluene [2:1]; *Temp*: 65 °C.

We suspected that en-ynamide **17** was derived from the Sonogashira coupling of ynamide **9** with α-iodo-enamide **18**, which was likely a result of addition of HI to **9** on the basis of what we had previously observed in the formation of α-iodo-enamides via hydrohalogenation of ynamides using metal halides.[3c,4a] Because CuI was shown not to give any hydrohalogenation products,[3c] we further suspected that it could be the presence of untrapped HI, produced in the coupling reaction.

However, when measures were taken to reduce HI by using Et$_3$N as solvent, en-ynamide **17** was found as the sole product, or when Hünig's base was used as solvent or as a cosolvent with THF (1:1), **16** and **17** were isolated with a 1:1 ratio. Further experiments also suggest that alkylammonium iodide salts do not hydrohalogenate ynamides to the corresponding α-iodo-enamide. These preliminary findings imply that palladium associated intermediates might be involved in the process of either yielding **18** or going directly to **17**. We are currently further examining this issue.

Having established this Sonogashira coupling protocol, we turned our attention to sulfonyl-substituted ynamides, and consequently, we encountered similar difficulties as those reported in the literature[2c,8] using sulfonyl-substituted ynamide **19** as shown in Scheme 4. The same protocol (see Method A), used in coupling of ynamide **9**, was not useful for **19**, leading to phenyl-substituted ynamide **20** in only 20% yield with the major product being the homocoupling (or a Glaser-type coupling) of **19**.[2a,c,8]

Fortuitously, only a minor tweaking to the conditions was necessary (see Method B). The addition of the copper catalyst was carried out after premixing ynamide **19** and iodobenzene with the palladium catalyst, although at a much reduced amount at 1.5 mol % (the range was 0.3−1.5 mol %) instead of the original 7 mol %, and the temperature was also raised to 65 °C.[15] These minor changes in the reaction conditions led to **20** in 60% yield with the homocoupling pathway being mostly suppressed.

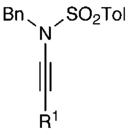
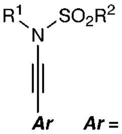
---

[15] **Typical Procedure, Method A.** See the Supporting Information. **Typical Procedure, Method B.** To a reaction flask were added 428.0 mg of ynamide **19** (1.5 mmol), 497.0 mg of ethyl 4-iodobenzoate (1.8 mmol), 86.0 mg of Pd(PPh$_3$)$_4$ (0.075 mmol, 5 mol %), 8 mL of TEA, and 4 mL of toluene. The solution was stirred at room temperature for 10 min, and 4.3 mg of CuI (1.5 mol %) was then added. After heating the reaction mixture at 60 °C for 2 h, the mixture was diluted with EtOAc, filtered through Celite, and concentrated in vacuo. The resulting crude residue was purified by silica gel flash column chromatography (gradient 10% to 20% EtOAc in hexanes) to afford 473.0 mg (73% yield) of aryl ynamide **22**.

[16] (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422. (b) For a review see: Cadiot, P.; Chodkiewicz, W. Coupling of acetylenes. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 597−647. (c) For a recent review, see: Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew Chem., Int. Ed.* **2000**, *39*, 2632.

[17] The X-ray structure reveals that there is a slight bend along the acetylenic axis (N1−C10−C11−C12). More interestingly, the two planes of the *o*-methoxyphenyl ring and the oxazolidinone ring have an approximate dihedral angle of ∼79.9°, which is almost orthogonal as shown in the ChemDraw reproduction.

Table 2.

entry	products[a]	R^1 =	R^2	yield[b]
1	 **21**	4-NO_2-Ph		78
2	**22**	4-EtO_2C-Ph		73
3	**23**	2-furyl		59[c]
4	**24**	2-thiophene		82
5	**25**	2-pyridyl		44[c]
6	**26**	3-pyridyl		81
7	**27**	*trans*-CH=CH-*n*-Bu		42[d]
8	**28**	*trans*-CH=CH-*n*-hex		31[d]
9	 **29**	Bn	Me	77
10	**30**	Bn	4-anisyl	96
11	**31**	(-)-α-Phenethyl	Ph	85

Ar = 4-NO_2-Ph

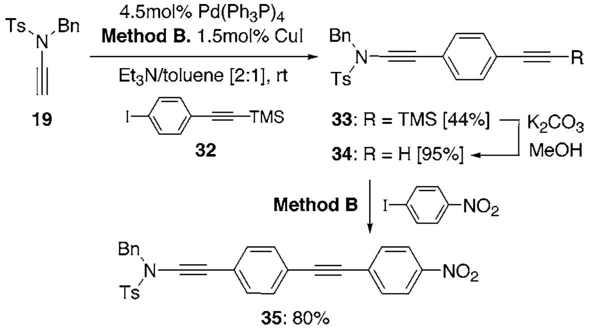
[a] All reactions employed Method B. [b] Isolated yields. [c] The reaction was run at room temperature. [d] 15 mol % CuI was used, and reaction was run at room temperature.

The minor tweaking of the reaction conditions to render the Sonogashira coupling feasible is noteworthy. Although König[2c] did not comment on specific conditions in their Sonogashira attempts, Saá[8] reported that under similar conditions ($PdCl_2(Ph_3P)_2$ was used), the Sonogashira coupling of the sulfonyl ynamide (they used Ts(**Ph**)NC≡CH) led to complex mixture with homocoupling as the major pathway. We used ynamide **19** with a **Bn** substituent on the nitrogen atom because we had speculated that it could be a substituent effect, and in addition, we avoided $PdCl_2(Ph_3P)_2$ since $Pd(Ph_3P)_4$ was better a catalyst in our study. However, the fact that we encountered the same outcome suggests that it was likely not due to the difference in substituents or the nature of Pd catalysts.

Therefore, a successful Sonogashira coupling of sulfonyl ynamide **19** was achieved by effectively delaying the addition of the copper catalyst, which implies that there is an order of the event. It can be suggested that this delay avoids a quick buildup of the copper-acetylide species, which can be funneled toward the homocoupling pathway. Concomitantly, having a sufficient amount of presence of the oxidative-addition intermediate derived from iodobenzene and $Pd(Ph_3P)_4$ prior to the addition of the copper catalyst allows the transmetalation to compete more effectively with the homocoupling for the available copper-acetylide species.[18]

This new protocol (Method B) proved to be general for preparations of various aryl-substituted sulfonyl ynamides (Table 2). Most notably in Table 2, we were able to construct a series of heteroaryl-substituted ynamides **23**−**26** (entries 3−6) and succeeded in coupling **19** with vinyl iodides, providing en-ynamides **27** and **28** (entries 7 and 8) in moderate yields, albeit 15 mol % of CuI was needed. Vinyl bromide again was very slow and did not couple well.

Scheme 5



Finally, to take measures toward establishing the concept of constructing an extended conjugated phenylacetylenic system that terminates with an amide group, we prepared aryl iodide **32** (Scheme 5),[19] and its coupling with ynamide **19** led to the isolation of TMS-capped acetylene **33** in 44% yield with about 80% conversion. Subsequent desilylation using K_2CO_3 and MeOH and a second Sonogashira coupling of the resulting ynamide **34** with *p*-nitro-iodobenzene gave the conjugated phenylacetylene **35** in 80% yield.

We have described here the first successful Sonogashira coupling of ynamides with aryl and vinyl iodides. Our coupling protocol circumvents the problem of competing homocoupling of ynamides and provides a practical entry to novel urethane- and sulfonamide-terminated conjugated acetylenic systems. Applications of this method in preparation of new materials and other synthetic applications are currently underway.

Acknowledgment. The authors thank the NSF (CHE-0094005) for support. We are grateful to Dr. Victor G. Young for providing single-crystal X-ray structural analysis.

Supporting Information Available: Experimental details and ^1H NMR spectral, characterizations, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0493251

---

(18) We are not certain as to why urethane-substituted ynamide **9** does not suffer to the same extent from the problem of homocoupling, with no need in controlling the addition order. However, from our available experiences now working with both urethane- and sulfonyl-substituted ynamides, the latter appears to be much more reactive than the former. Method B is also suitable for preparing these urethane-substituted ynamides

(19) (a) Hsung, R. P.; Babcock, J. R.; Chidsey, C. E. D.; Sita, L. R. *Tetrahedron Lett.* **1995**, *36*, 4525. (b) Hsung, R. P.; Chidsey, C. E. D.; Sita, L. R. *Organometallics* **1995**, *14*, 4808. (c) Lavastre, O.; Ollivier, L.; Dixneuf, P. H.; Sibandhis, S. *Tetrahedron* **1996**, *52*, 5495.