Synthesis of Disubstituted Ynamides from β,β-Dichloroenamides and Electrophiles

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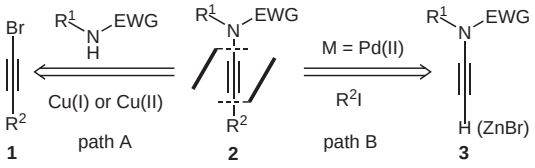
Abstract: Treatment of β,β-dichloroenamides with *n*-butyllithium, followed by addition of an electrophile, provides disubstituted ynamides in far greater yield than direct functionalization of terminal ynamides.

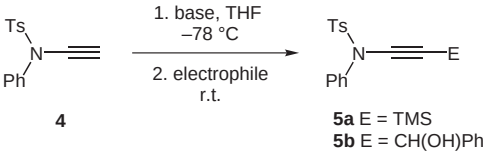
Key words: alkynes, dihaloenamides, disubstituted ynamides

Ynamides have emerged as potentially more useful than ynamines[1] for organic synthesis because of their superior thermal stability, and their preparation has accordingly attracted renewed interest.[2–4] The most recent methods, which involve the copper-promoted or copper-catalyzed coupling of amides with alkynyl bromides **1**[2] require the preparation of a different alkynyl bromide for each desired ynamide (path A in Scheme 1). For the synthesis of (hetero)aryl ynamides, palladium-catalyzed cross-coupling strategies have been applied (path B in Scheme 1), the Negishi procedure by our group[5] and the Sonogashira procedure by Hsung.[6] However, the synthesis of nonaryl-substituted derivatives starting from terminal ynamides **3** has not been explored thoroughly. To our knowledge, there have been a few isolated reports of the introduction of alkyl chains using metalated ynamides, with reaction yields ranging from 30% to 60%.[7] Considering that terminal ynamides can easily be prepared at gram scale,[3b,c] we envisaged that the development of a reliable path-B procedure for the introduction of nonaromatic substituents would be a desirable complement to path A for the preparation of novel families of ynamides.



Scheme 1

We began by studying the silylation of model ynamide **4**, treating it with a strong base followed by TMSCl (Scheme 2). Surprisingly, the reaction proceeded smoothly but the yields were only moderate (Table 1): when *n*-BuLi, KHMDS, or EtMgBr was used as base, ynamide **5a** was obtained in only 45%, 51% and 53% yield, respectively (entries 1, 2, and 3). The best yield, 70%, was achieved with LDA as deprotonating agent (entry 4), somehow indicating that the metalation of terminal ynamides is incomplete.[8] Attempts to apply this procedure to other electrophiles, e.g. benzaldehyde, were discouraging, ynamide **5b** being isolated in only 36% yield in the most favorable conditions (entry 5).



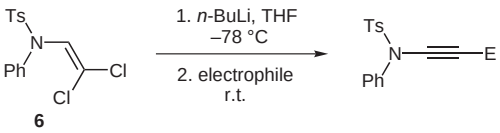
Scheme 2

Table 1 Preparation of Ynamides **5a** and **5b** Starting from Ynamide **4**[a]

Entry	Base	Electrophile	Yield (%)[b]
1	*n*-BuLi	TMSCl	45
2	KHMDS	TMSCl	51
3	EtMgBr	TMSCl	53
4	LDA	TMSCl	70
5	LDA	PhCHO	36

[a] Reactions were carried out using THF as solvent, 1.1 equiv of base and 2 equiv of electrophile.
[b] Isolated yield after column chromatography.

At this point we reconsidered our objectives and decided to explore the versatility of β,β-dichloroenamide **6**, which in previous work[5d] had been transformed into **5a** in 78% yield by treatment with *n*-Buli and entrapment of the resulting acetylide with TMSCl (Scheme 3).[9,10] Probably, the mechanism involves halogen–metal exchange as had been suggested by Brückner.[3b,c]



Scheme 3

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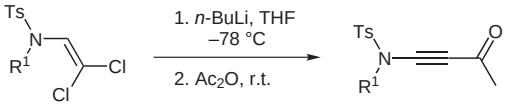
With benzaldehyde as electrophile, the reaction of Scheme 3 afforded **5b** in much better yield (88%) than starting from ynamide **4** (Table 2, entry 2). Similarly, methyl ynamide **5c** was obtained in 74% yield by trapping the acetylide intermediate with dimethyl sulfate (entry 3),[11] and trapping with acetic anhydride, ethyl chloroformate, or carbon dioxide afforded the corresponding push–pull ynamides **5d**–**f** in excellent yields (entries 4, 5. and 6). *tert*-Butyl isocyanate and diethyl chlorophosphate (entries 7 and 8) gave ynamides with previously unreported substitution patterns.[12]

Table 2 Preparation of Ynamides **5** Starting from Dichloroenamide **6**[a]

Entry	Electrophile	Ynamide **5**	Yield (%)[b]
1	TMSCl	**a** E = TMS	78
2	PhCHO	**b** E = CH(OH)Ph	88
3	Me_2SO_4	**c** E = Me	74
4	Ac_2O	**d** E = COMe	90
5	$ClCO_2Et$	**e** E = CO_2Et	96
6	CO_2	**f** E = CO_2H	90
7	*t*-BuNCO	**g** E = C(O)NH*t*-Bu	53
8	$ClP(O)(OEt)_2$	**h** E = $P(O)(OEt)_2$	73

[a] Reactions were carried out using THF as solvent, 2.2 equiv of *n*-BuLi and 1.3 equiv of electrophile.
[b] Isolated yield after column chromatography.

When dichloroenamides **7a**–**d**[13] were employed, in which the Ph of **6** had been replaced by other substituents, treatment with *n*-butyllithium, and acetic anhydride (Scheme 4) afforded acetyl ynamides **8a**–**d** in yields slightly inferior to that obtained for **5d**.[14]

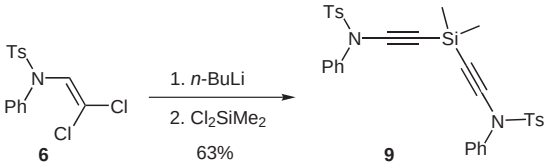


7a R^1 = *p*-MeC_6H_4
7b R^1 = Bn
7c R^1 = Pr
7d R^1 = allyl

8a R^1 = *p*-MeC_6H_4 (86%)
8b R^1 = Bn (84%)
8c R^1 = Pr (84%)
8d R^1 = allyl (77%)

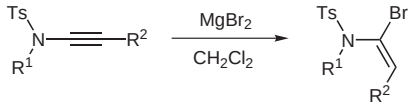
Scheme 4

Difunctionalized compounds can be prepared using biselectrophiles as trapping agents. Gratifyingly, when dichlorodimethylsilane was used (Scheme 5), silyl bisynamide **9** was isolated in 63% yield as a white solid.[15] This compound is stable to air and moisture, and was amenable to purification by silica gel column chromatography.[16]



Scheme 5

Finally, to exemplify the utility of the products of this new methodology, the novel ynamides **5c** and **8c** were smoothly transformed into their corresponding bromoenamides, **10a** and **10b**, under the reaction conditions recently reported by Hsung[17] (Scheme 6).



5c R^1 = Ph, R^2 = Me
8c R^1 = Pr, R^2 = COMe

10a R^1 = Ph, R^2 = Me (97%)
10b R^1 = Pr, R^2 = COMe (86%)

Scheme 6

In conclusion, we have developed a new protocol for the synthesis of disubstituted ynamides starting from easily accessible β,β-dichloroenamides. Treatment of the latter with *n*-butyllithium, followed by the desired electrophile, has allowed the construction of new ynamide substitution patterns, and the preparation of silyl bisynamides.

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References and Notes

(1) For recent reviews of ynamides, see: (a) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455. (b) Zhang, Y.; Hsung, R. P. *Chemtracts* **2004**, *17*, 442. (c) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575. See also: (d) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. (e) Viehe, H. G. *Chemistry of Acetylenes*; Marcel Dekker: New York, **1969**, Chap. 12, 861–912. (f) Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 767. (g) Himbert, G. In *Methoden der Organischen Chemie (Houben–Weyl)*; Kropf, H.; Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, **1993**, 3267–3443.

(2) (a) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170. (b) Hirano, S.; Fukudome, Y.; Tanaka, R.; Sato, F.; Urabe, H. *Tetrahedron* **2006**, *62*, 3896. (c) Villeneuve, K.; Riddell, N.; Tam, W. *Tetrahedron* **2006**, *62*, 3823. (d) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011.

(3) (a) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997. (b) Brückner, D. *Synlett* **2000**, 1402. (c) Brückner, D. *Tetrahedron* **2006**, *62*, 3809. (d) Witulski, B.; Stengel, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 489.

(4) (a) For a special issue devoted to the chemistry of ynamides, see: *Tetrahedron* **2006**, *62*, issue 16. For recent references, see: (b) Zhang, X.; Li, H.; You, L.; Tang, Y.; Hsung, R. P. *Adv. Synth. Catal.* **2006**, *348*, 2437. (c) Tracey, M. R.; Oppenheimer, J.; Hsung, R. P. *J. Org. Chem.* **2006**, *71*, 8629. (d) Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6726. (e) Couty, S.; Meyer, C.; Cossy, J. *Tetrahedron Lett.* **2006**, *47*, 767. (f) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586. (g) Buissonneaud, D.; Cintrat, J.-C. *Tetrahedron Lett.* **2006**, *47*, 3139. (h) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776. (i) Tanaka, R.; Yuza, A.; Watai, Y.; Suzuki, D.; Takayama, Y.; Sato, F.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 7774. (j) Couty, S.; Barbazanges, M.; Meyer, C.; Cossy, J. *Synlett* **2005**, 905. (k) Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681. (l) Zhang, Y. *Tetrahedron Lett.* **2005**, *46*, 6483.

(5) (a) Rodríguez, D.; Castedo, L.; Saá, C. *Synlett* **2004**, 783. For our contributions, see: (b) Martínez-Esperón, M. F.; Rodríguez, D.; Castedo, L.; Saá, C. *Tetrahedron* **2006**, *62*, 3843. (c) Martínez-Esperón, M. F.; Rodríguez, D.; Castedo, L.; Saá, C. *Org. Lett.* **2005**, *7*, 2213. (d) Rodríguez, D.; Castedo, L.; Saá, C. *Synlett* **2004**, 377.

(6) Tracey, M. R.; Zhang, Y.; Frederick, M. O.; Mulder, J. A.; Hsung, R. P. *Org. Lett.* **2004**, *6*, 2209.

(7) In most of these articles, the authors have reported the preparation of a single compound using this procedure. See: (a) Marion, F.; Coulomb, J.; Servais, A.; Courillon, C.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2006**, *62*, 3856. (b) See ref. 4i. (c) Witulski, B.; Alayrac, C.; Tevzadze-Saeftel, L. *Angew. Chem. Int. Ed.* **2003**, *42*, 4257. (d) Witulski, B.; Lumtscher, J.; Bergsträßer, U. *Synlett* **2003**, 708. (e) 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. (f) Two push–pull ynamides have been reported using the same procedure and $ClCO_2Et$ as electrophile, with very different efficiency: Ref. 7a, 90% yield. (g) Ref. 2c, 11% yield.

(8) Deuteration studies of **4** using EtMgBr and LDA as bases and MeOD as deuterium source showed 50% and 66% deuterium incorporation, respectively (by ^{1}H NMR integration). These results showed the incomplete efficiency of metalation of terminal ynamides.

(9) This strategy has been widely used for the synthesis of substituted ynamines, see: (a) Löffler, A.; Himbert, G. *Synthesis* **1994**, 383; and references therein. (b) For a recent report on the synthesis of *N*-(ethynyl)benzotriazoles, see: Katritzky, A. R.; Singh, S. K.; Jiang, R. *Tetrahedron* **2006**, *62*, 3794. (c) During our research, the same methodology has been reported for the synthesis of a single push–pull ynamide, see: Mori, M.; Wakamatsu, H.; Saito, N.; Sato, Y.; Narita, R.; Sato, Y.; Fujita, R. *Tetrahedron* **2006**, *62*, 3872.

(10) Disubstituted ynamides have previously been synthesized from dichloroenamides by a Suzuki–Miyaura cross-coupling reaction followed by HCl elimination. See ref. 4j.

(11) Other electrophiles such as MeI and EtI also work but with lower yields (30–35%), ynamide **4** was also obtained as secondary product.

(12) **Typical Procedure for *N*-(3-Oxobut-1-ynyl)-*N*-phenyl Tosylamide (5d)**
n-Butyllithium (0.64 mL, 1.6 M in hexane) was slowly added to a solution of **6** (0.16 g, 0.47 mmol) in dry THF (7 mL) at –78 °C. After 5 min, Ac_2O (57 μL, 0.61 mmol) was added and the mixture was allowed to reach r.t. (TLC showed clean conversion). The volatiles were removed and the residue was dissolved in EtOAc (20 mL) and washed with brine (2 × 30 mL). The organic layer was dried over anhyd Na_2SO_4 and evaporated to dryness. The crude residue was purified by column chromatography on silica gel using 5:1 hexane–EtOAc as eluent, yielding **5d** (0.13 g, 90%) as colorless prisms; mp 110–112 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.4 Hz, 2 H), 7.38–7.28 (m, 5 H), 7.21–7.15 (m, 2 H), 2.44 (s, 3 H), 2.32 (s, 3 H). ^{13}C NMR + DEPT (62.83 MHz, $CDCl_3$): δ = 183.0 (CO), 145.9 (C), 137.1 (C), 132.7 (C), 129.9 (2 × CH), 129.4 (2 × CH), 129.2 (CH), 128.1 (2 × CH), 126.4 (2 × CH), 88.3 (C), 75.7 (C), 31.8 (CH_3), 21.7 (CH_3). HRMS: *m/z* calcd for $C_{17}H_{15}NO_3S$: 313.0772; found: 313.0770.

(13) Prepared as described in ref. 3b.

(14) Methylation of **7a**–**d** was also accomplished in satisfactory yields following the same procedure as for **5c**.

(15) Bisynamide **9**: white solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.3 Hz, 4 H), 7.32–7.22 (m, 14 H), 2.41 (s, 6 H), 0.33 (s, 6 H). ^{13}C NMR + DEPT (62.83 MHz, $CDCl_3$): δ = 145.1 (2 × C), 138.2 (2 × C), 132.5 (2 × C), 129.4 (4 × CH), 129.1 (4 × CH), 128.3 (2 × CH), 128.3 (4 × CH), 126.1 (4 × CH), 96.0 (2 × C), 70.3 (2 × C), 21.7 (2 × CH_3), 0.5 (2 × CH_3). HRMS: *m/z* calcd for $C_{32}H_{30}N_2O_4S_2Si$: 598,1416; found: 598.1414.

(16) Other members of the silyl bisynamide series exemplified by **9** have also been prepared. Optimization of this procedure for the synthesis of nonsymmetrical derivatives is in progress.

(17) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H.; Frederick, M. O.; Shen, L.; Zificsak, C. A. *Org. Lett.* **2003**, *5*, 1547.