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Practical Synthesis of (*Z*)-Polyaromatic and Heteroaromatic Vinylacetylenes

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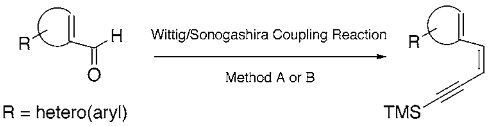
ABSTRACT



Two synthetic routes to several (*Z*)-polyaromatic and heteroaromatic substituted vinylacetylenes are described. The nature of aryl- or heteroaryl-substituted carboxaldehyde used as starting material dictated the choice of Wittig salt employed. A very attractive way to construct polyaromatic and pyridine-containing enynes is the reaction of polyaromatic and pyridine-containing aldehydes with bromomethyltriphenylphosphonium bromide in the presence of potassium *tert*-butoxide followed by a Sonogashira desilylation procedure (method B).

Vinylacetylenes are useful in organic synthesis as important precursors for regio- and stereoselective synthesis of conjugated π-systems, including dienic, diacetylenic, and substituted aromatic compounds.[1] Such important structural units are known to be integral parts of highly potent antitumor antibiotics,[1] antifungal agents,[2] sex pheromones,[3] and novel conducting polymeric materials.[4] As such, several excellent synthetic methods have been reported for their preparation. However, the vast majority of the reported methods are either limited to simple aliphatic and carbocyclic aromatic substrates or/and are tedious procedures not practical for multigram-scale synthesis.[1−5]

Our laboratory has been interested in the synthesis of geometrically pure (*Z*)-heteroaromatic and polyaromatic vinylacetylenes as starting material in the synthesis of benzofused heterocycles via their reaction with Fischer carbene complexes.[6] The preparation of substituted vinylacetylenes through palladium-catalyzed cross-coupling of (*Z*)-vinylhalides, derived from aldehydes, with terminal alkynes was attractive, since this method has proven to be successful for the stereoselective synthesis of many enynes containing diverse functional groups at ambient conditions.[1a,7] In seeking a practical and general route for the transformation

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(1) (a) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (b) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (c) Gung, W, B.; Kumi, G. *J. Org. Chem.* **2004**, *69*, 3488. (d) Nicolaou, K. C.; Dai, W. M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (e) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453. (f) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057.

(2) (a) Faulkner, D. J. *Nat. Prod. Rep.* **2000**. *17*, 7. (b) Nussbaumer, P.; Leitner, L.; Marz, K.; Stutz, A. *J. Med. Chem.* **1995**, *38*, 1831.

(3) (a) Rossi R.; Carpita, Quirici, M. G. Gaudenzi T. *Tetrahedron* **1982**, *38*, 631. (b) Guerrero, A.; Camps, F.; Coll, J.; Riba, M.; Einhorn, J.; Descoins, Ch.; Lallemand, J. Y. *Tetrahedron Lett.* **1981**, *22*, 2013.

(4) (a) Nicolaou, K. C.; Smith, A. L. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995. (b) Gobbi, L.; Seiler, P.; Diederich, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 674. (c) Hynd, G.; Jones, G. B.; Plourde, G. W.; Wright, J. M. *Tetrahedron Lett.* **1999**, *40*, 4481.

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(6) (a) Herndon, J. W.; Hayford, A. *Organometallics* **1995**, *14*, 155. (b) Hayford, A. Reactions of Z-Phenylvinylacetylenes and Cyclopropylacetylenes with Fischer Carbene−Chromium Complexes, Ph.D. Thesis, University Of Maryland, College Park, MD, 1994. (c) Hayford, A.; Kaloko, J. Jr.; Bass, G.; Aber, L. C.; Bailey, D. L. Synthesis and Benzannulation Reactions of Heteroaromatic-Vinylacetylenes with Fischer Carbene Complexes, *Abstracts of Papers*, 226th National Meeting of the American Chemical Society, New York, September 7−11, 2003; American Chemical Society: Washington, DC, 2003; Section CHED, Paper 0187.

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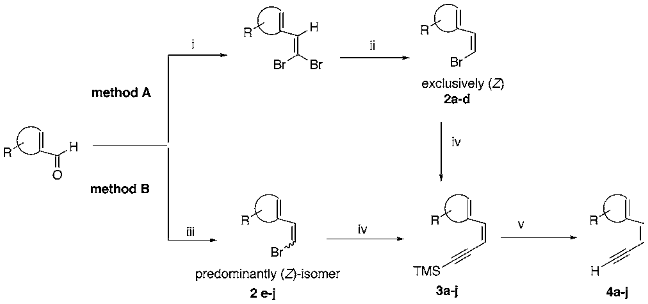
of both aromatic and heteroaromatic aldehydes to their corresponding (*Z*)-vinylacetylenes, we have investigated a stereoselective (method A) as well as a nonstereoselective method (B) for their synthesis (Scheme 1).[7,8]

Scheme 1[a]



[a] Reagents and conditions: (i) CBr$_4$, PPh$_3$, CH$_2$Cl$_2$ or CH$_3$CN, 0 °C; (ii) Bu$_2$SnH, Pd(PPh$_3$)$_4$, CH$_2$Cl$_2$ or benzene, rt; (iii) Br^{-} $^{+}$PPh$_3$CH$_2$Br, *t*-BuOK, THF, −78 °C; (iv) ≡−TMS, CuI, Pd(PPh$_3$)$_2$Cl$_2$, Et$_3$N; (v) K$_2$CO$_3$, MeOH, 0 °C/rt.

Initial attempts to prepare both π-excessive and π-deficient heteroaromatic substituted (*Z*)-vinyl bromides via the stereoselective tributyltin hydride reduction of *gem*-dibromide heterocycles (method A)[8a−c] gave disappointing results in terms of purity and isolated yields (0−71%) for O- and N-functionalized bromoolefins. For example, significant decomposition of pyridine-containing precursors was observed under tributyltin hydride reduction conditions, and heteroarylaldehydes with sensitive functional groups such as pyrrole-2-carboxaldehyde failed to yield the expected products. Furthermore, depending on the nature of the heteroaromatic substrate and the synthetic strategy employed, the reaction required a stoichiometric amount of expensive and highly toxic [*n*-Bu$_3$SnH] reagent (1.2−5 equiv) in the hydrogenolysis step.[8a−c] In fact, the removal of the pervasive stannous byproducts from the reaction mixtures was extremely difficult and greatly reduced the purity, stability and overall yield of the reaction products. However, this problem was greatly reduced by the addition of aqueous potassium fluoride to the reaction mixture and also using finely ground potassium fluoride as an additive to silica or basic alumina

Table 1. Synthesis of π-Excessive Heteroaromatic Vinylacetylenes via Method A

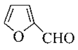
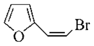
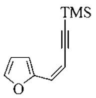
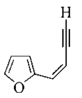
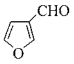
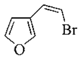
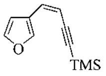
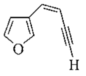
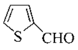
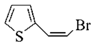
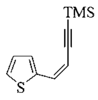
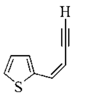
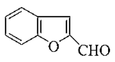
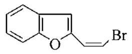
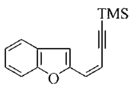
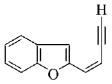
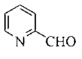
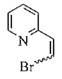
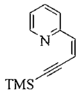
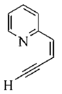
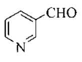
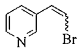
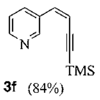
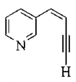
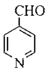
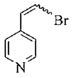
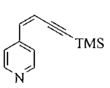
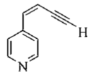
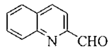
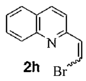
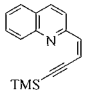
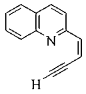
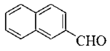
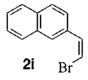
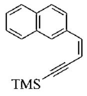
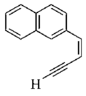
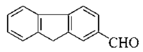
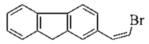
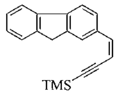
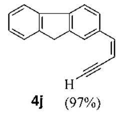
Entry	Starting Material 1	2 Yield(%)	3 Yield(%)	4 Yield(%)
a	 **1a**	 **2a** (41%)	 **3a** (100%)	 **4a** (95%)
b	 **1b**	 **2b** (30%)	 **3b** (55%)	 **4b** (unstable)
c	 **1c**	 **2c** (60%)	 **3c** (81%)	 **4c** (67%)
d	 **1d**	 **2d** (71%)	 **3d** (99%)	 **4d** (55%)

Table 2. Synthesis of π-Deficient Heteroaromatic Vinylacetylenes via Method B

Entry	1	2	Ratio (Z:E)[d]	Overall Yield(%)	3(*Z*) Yield (%)	4(*Z*) Yield (%)
e	 **1e**	 **2e**	90:10	95%[a]	 **3e** (100%)	 **4e** —[b]
f	 **1f**	 **2f**	95:5	91%[a]	 **3f** (84%)	 **4f** (95%)
g	 **1g**	 **2g**	—[b]	—[b]	 **3g** (45%, 2 steps)	 **4g** —[b]
h	 **1h**	 **2h**	93:7	80%[a]	 **3h** (76%)	 **4h** (94%)
i	 **1i**	 **2i**	100:0	92%[c]	 **3i** (75%)	 **4i** (100%)
j	 **1j**	 **2j**	100:0	44%	 **3j** (97%)	 **4j** (97%)

[a] Yields reported via method A (43−65%).[8c] [b] Unstable compound rapidly decomposed on isolation. [c] Yields reported via method A (86%).[8c] [d] Z/E ratio determined by separation of compounds after purification from flash column chromatography.

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(7) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467. (b) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627. (c) Sakamoto, T.; Shiraiwa, M.; Kondo, Y.; Yamanaka, H. *Synthesis* **1983**, 312. (d) Sonogashira, K. *In Comprehensive Organic Chemistry*; Fleming, I., Trost, B. M., Eds.; Pergamon: Oxford, 1991; Vol. 3.

(8) (a) Uenishi, J.; Kawahama, R.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 6759. (b) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1996**, *61*, 5716. (c) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965. (d) Herz, H. G.; Queiroz, M. J.; Maas, G. *Synthesis* **1999**, *6*, 1013. (e) Matsumoto M.; Kuroda, K. *Tetrahedron Lett.* **1980**, *21*, 4021.

(9) Harrowven, D. C.; Guy, I. L. *Chem. Commun.* **2004**, 1968 and references therein.

during chromatographic purification as described recently by Harrowven and co-workers.[9] Notably, the synthesis of heteroaromatic substrates such as furan, benzofuran, and thiophene vinylacetylenes (Table 1) was best accomplished via method A.

Given the marginal and unreliable yields, as well as workup procedural difficulties encountered with method A, an alternative synthetic procedure, involving the Wittig bromovinylation of aromatic and heteroaromatic aldehydes with bromomethyltriphenylphosphonium bromide, was explored (method B).[8e] This protocol, which gave cleaner reactions and satisfactory yields, led to the isolation of gram quantities of several aryl- and heteroaryl-substituted enynes with high Z/E stereoselectivity (Table 2). Thus, using method B, a variety of substituted pyridine and quinoline vinylbromides (**2e**−**h**) were effectively synthesized. In addition, polyaromatic aldehydes naphthalene-2-carboxaldehyde (**1i**) and fluorene-2-carboxaldehyde (**1j**) gave the corresponding (Z) bromoolefins with selectivity as high as 100:0 (Z:E), demonstrating the high efficiency of this method for both π-deficient and aromatic substrates. Fortuitously, the polarity of the predominantly (Z)-isomers was significantly different from that of the (E)-isomers, as such allowing them to be separated via chromatography. It is noteworthy that the bromoolefins (**2a**−**j**) coupled well with trimethylsilylacetylene in the presence of CuI/Pd (II) catalyst in amine solvent to give the (Z)-silylated vinylacetylenes in good to excellent yields (Tables 1 and 2).[7]

Attempts were also made to transform several electron-rich heteroaromatic carbaldehydes (**1a**−**d**) to their corresponding bromolefins and vinylacetylenes using method B. It is worth noting that the conversion proceeded smoothly; however, contrary to the π-deficient heteroaromatic series, the similarities of R_f values of the π-excessive derivatives did not permit efficient separation of the isomeric bromoolefins and 1,3-enyne derivatives. As such, the synthesis of the desired (Z) electron-rich heteroaromatic enynes was conveniently carried out via the former alternative pathway (method A).

In conclusion, the synthetic strategies depicted in Scheme 1 are extremely valuable and provide two alternative and general pathways to predominantly (Z)-polyaromatic and heteroaromatic enynes depending on precursors employed. The synthetic utility of these methods is illustrated by transformation of electron-rich (method A) and electron-deficient heteroaromatic as well as aromatic carboxaldehydes (method B) to their (Z)-vinylacetylenes in good to excellent yields.

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Supporting Information Available: Characterization data. ^{1}H NMR, and ^{13}C NMR of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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