Pergamon

Tetrahedron Letters 39 (1998) 3647–3650

TETRAHEDRON LETTERS

The Solid Phase Synthesis of Complex Propargylamines Using the Combination of Sonogashira and Mannich Reactions

Alexey B. Dyatkin* and Ralph A. Rivero

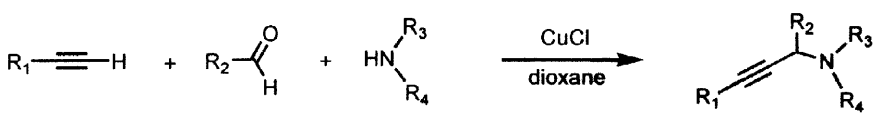
The R. W. Johnson Pharmaceutical Research Institute,
Spring House, PA 19477-0776
USA

Received 23 February 1998; accepted 11 March 1998

Abstract: The Sonogashira reaction of a resin-bound iodobenzoic acid with trimethylsilyl acetylene followed by TBAF desilylation provided a polymer-supported aryl acetylene, **3**. Treatment of **3** with an aldehyde and a secondary amine in dioxane in the presence of CuCl catalyst results in the generation of resin-bound propargylamines. The final products (**4**) were cleaved from the resin and obtained in excellent yields and purity.

Multiple-component condensation reaction schemes are one of the most valuable strategies available for the preparation of combinatorial libraries.[1] The opportunity to introduce several elements of diversity in one transformation, "one pot", and avoid extensive manipulation can potentially provide diverse libraries of "drug-like" compounds in a very efficient manner.

Scheme 1

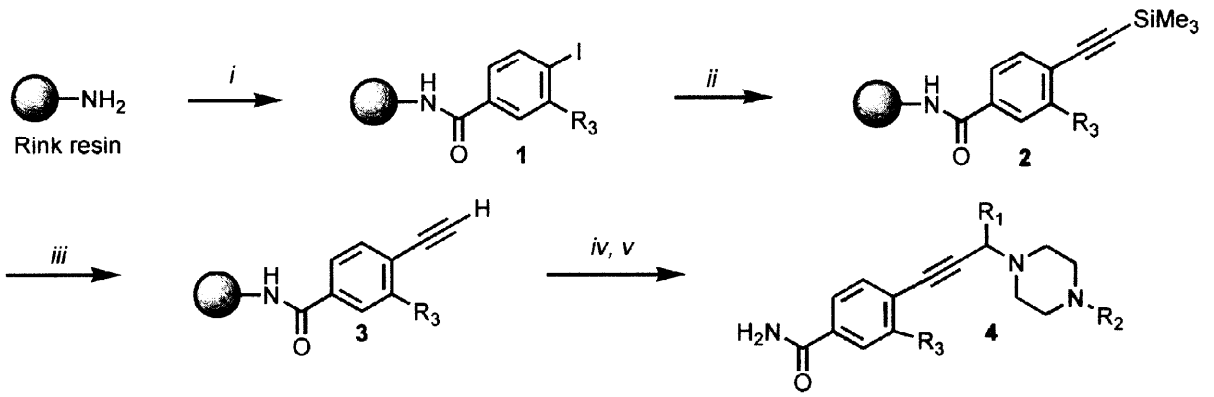


The polymer-supported 3-component Mannich condensation of acetylenes, aldehydes and secondary amines, where any of the reactants can be attached to the polymer, represents a very powerful method for the rapid synthesis of complex propargylamines[2] **(Scheme 1)**. While there are many commercially available amines and aldehydes, the number of acetylenes is limited. The inclusion of the Sonogashira reaction at the beginning of this reaction sequence greatly increases the number of potential acetylenes available. An increment in the variety of any of the components translates into an increase in the overall diversity of the library. Herein we wish to report the straightforward synthesis of diverse libraries of complex propargylamines using the combination of the Sonogashira and Mannich reactions.

0040-4039/98/$19.00
PII: S0040-4039(98)00639-X

The Sonogashira reaction[3] (condensation of aryl halides with terminal alkynes in the presence of Cu(I) and Pd(0) catalysts) has been used for the preparation of polymer-supported aryl acetylenes[4]. We envisioned that this method would provide us with a larger set of diverse building blocks for the Mannich condensation. The reaction pathway is illustrated in **Scheme 2**.

Scheme 2



Reagents and conditions: i) 4-iodobenzoic acid (5 eq.), DIC (5 eq.), DMF, rt, overnight; ii) trimethylsilylacetylene (7 eq.), CuI (10 mol%), $Pd(PPh_3)_4$ (10 mol%), THF/ Et_3N (1:1), rt, 40 h.; iii) TBAF, 1.0 M solution in THF, 5 h., rt; iv) aldehyde (4 eq.) piperazine (4 eq.) CuCl (10 mol%), dioxane, 90° C, 36 h.; v) TFA/H_2O (9:1), rt, 0.5 h.

Table 1

Entry	R_1	R_2	R_3	Yield (%)[a]	Purity (%)[b]
4a	(4-Me)-Ph	*(E)*-PhCH=CH-CH_2	H	71	95
4b	(3-F)-Ph	$(2,3\text{-Me})_2$-Ph	H	85	>95
4c	(3-PhO)-Ph	(2-F)-Ph	H	75	>95
4d	1-Naphthyl	Cyclohexyl	H	89	94
4e	(4-Me)-Ph	$PhCH_2$	H	90	>95
4f	(4-Ph)-Ph	(2-F)-Ph	H	88	>95
4g	(2-Me)-Ph	(2-Cl)-Ph	H	88	89
4h	2-Naphthyl	$PhCH_2$	Me	73	82
4i	Ph	Ph	Me	70	85

[a]Yields based on the original loading of the Rink Amide Resin.

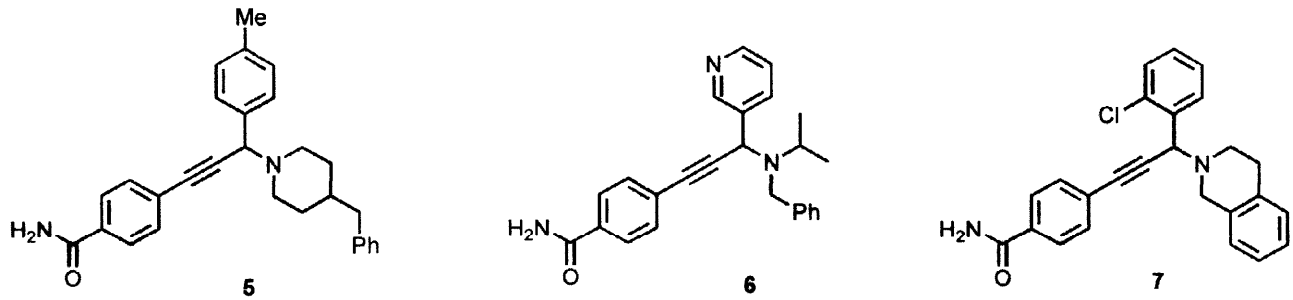
[b]Purity of the compounds was determined by HPLC @220 nm; the only other remaining material was unreacted aryl acetylene.

4-Iodobenzoic acid was coupled to commercially available Rink-amide resin (Novabiochem) using diisopropylcarbodiimide (DIC) in DMF at 20° C. The completion of the reaction was confirmed by a Kaiser test.[5] The reaction of iodobenzamide **1** with trimethylsilyl acetylene in the solution of THF/ Et_3N (1:1) mixture catalyzed by CuCl and $Pd(PPh_3)_4$ at room temperature for 40 hours followed by desylilation with tetrabutylammonium fluoride (TBAF) in THF provided aryl acetylene **3** in excellent yield and purity. The extent of the Sonogashira reaction was confirmed by ^1H NMR analysis of the cleavage product of a small portion of resin **3**. Substituted piperazines, well known as potent pharmacophores in many biologically active

compounds,[6] were chosen as the amine component in the subsequent Mannich condensation. TFA-induced cleavage provided complex propargylamines (**4**) in good yield.[7] Similar results were obtained with 4-iodo-3-methyl benzoic acid as shown in the **Table 1**.

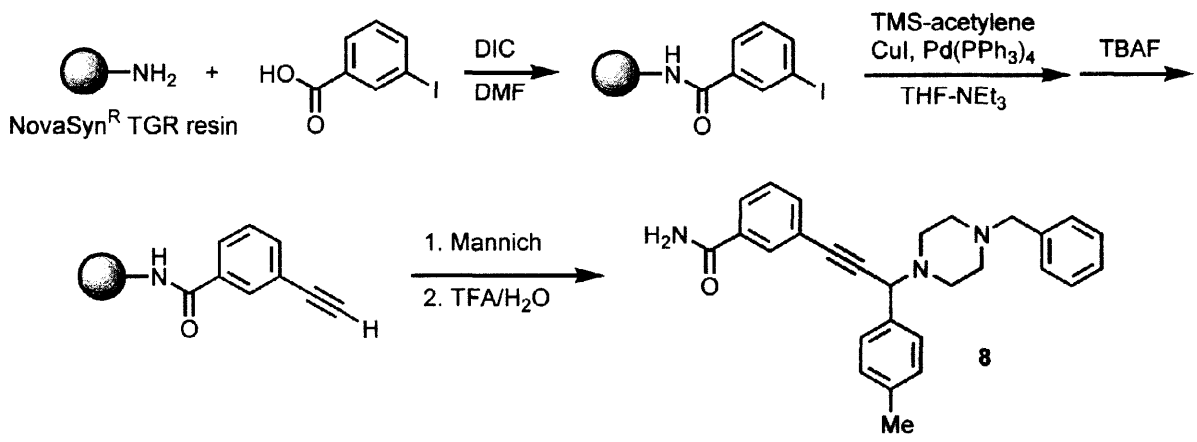
Secondary amines other than piperazines also provide desired products.[8] A few examples of condensation products with piperidines, N-substituted benzylamines and tetrahydroisoquinolines are illustrated below in **Figure 1**.[9]

Figure 1



Attempts to use *o*- or *m*- substituted iodobenzoic acids linked to Rink amide resin (cross-linked polystyrene resin with Rink linker) as components in the Sonogashira reaction were unsuccessful. After cleavage of the resin, only trace amounts of desired aryl acetylenes were detected. These compounds; however, can be prepared using NovaSyn^{TR} TGR resin (PEG-resin with Rink linker). The route illustrated in **Scheme 3** was used to generate the regioisomeric propargylamines. (Compound **8** represents one in the series of compounds).

Scheme 3



In summary, we have demonstrated that complex propargylamines **4** - **8** can be synthesized from resin bound iodobenzoic acids in 3 three steps in 70 - 89 % overall yields and 80 - 95 % purity.

Acknowledgments: The authors would like to acknowledge Scott Dax, James McNally and Mark Youngman for helpful discussions.

References and Notes

1. Armstrong, R. W.; Brown, S. D.; Keating, T. A.; Tempest, P. A. *Combinatorial Synthesis Exploiting Multiple-Component Condensations, Microchip Encoding, and Resin Capture* in *Combinatorial Chemistry. Synthesis and Application*, Wilson S. R. and Czarnik A. W.; Ed., Wiley, NY **1997**, 153.

2. a) Youngman, M. A.; Dax, S. L. *Tetrahedron Lett.* **1997**, *38*, 6347-6350. b) McNally, J. J.; Youngman, M. A.; Dax, S. L. *Tetrahedron Lett.* **1998**, *39*, 967-970.

3. a) Sonogashira, K.; Tohda, Y.; Nagihara, N. *Tetrahedron Lett.* **1975**, 4467-4470. b) Sakamoto, T.; Shiraiwa, M.; Kondo, Y.; Yamanaka, H. *Synthesis* **1983**, 312-314.

4. a) Young, J. K.; Nelson, J. C.; Moore, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 10841-10842. b) Fagnola, M. C.; Candiani, I.; Vinsentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307-2310. c) Fancelli, D.; Fagnola, M. C.; Severino, D.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2311-2314. d) Bolton, G. L. *Tetrahedron Lett.* **1996**, *37*, 3433-3436. e) Jones, L.; Schumm, J. S.; Tour, J. M. *J. Org.. Chem.* **1997**, *62*, 1388-1410. f) Collini, M.D.; Ellingboe, J. W. *Tetrahedron Lett.* **1997**, *46*, 7963-7966.

5. Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595-598.

6. a) Meyer, W.E.; Tomcufcik, A.S.; Chan, P.S.; Haug, M. *J. Med. Chem.* **1989**, *32*, 593-597. b) Kreutzberger , A.; Kochanowski, R. *Arch. Pharm.* **1988**, *321*, 837-840.

7. We investigated the reaction of different aldehydes with polymer-supported acetylene carboxylates and amines. Substituted benzaldehydes, aryl acetaldehydes, heteroaryl aldehydes as well as cyclic and non-cyclic secondary amines were successfully used in this transformation. The scope and limitations of the condensation will be presented in a future publication.

8. The purity of the condensation products with piperidines and non-cyclic secondary amines was usually more than 85%. In the tetrahydroisoquinoline case (7), the purity of the crude (direct from cleavage) product was 40 - 60% by HPLC.

9. The products were cleaved from the resin as TFA salts. Free amines were obtained by the treatment of the crude products with NEt_3 followed by column chromatography. The spectral data (^1H NMR, ESI MS) of all the products described was consistent with the structure assigned.

   Compound **4e** (free amine): ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J*=8 Hz, 2H), 7.55 (d, *J*=8 Hz, 2H), 7.45 (d, *J*=8 Hz, 2H), 7.55 (d, *J*=8 Hz, 2H), 7.35-7.20 (m, 5H), 7.15 (d, *J*=8 Hz, 2H), 6.11 (bs, 1H), 5.86 (bs, 1H), 4.77 (s, 1H), 3.52 (s, 2H), 2.65-2.30 (m, 8H), 2.35 (s, 3H); mass spectrum (ESI) m/z 424.2 ($M + H^+$).
   Compound **5** (TFA salt): ^1H NMR (300 MHz, DMSO-d_6) δ 8.12 (bs, 1H), 7.93 (d, *J*=8 Hz, 2H), 7.73-7.60 (m, 2H), 7.60-7.41 (m, 2H), 7.40-7.00 (m, 8H), 5.89 (s, 1H), 3.10-2.85 (m, 2H), 2.60-2.49 (m, 4H), 2.36 (s, 3H), 1.90-1.65 (m, 3H), 1.55-1.30 (m, 3H); mass spectrum (ESI) m/z 423.2 ($M + H^+$).
   Compound **6** (free amine): ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J*=7 Hz, 1H), 7.86 (d, *J*=8 Hz, 2H), 7.59 (d, *J*=8 Hz, 2H), 7.53 (d, *J*=9 Hz, 1H), 7.40 (d, *J*=7 Hz, 2H), 7.25 (t, *J*= 7 Hz, 2H), 7.14 (t, *J*= 7 Hz, 1H), 6.84 (s, 1H), 6.61-6.58 (m, 1H), 6.45-6.35 (m, 1H), 6.10 (bs, 1H), 5.90 (bs, 1H), 4.23 (s, 2H), 3.42-3.30 (m, 1 H), 1.12 (d, *J*=7 Hz, 6H); mass spectrum (ESI) m/z 384.2 ($M + H^+$).