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A one-pot synthesis of 1-arylalka-1,3-diynes by sequential acetylene zipper and Sonogashira reactions

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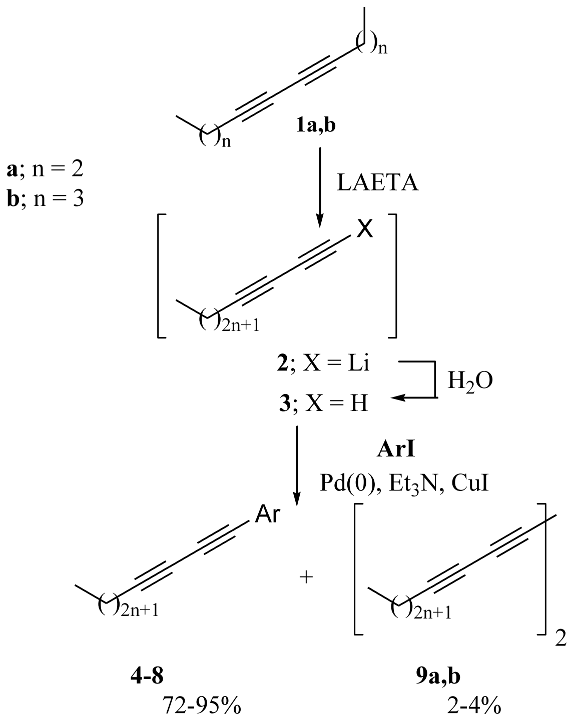
Abstract—1,3-Diynes, formed in situ by base-induced acetylene zipper reactions, following anion quenching with water, undergo smooth Sonogashira-type couplings with functionalized aryl iodides, to give good overall yields of 1-arylalka-1,3-diynes. © 2002 Elsevier Science Ltd. All rights reserved.

Since the discovery of the Pd–Cu-catalyzed cross-coupling reactions of terminal acetylenes with aryl iodides or bromides, now commonly referred to as the Sonogashira reaction,[1] these have enjoyed many applications in organic synthesis especially in the preparation of a very wide range of aryl- and heteroarylacetylenes.[2] Indeed, this reaction is probably one of the most frequently used C–C bond forming processes in organic chemistry. However, there are very few examples known of similar couplings with 1,3-diynes in general, most likely due to difficulties associated with the synthesis and especially the stability of such intermediates.[3] Hence, Cadiot–Chodkiewicz couplings are often used to obtain unsymmetrical diynes, including 1-(hetero) aryl-1,3-diynes. However this reaction often leads to a mixture of the target and by-products of symmetrical couplings and delivers moderate isolated yields.[4]



Scheme 1.

A commonly used tactic when intermediates are unstable or difficult to handle is to generate such species in situ and carry out a subsequent reaction without isolation. Herein, we report that just such a strategy is highly effective for the elaboration of 1-arylalka-1,3-diynes by a combination of the Sonogashira method with a preceeding multi-positional prototropic isomerization ('acetylene zipper' reaction) of a disubstituted diyne. In this remarkably rapid zipper reaction, a disubstituted alkyne is typically treated with an alkaline metal amide of an α,ω-alkanediamine (K,[5a] Na[5b] or Li[5c]), and the multiple isomerizations concluded by formation of a much more stable 1-acetylide. This isomerization is also applicable to disubstituted alkadiynes when the product is the lithium salt of the corresponding alka-1,3-diyne.[6] Therefore, by quenching the latter salts using water, solutions of the free alka-1,3-diynes are obtained. We have found that these are

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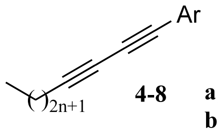
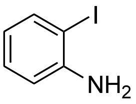
then suitable for subsequent Sonogashira couplings, especially as these are carried out in the presence of an organic amine base and hence the residual α,ω-diamine does not interfere, thereby obviating the need to isolate the sensitive alka-1,3-diynes. The method is summarized in Scheme 1.

For example, starting with dodeca-5,7-diyne **1b**, treatment with three equivalents of lithium 2-aminoethylamide (LAETA) at 16–18°C for 10 min results in complete isomerization, following which, a small amount of water is added to release the free alka-1,3-diyne **3b** from the salt **2b**. This is followed by the addition of an aryl iodide, palladium(II) acetate, triphenylphosphine, triethylamine and copper(I) iodide in this order, to set up the catalyst system usually associated with the Sonogashira coupling reaction.[1] In all cases, these final coupling reactions took place under very mild conditions, either at ambient temperature or slightly above (35–45°C) during 3–8 h. A routine work-up and chromatography then delivered the isolated yields of the representative 1-arylalka-1,3-diynes **4**–**8**.[7]

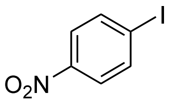


4-8 **a**; n = 2; **b**; n = 3

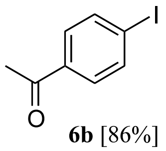
ArI [Isolated yields of 4-8 in parenthesis]



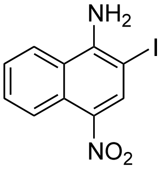
4a [87%]
4b [95%]



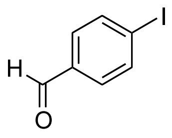
5b [72%]



6b [86%]



7a [88%]
7b [92%]



8a [77%]

In our initial experiments, a 10% excess of the aryl iodide relative to the diyne **3b** was used. Under these conditions, between 4 and 10% of the dehydrodimerization product **9b** was formed as a by-product. With a view to reducing this amount, we investigated the effect of varying the stoichiometry of the diyne and the aryl iodide and found the best yields of the aryl-1,3-diynes **4**–**8** were obtained using a molar ratio of 1.2:1 of these two reactants, that is, slightly less aryl iodide than formally required to react with all of the diyne. It is also important that the copper(I) iodide is added last. Given these two conditions, yields of the tetrayne by-products **9** were reduced from levels of ca. 10% to 2–4%.[8] It is also worth noting that, under the mild coupling conditions used, no intramolecular cyclization products were formed during the synthesis of the *ortho*-aminoarylalka-1,3-diynes **4** and **7**.

Although most examples of aryl iodides in this present study are relatively electron poor and hence particularly well suited to Sonogashira coupling reactions, the finding that 1-amino-2-iodobenzene (cf. **4**) also participates very efficiently indicates that this 'one-pot' method should be widely applicable to a range of both aryl and heteroaryl halides.

Acknowledgements

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7. Full spectroscopic and analytical data has been obtained for all compounds reported herein. For example, 2-(dodeca-1,3-diynyl)aniline (**4b**): δ_H (300 MHz, $CDCl_3$): 0.88 (3H, t, $J=7$ Hz, Me), 1.21–1.42 (10H, 5×CH_2), 1.57 (2H, p, $J=7$ Hz, CH_2), 2.37 (2H, t, $J=7$ Hz, CH_2C), 4.47 (2H, s, NH_2), 6.67–6.75 (2H, m), 7.12 (1H, t, $J=7$ Hz, Ar-H) and 7.28 (1H, t, $J=7$ Hz, Ar-H); δ_C (75 MHz, $CDCl_3$): 14.5 (Me), 20.1 (CH_2C), 23.1, 28.7, 29.3 29.5, 29.6, 32.3 (all CH_2), 65.4, 72.0, 80.0, 86.4 (all C), 107.1, 114.8, 118.4, 130.6 133.5, and 149.6 (all ArC), m/z 253 ($C_{18}H_{23}N=253$). Anal. found: C, 85.24; H, 9.12; N, 5.63. $C_{18}H_{23}N$ requires: C, 85.32; H, 9.15; N, 5.53%.
8. *Typical experimental procedure*: LAETA was obtained by the reaction of Li (53 mg, 7.5 mmol) with absolute EDA (0.6 ml, 7.5 mmol) in dry THF (1.8 ml) under Ar. After the addition of benzene (1.8 ml) and hexane (1.8 ml), the

suspension of LAETA was cooled to 16°C, the diacetylenic hydrocarbon (2.5 mmol) added and the resulting mixture stirred for 10 min. After this, 0.5 ml of water was added to the dark-brown reaction mixture. The aryl iodide (2 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), PPh_3 (52.5 mg, 0.2 mmol), Et_3N (5 ml) and CuI (57 mg, 0.3 mmol) were then added subsequently in this order to the stirred reaction mixture. TLC was used to monitor the reaction. When the reaction was complete, the mixture was poured into ice–water and the resulting mixture extracted with CH_2Cl_2 (4×25 ml). The combined organic extracts were washed with water and dried over $MgSO_4$. After solvent evaporation, the product was isolated by flash chromatography on silica gel, eluting with hexane, then hexane/CH_2Cl_2 mixtures.