Microwave Enhancement of a 'One-Pot' Tandem Azidation–'Click' Cycloaddition of Anilines

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Dedicated to 'The Prof': Sir Jack Baldwin, FRS, on the occasion of his 70th birthday

Abstract: The practical and efficient one-pot azidation of anilines with the reagent combination *t*-BuONO and $TMSN_3$ has become a useful addition to the click-chemistry toolbox. Herein we report a modification of this methodology, using microwave radiation to significantly enhance the rate of formation of 1,4-triazoles from in situ generated azides.

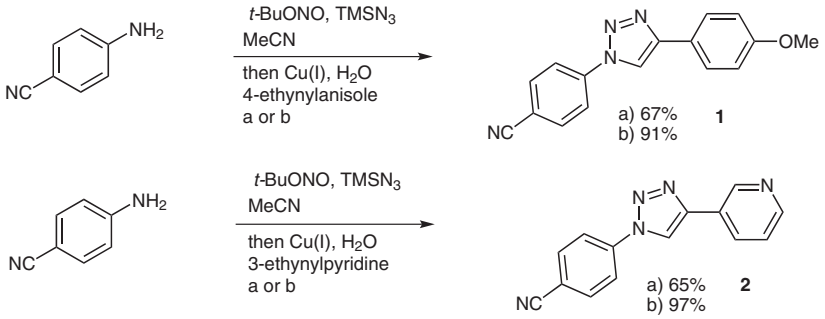
Key words: click chemistry, aromatic azides, Huisgen cycloaddition, chemoselectivity, 1,4-triazoles

Aromatic azides are valuable synthetic intermediates with immediate application in organic and bioorganic chemistry.[1] Although organic azides are often stable under most reaction conditions, compounds with low molecular weight can sometimes be explosive, and so-called 'azidophobia' has perhaps, until recently, resulted in a neglect of this functional group by the modern organic chemist.[2] However, with the recent advent of 'click' chemistry[2] and discovery of the powerful 1,4-triazole forming Cu(I)-catalysed Huisgen reaction,[3] there is a growing demand for new methodology to facilitate access to this functionality. This powerful fusion process has found widespread application in drug discovery,[4,5] materials science,[5,6] and bioconjugation amongst others.[5,7]

In order to minimise the potential explosive hazard,[2] procedures which enable the in situ generation of organic azides followed by their immediate reaction, is an attractive option. In the context of 'click' chemistry, several procedures have recently been reported where in situ azide formation is followed immediately by azide–alkyne cycloaddition under Cu(I)-mediated conditions, to yield the corresponding 1,4-triazole linkage. Examples include three-component azide substitution with NaN_3 on reactive alkyl and aryl halides,[8] epoxides,[9] and Baylis–Hilman adducts.[10] Copper triflate has also been used as a catalyst for both azidation of benzylic acetates and subsequent Cu(I) reaction in one pot.[11] Aliphatic and aromatic primary amines have also been used in conjunction with TfN_3 as a diazo transfer reagent,[12] along with our own diazotization–azidation procedure utilising *t*-BuONO and $TMSN_3$ with anilines.[13]

In our previous work, ambient conditions for the Cu(I)-catalysed cycloaddition stage of the reaction were described. Although good yields for a selection of triazole products were obtained, for some combinations of starting materials, the reaction was hampered by undesirable long reaction times and low yields. We now report a convenient and reliable modification using microwave radiation to reduce reaction times from hours to minutes, with greatly increased yields. Scheme 1 illustrates a direct comparison with two examples, where 4-aminobenzonitrile was reacted with 4-ethynylanisole and 3-ethynylpyridine. In both cases, reaction times were dramatically reduced and product yields greatly increased.

To investigate the generality of this protocol, a variety of 1,4-triazole products was synthesised from a selection of readily available anilines and acetylenes. Many of these combinations were not amenable to room-temperature conditions. In each case overall reaction times were significantly reduced, ranging from 15 minutes to 2.5 hours, a dramatic improvement lending itself to high-throughput



Scheme 1 *Reagents and conditions*: (a) r.t., overnight; (b) MW heating, 80 °C (125 W max.), 10 min.

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synthesis (Table 1). The initial azidation reaction with one equivalent of *t*-BuONO followed by one equivalent of $TMSN_3$ proceeded cleanly to completion in less than five minutes for both 4-nitroaniline and 4-aminobenzonitrile. In the case of iodoaniline slightly longer reaction times of 30 minutes were required with the same reagent ratios. Aniline was found to be sluggish under these conditions, requiring up to 16 hours, although this could be reduced to two hours using slight excess of reagents (1.5 equiv of *t*-BuONO followed by 1.2 equiv of $TMSN_3$).[14] After complete azide formation (as indicated by TLC analysis), an aqueous solution of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate was added to generate the [Cu(I)] catalyst in situ, followed by the corresponding terminal acetylene. The reaction vials were capped and heated in the microwave at 80 °C, until full conversion of azide as indicated by TLC analysis (maximum 10 min). The products were isolated by simple filtration and in most cases required no further purification.

The procedure with electron-deficient anilines was found to work equally well with both electron-deficient (e.g., entries 1, 4, 8, 13, 15, 19, 20) and electron-rich acetylenes (e.g., entries 3, 5, 7, 9, 12).

In summary, this approach offers a genuinely quick and reliable procedure for the synthesis of a variety of 1,4-triazole products. The procedure is particularly amenable to electron-deficient anilines, and works well with a wide variety of alkynes including aromatic, conjugated, aliphatic, electron-rich and electron-deficient varieties. The products were rapidly isolated by precipitation and filtration directly from the reaction mixture with no further purification. This procedure offers advantages over current methodologies in terms of safety, ease of execution, and efficiency, and should prove especially useful when unstable, low molecular weight, and polyvalent aromatic azides are required.

Table 1 Results for One-Pot Azidation and Cu(I)-Catalysed Huisgen Reaction

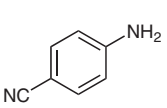
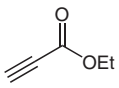
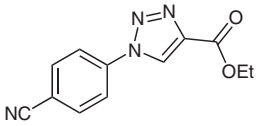
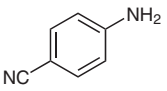
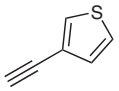
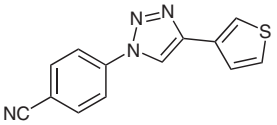
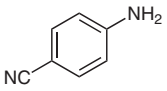
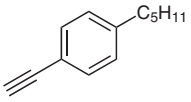
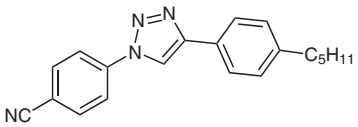
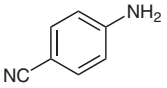
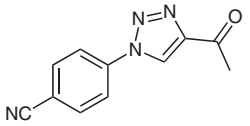
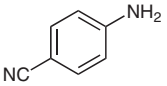
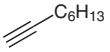
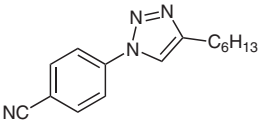
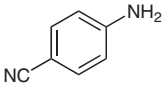
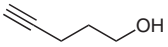
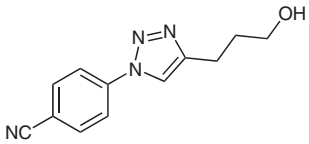
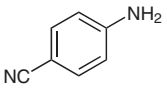
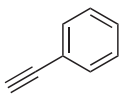
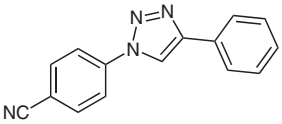
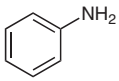
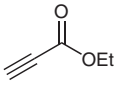
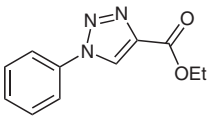
Entry	Aniline	Alkyne	Product		Yield (%)
1				**3**	85[a,d]
2				**4**	>99[d]
3				**5**	94[d]
4				**6**	94[d]
5				**7**	96[d]
6				**8**	96[d]
7				**9**	92[d]
8				**10**	82[b,d]

Table 1 Results for One-Pot Azidation and Cu(I)-Catalysed Huisgen Reaction (continued)

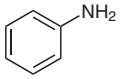
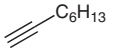
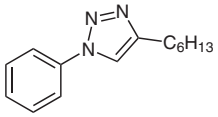
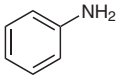
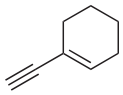
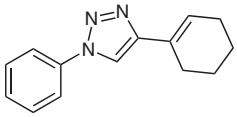
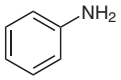
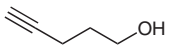
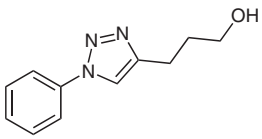
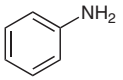
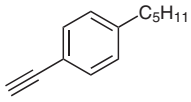
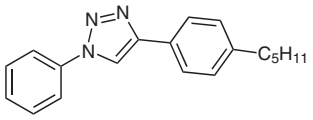
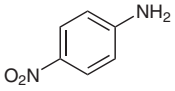
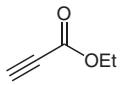
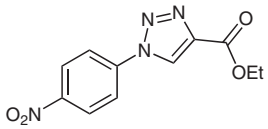
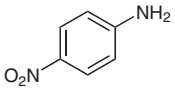
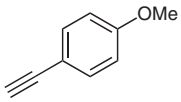
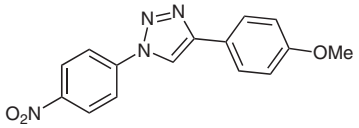
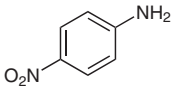
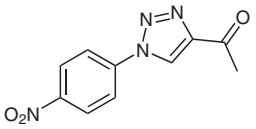
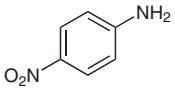
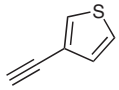
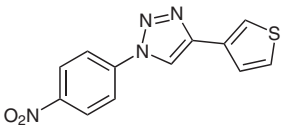
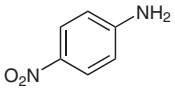
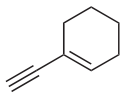
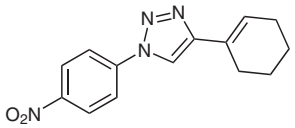
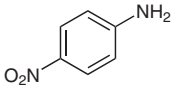
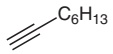
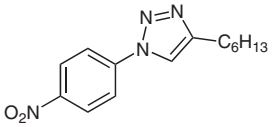
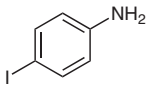
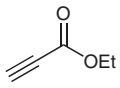
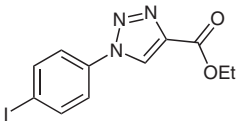
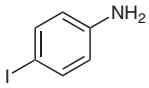
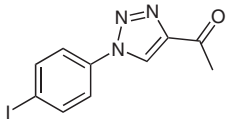
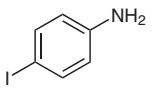
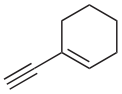
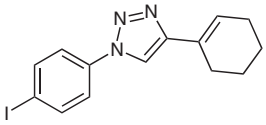
Entry	Aniline	Alkyne	Product		Yield (%)
9				**11**	84[d]
10				**12**	88[d]
11				**13**	85[d]
12				**14**	80[d]
13				**15**	96[e]
14				**16**	86[d]
15				**17**	89[e]
16				**18**	94[e]
17				**19**	96[d]
18				**20**	82[d]
19				**21**	91[c,e]
20				**22**	92[d]

Table 1 Results for One-Pot Azidation and Cu(I)-Catalysed Huisgen Reaction (continued)

Entry	Aniline	Alkyne	Product		Yield (%)
21				**23**	98[e]

[a] Reaction conditions (azidation): $TMSN_3$ (1 equiv), *t*-BuONO (1 equiv), MeCN, r.t., 2 min.
[b] Reaction conditions (azidation): $TMSN_3$ (1.2 equiv), *t*-BuONO (1.5 equiv), MeCN, r.t., 2 h.
[c] Reaction conditions (azidation): $TMSN_3$ (1 equiv), *t*-BuONO (1 equiv), MeCN, r.t., 30 min.
[d] Reaction conditions [Cu(I) step]: $CuSO_4{\cdot}5H_2O$ (0.1 equiv), sodium ascorbate (0.5 equiv), acetylene (1.5 equiv), MW, 80 °C (125 W max), 10 min.
[e] Reaction was complete, MW, 80 °C (125 W max), 2 min.

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(13) Barral, K.; Moorhouse, A. D.; Moses, J. E. *Org. Lett.* **2007**, *9*, 1809.
(14) **Typical Procedure – Synthesis of 4-{4-(4-Methoxyphenyl)-[1,2,3]triazol-1-yl}benzonitrile (1)**
To a stirred solution of 4-aminobenzonitrile (200 mg, 1.69 mmol) in MeCN (2 mL) was added *t*-BuONO (0.22 mL, 1.69 mmol) at 0 °C in a 2–5 mL microwave reaction vial. To this solution was added $TMSN_3$ (0.20 mL, 1.69 mmol) dropwise at 0 °C. The solution was stirred for 2 min at r.t., before completion of transformation to azide (monitored by TLC). At this point, 1-ethynyl 4-methoxybenzene (0.33 mL, 2.54 mmol) was added to the reaction mixture, followed by the addition of $CuSO_4{\cdot}5H_2O$ (42 mg, 0.169 mmol) and sodium ascorbate (167 mg, 0.845 mmol) in H_2O (1 mL). The vial was capped, then placed in a microwave reactor, and heated to 80 °C (125 W max) (Biotage® Initiator 2.0, 400 W). The reaction mixture was stirred at this temperature for 10 min before completion of reaction was observed by TLC analysis. The product was then precipitated by the addition of H_2O (25 mL). The product was isolated by filtration then washed with H_2O (2 × 10 mL), then PE (40–60, 2 × 10 mL). This gave the product as an orange powder (423 mg, 91%). IR ($CHCl_3$): 3010.24 (CH), 2234.19 (C≡N) cm^{-1}. ^1H NMR (400 MHz, DMSO): δ = 3.81 (s, 3 H, CH_3), 7.07 (d, *J* = 8.9 Hz, 2 H, 2 × CH), 7.86 (d, *J* = 8.9 Hz, 2 H, 2 × CH), 8.11 (d, *J* = 9.0 Hz, 2 H, 2 × CH), 8.17 (d, *J* = 9.0 Hz, 2 H, 2 × CH), 9.32 (s, 1 H, CH). ^{13}C NMR (100 MHz, DMSO): δ = 55.1, 110.8, 114.4, 118.0, 118.6, 120.1, 122.2, 128.7, 134.2, 139.4, 147.6, 159.4. HRMS: *m/z* calcd for $C_{16}H_{13}N_4O$: 277.1084; found: 277.1076. Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28; Found: C, 69.32; H, 4.32; N, 20.11.