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Microwave-assisted in situ deprotection and ω-methoxylation of TMS-protected aryl alkynes

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Abstract—Using microwave technology, rapid ω-methoxylation of aryl alkynes is possible.
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Direct alkoxylation of alkynes, especially in the absence of halides or metal catalysts, has been reported only for single examples since the early 1920s.[1] Only a few detailed studies are described in the literature as for example the methoxylation of ethynyl-*N*-heteroarenes by Yamanaka and co-workers.[2] Typical reaction times are around 5–16 h at solvent reflux, mainly using electron poor heteroaromatic- or substituted nitrobenzene alkynes.[2,3]

During our drug discovery program we were searching for possibilities to facilitate this reaction type and investigated the scope of this reaction. Thus we chose a set of model substrates having different electronic properties and used them to compare conventional heating with microwave irradiation, the latter technique having been shown to increase reaction speeds significantly.[4]

As standard reaction conditions, we chose potassium carbonate in methanol, since potassium carbonate is easily accessible, inexpensive, simple to handle and gave rise to less or no unidentifiable by-products in both the pure thermal and microwave assisted reactions.[5] Furthermore, these conditions are commonly used in the deprotection of TMS-alkynes,[6] allowing the direct use of protected alkynes. The latter can be made using a typical Sonogashira coupling protocol.[7]

The results are summarized in Table 1. Reaction at ambient temperatures led solely to deprotection for all the substrates besides the quinoxaline.[8] However, at elevated temperatures (methanol reflux for 24 h) the more electron deficient substrates showed partial to full conversion to the corresponding enol ethers and acetals, respectively. Employing microwave assisted chemistry at 120–130°C for 15 min led to an even faster substrate consumption.[9] 2-Pyridyl-, 2-cyano- and 4-nitrobenzenes gave particularly good conversions compared to the thermal method.[2,3] Conversions for halobenzenes were low using microwave synthesis and the thermal method led solely to deprotection, i.e. no addition to the triple bond took place at all. Electron rich substrates such as the phenyl or *p*-methoxybenzene derivative showed no addition products even under microwave irradiation. The microwave protocol is advantageous in terms of cleaner conversions leading to less by-products when comparing the GC, TLC or NMR of the crude reaction mixtures. Albeit in most cases incomplete diacetal formation was obtained and one can hydrolyze the product mixture to form aryl ethyl aldehydes as described by Yamanaka and co-workers.[2]

The necessity of electron-withdrawing substituents is in accordance with previously reported results.[2,3] However, these cannot be attributed to a pure mesomeric effect,[3] if comparing the partial addition to substrates like halobenzenes with cyano or nitrobenzenes. Rather, a mixture of electronic as well as conjugative effects seems to be important, with a predominance of conjugative effects.

In summary we have shown that methoxylation of electron poor aryl alkynes under microwave irradiation is possible leading to faster substrate conversions compared to conventional heating. TMS-protection does not pose a limitation since in situ deprotection occurs. Further improvements and use of different nucleophiles are currently in progress.

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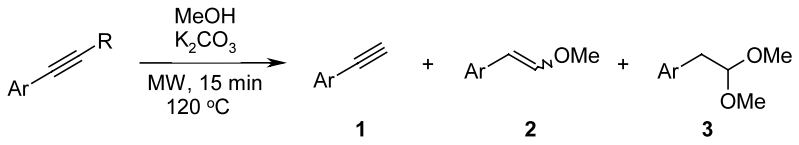
Table 1. Methoxylation of aryl alkynes



Substrate	**1**:**2**:**3** at rt[a]	**1**:**2**:**3** at reflux[b]	**1**:**2**:**3** in a microwave oven[c]
R = H, Ar = 4-MeO-Ph	No reaction	No reaction	No reaction
R = TMS, Ar = Ph	100:0:0	100:0:0	100:0:0
R = TMS, Ar = 3-Pyridyl	100:0:0	N.d. (55% **2** (72 h), Ref. 2)	75:25:0
R = TMS, Ar = 2-Pyridyl	100:0:0	N.d. (60% **2** (5 h), Ref. 2)	6:94:0
R = TMS, Ar = 2-NC-Ph	100:0:0	75:20:5	9:82:9
R = TMS, Ar = 4-O_2N-Ph	100:0:0	0:0:100 (72 h)[d] 23:35:42 (24 h)	0:2:98[f]
R = TMS, Ar = 2-O_2N-Ph	100:0:0	40:60:0	0:8:92[f]
R = TMS, Ar = 2-Quinoxalyl	0:0:100[e]	N.d.	0:03:97[f]
R = TMS, Ar = 2-Cl-Ph	N.d.	100:0:0	56:8:36[g]
R = TMS, Ar = 3-Br-Ph	N.d.	100:0:0	91:9:0[g]
R = TMS, Ar = 4-Br-Ph	N.d.	100:0:0	86:14:0[g]

[a] 10 equiv. K_2CO_3, MeOH, rt, 24 h.
[b] 10 equiv. K_2CO_3, MeOH, reflux, 24 h.
[c] 10 equiv. K_2CO_3, MeOH, 120–130°C, 15 min, microwave irradiation.[10] Ratios given are proton NMR integral ratios.
[d] Quantitative isolated yield.
[e] 92% isolated.
[f] Combined isolated yield: quant.
[g] Ratios given are non standardized CI-GC/MS ratios. Note that in EI-GC/MS the diacetals in some cases only show M^+–31 (i.e. M^+–MeO), which can be mistaken for the mono-adduct.

Acknowledgements

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3. (a) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1985**, *33*, 626–632; (b) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1986**, *34*, 2362–2368.
4. For a recent highlight see: Kuhnert, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1863–1866.
5. Alternatively, CsOH and NaOH were employed since they have been reported elsewhere, see e.g. Ref. 2, or Tischler, A. N.; Lanza, T. J. *Tetrahedron Lett.* **1986**, *27*, 1653–1656 and Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193–6195.
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7. See e.g.: (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470; (b) Lee, J.-H.; Park, J.-S.; Cho, C.-G. *Org. Lett.* **2002**, *4*, 1171–1173.
8. This is in stark contrast to Dinsmore, A.; Birks, J. H.; Garner, C. D.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 801–807. The authors report a high yield for 2-ethynylquinoxaline after 19 h in K_2CO_3/MeOH.
9. Higher temperatures can be achieved by the addition of a few drops of DMF. (Anders Franzén, Personal Chemistry, Sweden, personal communication). Under such conditions conversions slow down and the reactions proceed less cleanly.
10. Microwave reactions were run in 5 mL heavy-walled glass Smith process vials sealed with aluminum crimp caps fitted with a silicone septum. The oven was a Smith Synthesizer Single-mode microwave cavity producing continuous irraditation at 2450 MHz (Personal Chemistry AB, Uppsala, Sweden). General experimental procedure: 0.6 mmol of aryl (trimethylsilyl)ethyne and 6.0 mmol of potassium carbonate were mixed in 5 mL methanol in a 5 mL reaction tube and irradiated at 120 or 130°C for 15 min. Work-up was performed by adding ethyl acetate, followed by filtration and evaporation to dryness. NMR analysis of the crude product gave conversion ratios. Flash chromatography (heptane/ethyl acetate) gave isolated products.