COMMUNICATION

The microwave-assisted Dötz benzannulation process

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Chromium carbene-mediated Dötz benzannulation has been shown to proceed remarkably rapidly and with enhanced efficiency under developed microwave-assisted conditions.

In 1975 Dötz reported the first example of the formation of a highly substituted benzenoid compound from the reaction of a phenylchromium carbene complex and diphenylacetylene.[1] Over the subsequent years the efficiency and scope of this Dötz benzannulation process have been extensively investigated.[2] Traditionally the reaction has been carried out under thermal conditions in a donor solvent. However, use of such techniques can often lead to prolonged reaction times and low yields. Consequently, attempts have been made to address these drawbacks: *e.g.* high intensity photolytic irradiation has been employed[3] and work in our own laboratory has led to the development of both ultrasound[4] and dry state techniques[4,5] that provide much more rapid and higher yielding processes.
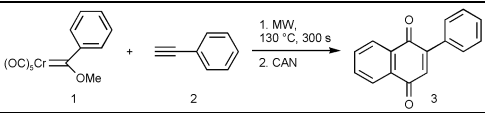
With regards alternative techniques that have the potential to provide preparative efficiency, microwave (MW) technology has been used in organic synthesis since 1986, when domestic ovens were initially used to accelerate reactions.[6] With the more recent ready availability of dedicated and focused reactors, which offer reliable and safe operation, there has been an exponential growth in MW-assisted organic synthesis.[7] In this respect, we envisaged that MW technology provided an opportunity to further improve the efficiency and flexibility of the compelling Dötz transformation, whilst potentially affording additional understanding of the scope and limitations of the relatively new and focused MW methods. We now describe our initial findings in this area.

At the outset, the reaction between the phenyl methoxy carbene complex **1** and phenylacetylene **2** was investigated. Using a Smith Creator™,‡ MW conditions of 130 °C and 300 seconds reaction time were initially chosen and the benzannulation was attempted, in sealed reactor vials, with a range of reaction solvents (Table 1). On completion of each short reaction, and following oxidative work-up with ceric ammonium nitrate (CAN), in every instance, other than the process performed in water, the desired naphthoquinone **3** was formed in moderate to excellent yield. In addition to showing that the Dötz reaction could be rapidly and efficiently mediated under controlled MW irradiation, this initial study showed that aprotic donor solvents gave optimal results, with the less basic di-*n*-butyl ether providing the highest yield.

Based on the results shown in Table 1, di-*n*-butyl ether and, the commonly used, THF were then selected as the solvents of choice for further investigations into the effects of reagent concentration on product yield. It is clear from Table 2 that use of di-*n*-butyl ether provided generally higher product yields than the equivalent reaction in THF; the use of no solvent provided a substantially lower yield. Overall and for both solvents, the optimal concentrations were found to be 0.05 M of complex **1** and 0.1 M of alkyne **2**. It is also worth noting that these optimised MW conditions are now significantly superior in terms of both reaction time and yield when compared to the thermal processes described in the literature.[8]

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Table 1 Reactions of **1** with **2** under MW irradiation

Solvent	Yield (%)
Toluene	58
CH_2Cl_2	36
Methanol	50
Ethanol	54
Ethylene glycol	58
Water	0
THF	73
Et_2O	82
$^nBu_2O$	88

The optimum techniques developed to this stage were then implemented in a study with carbene **1** and a range of alkynes in both di-*n*-butyl ether and THF (Table 3). Both internal and terminal alkynes performed well, providing good to excellent yields of the benzannulated products.§ In each case the reaction was complete in 300 s. Furthermore, where the equivalent reaction had previously been attempted under thermal conditions, by comparison the product yields were all substantially enhanced.[8,9] Additionally, on work-up the reaction mixture was homogeneous in all cases (unlike many thermal processes), easing product extraction and purification.

In attempts to investigate the reagents tolerated under the MW conditions, three additional complexes were then subjected to the developed optimum reaction protocol with a series of alkynes (Table 4). Once again, where there was literature precedent for the same transformation using thermal techniques, the reaction times were consistently far shorter and the product yields were greater.[10] It is also worth noting that the lower yields obtained for certain aryl alkynes with the furyl methoxy carbene complex are mirrored in the literature under thermal conditions.[11] In this regard, the developed MW-assisted methods can be considered to be complementary to our previously described dry state protocols,[4,5] which proved to be significantly more effective when used with the furyl methoxy

Table 2 Concentration effects in reaction of **1** with **2** under MW irradiation[a]

Solvent	[**1**] (M)	[**2**] (M)	Yield of **3** (%)
THF	0.01	0.01	70
	0.05	0.05	73
	0.5	0.5	64
	0.05	0.1	78
$^nBu_2O$	0.01	0.01	68
	0.05	0.05	88
	0.5	0.5	65
	0.05	0.1	91
—	0.05	10.5	47

[a] 130 °C and 300 s MW reaction conditions were used throughout, followed by oxidative work-up with CAN.

Table 3 Reaction of complex **1** with alkynes under MW irradiation[a]

Carbene	Alkyne	Product	Solvent	Yield (%)
(OC)₅Cr=C(Ph)(OMe)	phenylacetylene	2-phenyl-1,4-naphthoquinone	ⁿBu₂O / THF	91 / 78
(OC)₅Cr=C(Ph)(OMe)	1-phenylpropyne	2-methyl-3-phenyl-1,4-naphthoquinone	ⁿBu₂O / THF	70 / 86
(OC)₅Cr=C(Ph)(OMe)	4-tolylacetylene	2-(4-tolyl)-1,4-naphthoquinone	ⁿBu₂O / THF	73 / 75
(OC)₅Cr=C(Ph)(OMe)	1-pentyne	2-propyl-1,4-naphthoquinone	ⁿBu₂O / THF	91 / 68

[a] 130 °C and 300 s MW reaction conditions were used throughout (0.05 M **1**, 0.1 M alkyne), followed by oxidative work-up with CAN.

complex and such alkynes. In the final entry within Table 4 it can be seen that the MW methods also proved to be applicable to the less stable carbocyclic α,β-unsaturated complex, with the tetrahydronaphthoquinone being formed in a good 75% yield after only 5 min MW irradiation. In the cases where regioisomeric naphthoquinone products are possible, the sole isomer isolated was that which was anticipated based on literature precedent.[2]¶

In conclusion, we have now shown that modern focused MW reactors are readily utilisable and reliable tools for promotion of the Dötz reaction in a fast and effective manner. The use of such techniques result in remarkably enhanced reaction rates, with cyclisations being complete inside 5 min, and lead to annulated product yields which are often significantly greater than those from the traditional thermal processes. With the increasing use of such focused preparative MW instruments within pharmaceutical laboratories, one can envisage such annulation techniques being employed to gain efficient and rapid access to a diverse spectrum of functionalised aromatic compounds.

Table 4 Reaction of a range of complexes and alkynes under MW irradiation[a]

Carbene	Alkyne	Product	Yield (%)
(OC)₅Cr=C(4-tolyl)(OMe)	phenylacetylene	naphthoquinone	52
(OC)₅Cr=C(4-tolyl)(OMe)	1-phenylpropyne	methyl naphthoquinone	54
(OC)₅Cr=C(4-tolyl)(OMe)	4-tolylacetylene	tolyl naphthoquinone	57
(OC)₅Cr=C(4-tolyl)(OMe)	1-pentyne	propyl naphthoquinone	85
(OC)₅Cr=C(furyl)(OMe)	phenylacetylene	benzofuranone	29
(OC)₅Cr=C(furyl)(OMe)	1-phenylpropyne	benzofuranone	64
(OC)₅Cr=C(furyl)(OMe)	4-tolylacetylene	benzofuranone	0
(OC)₅Cr=C(furyl)(OMe)	1-pentyne	benzofuranone	72
(OC)₅Cr=C(cyclohexenyl)(OMe)	phenylacetylene	tetrahydronaphthoquinone	75

[a] 130 °C and 300 s MW reaction conditions were used throughout (0.05 M carbene, 0.1 M alkyne), followed by oxidative work-up with CAN.

Notes and references

§ Representative experimental procedure: All reactions were carried out using the Smith Creator™ with 'Fixed Hold Time' set to 'Off' and 'Absorption Level' set to 'High'. Carbene **1** (47 mg, 0.15 mmol) was added to a solution of alkyne **2** (30 mg, 0.30 mmol) in di-*n*-butyl ether (3 mL), the reaction vial sealed and placed in the microwave reactor. The reaction was irradiated to a temperature of 130 °C for 300 s. The reaction mixture was then automatically cooled and poured into a solution of CAN (0.6 g, 1.1 mmol) in water (3 mL). The mixture was stirred for a further 20 minutes and was then extracted with diethyl ether (3 × 20 mL). The organic extractions were combined and reduced *in vacuo* and the crude product was purified by silica column chromatography (eluting with petrol/diethyl ether 7:1). 2-Phenyl-1,4-naphthalenedione **3** was obtained as a yellow crystalline solid (33 mg, 91%), mp 109–110 °C. IR (CH₂Cl₂): 1666 cm⁻¹; ¹H NMR (CDCl₃): δ 7.08 (1H, s), 7.47–7.49 (5H, m), 7.77–7.79 (2H, m), 8.11–8.22 ppm (2H, m); ¹³C NMR (CDCl₃): δ 126.0, 127.1, 128.5, 129.4, 130.0, 132.1, 132.4, 133.4, 133.8, 133.9, 135.2, 148.1, 184.5, 185.2 ppm.[8] All other compounds exhibited satisfactory spectral and analytical data.

¶ In the cases where the naphthoquinone was known, the regioisomer isolated was identified as that resulting from the equivalent thermal process; all other single regioisomers were tentatively assigned by comparison.

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