Fused-Ring Systems

DOI: 10.1002/anie.200603416

A Remarkably Simple and Efficient Benzannulation Reaction**

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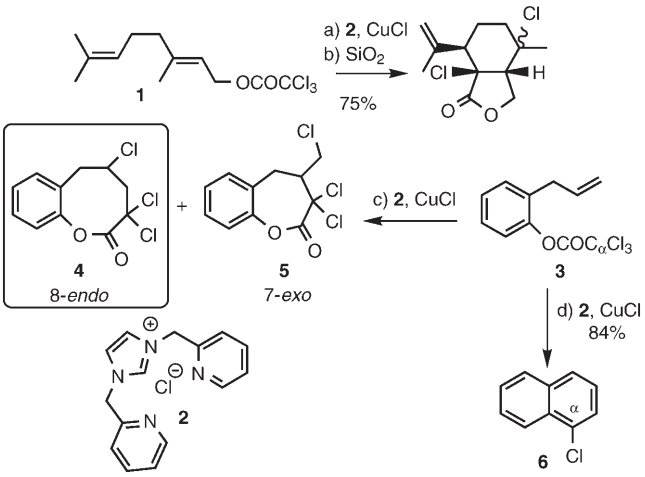
Dedicated to Professor E. J. Thomas on the occasion of his 60th Birthday

Whereas the application of atom-transfer radical cyclization reactions[1] (ATRC reactions) to the synthesis of γ-butyrolactams and γ-butyrolactones is now reasonably well established,[2] the same cannot be said of this approach to the synthesis of medium-sized rings.[3] Previously[4d] we had shown that the trichloroacetate **1** (Scheme 1) undergoes sequential 5-*exo*, 6-*exo* ATRC reactions to provide rapid access to the 2-oxabicyclo[4.3.0]nonane ring system. Alternate modes of cyclization (by 9-*exo* or 10-*endo* pathways[5]) were not observed. As a continuation of our interest[4] in this area we investigated the cyclization of trichloroacetate **3** (Scheme 1) under ATRC conditions. The synthesis of benzoxocins by radical cyclization reactions has received scant attention,[6,7] and at the outset we wished to determine if ATRC of **3** would occur by a 7-*exo* or 8-*endo* pathway[8] and whether structural features could be incorporated into the substrate to modify the regiochemical outcome of the reaction.[9] Furthermore, we also believed that this potentially problematic cyclization[10] reaction would also serve as a suitable test case for the development and evaluation of more efficient catalysts for ATRC reactions.[11]

Cyclization (CuCl, 5 mol%; **2**,[12,13] 5 mol%; toluene; reflux) of the readily available ester **3** proved to be rather sluggish (95% completion after 48 h) and afforded the labile[13] lactone **4** through an 8-*endo-trig* reaction.[7] This cyclization was also accompanied by the formation of a minor, wholly aromatic, by-product whose generation lagged behind the formation of lactone **4**. Repeating the ATRC reaction of **3** for 120 h in refluxing toluene resulted in the total consumption of both ester **3** and the lactone **4**, and the formation of 1-chloronaphthalene (**6**), which was isolated[14] in 23% yield after column chromatography. Moreover we were delighted to observe that irradiation[15–17] of a solution of the ester **3** in 1,2-dichloroethane containing our standard catalyst system in a microwave reactor[18] afforded **6** in 84% yield after a much reduced reaction time of two hours (Scheme 1).



Scheme 1. ATRC and benzannulation sequences catalyzed by CuCl in the presence of ligand **2**. a) **2** (5 mol%), CuCl (5 mol%), DCE, 80°C, 3.5 h; b) SiO_2, CH_2Cl_2, 75%; c) **2** (5 mol%), CuCl (5 mol%), DCE, 80°C, 48 h, quantitative; d) **2** (5 mol%), CuCl (5 mol%), DCE, microwave, 200°C, 2 h, 84%. DCE = 1,2-dichloroethane.

Wishing to establish the synthetic generality of this reaction, we subjected a variety of readily available aryl trichloroacetates (**8**, **10**, **12a**–**12f**; Scheme 2) to the same experimental protocol and found that, in each case, benzannulation proceeded smoothly over two hours at 200°C to produce their respective naphthalene derivatives. The requisite *ortho*-allyl phenols used in this study are themselves readily available from an *ortho*-Claisen rearrangement[19] of their respective allyl aryl ethers, a process which in many cases can also be efficiently accomplished in a microwave reactor.[20]

Of note is the observation that the benzannulation reaction proceeds with complete regiochemical control to afford an aryl chloride as a single regioisomer in each case. For example, subjecting the isomeric naphthyl esters **8** and **10** separately to our standard reaction conditions affords the known[21] chlorophenanthrenes **9** and **11** as the sole benzannulation products, an observation which is in agreement with the supposition that the aryl–oxygen bond of the ester undergoes *ipso* substitution by C_α during the course of the benzannulation sequence.[22] The incorporation of potentially reactive, yet useful, functionality (esters, enolizable ketones) is also accommodated (Scheme 2). Generally speaking both electron-releasing and electron-withdrawing substituents are tolerated in the cyclization sequence, although the lower yield in the case of **12e** (55%) may be attributed to a competing deacylation reaction during the course of the benzannulation.

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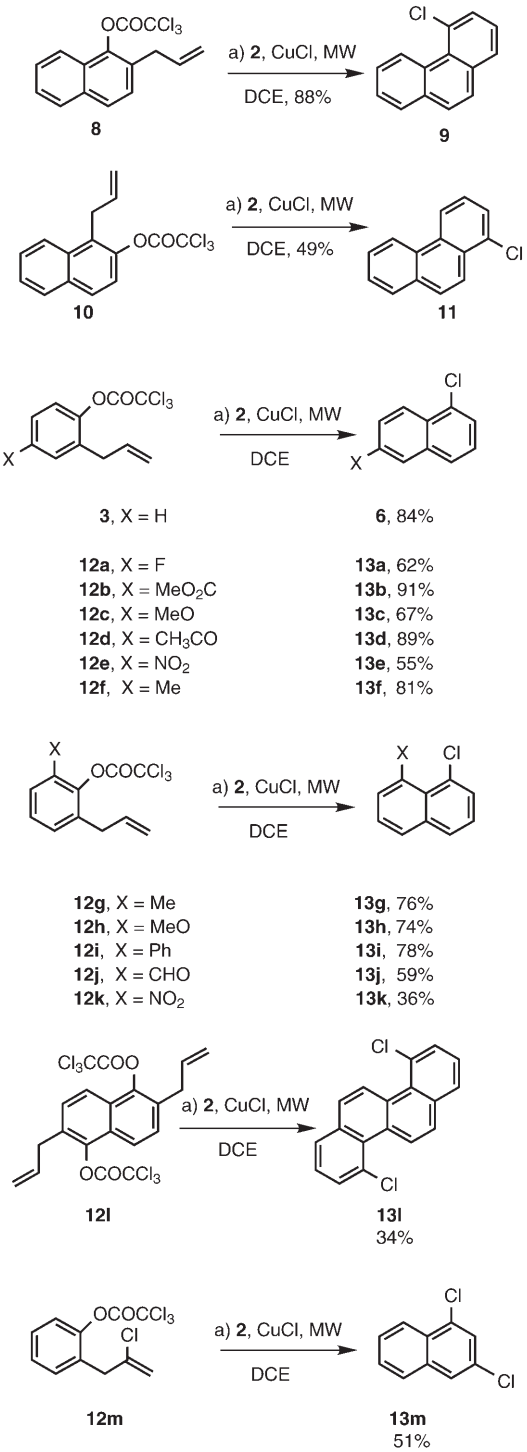
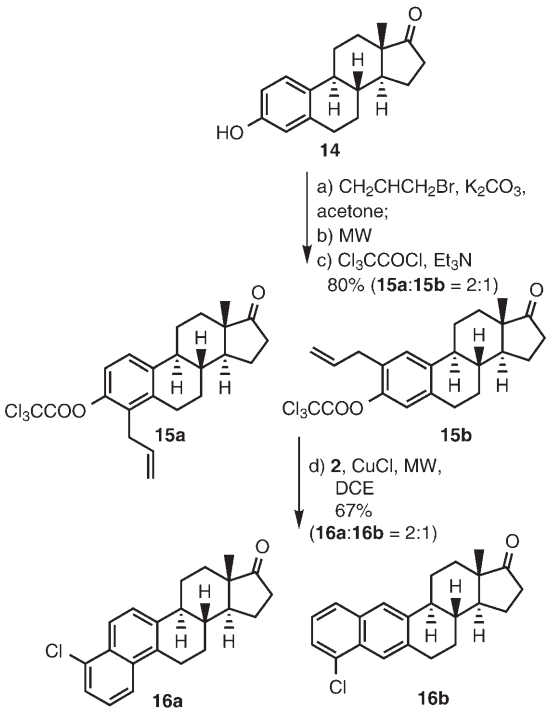
[**] We thank DyStar for generous funding of this research program and Dr. A. J. Lawrence for helpful discussions.



Scheme 2. Benzannulation sequences. a) **2** (5 mol%), CuCl (5 mol%), DCE, microwave, 200°C, 2 h. Yields are of purified products. MW = microwave.

The synthesis of 1,8-disubstituted naphthalenes **13g–k** is also amenable by this route from the corresponding esters **12g–k**. Again the introduction of a nitro substituent (**12k**) appears to be limiting in terms of the yield of the isolated product. We have also briefly investigated the possibility of multiple benzannulation reactions, as exemplified by the preparation of 4,10-dichlorochrysene (**13l**), from the readily available diester **12l**, in 34% yield. Benzannulation of substrates containing substituents in the allyl fragment also appears viable, as indicated by the cyclization of **12m** into **13m**.

The potential synthetic utility of our benzannulation sequence is illustrated by a four-step synthesis of the novel steroids **16a** and **16b** from estrone (**14**, Scheme 3). Allylation

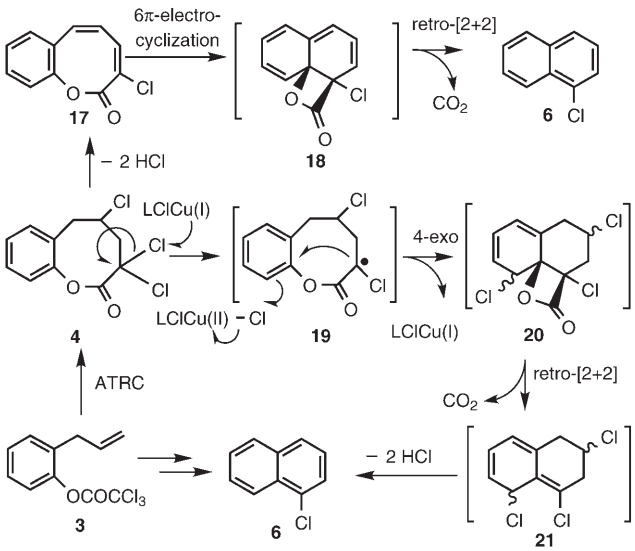


Scheme 3. Application of the benzannulation reaction to the synthesis of novel steroidal systems. a) CH_2CHCH_2Br (1.2 equiv), K_2CO_3 (1.2 equiv), 56°C; b) microwave, 215°C; c) Et_3N (1.2 equiv), Cl_3CCOCl (1.2 equiv), Et_2O, 0°C; d) **2** (5 mol%), CuCl (5 mol%), DCE, microwave, 200°C, 2 h.

of **14** as reported by Miescher and Scholtz[23] followed by *ortho*-Claisen rearrangement[24] and trichloroacetylation afforded a 2:1 mixture of the trichloroacetates **15a** and **15b**, which proved to be inseparable on a preparative scale. However microwave irradiation of the 2:1 mixture of crude esters **15a**,**b** in the presence of our standard catalyst system afforded the benzannulated steroid derivatives **16a**,**b** again as a 2:1 mixture of regioisomers in 67% yield.

Plausible pathways for the conversion of **3** into **6** are outlined in Scheme 4. Initially we considered that the initial product of the ATRC reaction, lactone **4**, could suffer double dehydrochlorination under the reaction conditions employed for the diene **17**. Electrocyclic ring closure[25] of **17** to the β-lactone **18** would then lead to the observed product **6** by loss of CO_2.[26]

However, whilst control experiments confirmed that the formation of **6** proceeds via the intermediacy of lactone **4**, microwave irradiation of **4** for two hours at 200°C in the absence of either Cu^I ions or ligand resulted in quantitative recovery of starting material **4**. Addition of our catalyst system to the reaction mixture at this stage followed by



Scheme 4. Proposed mechanism for the conversion of **3** into **6**.

irradiation as above then resulted in the quantitative conversion of **4** into **6**.

The fact that control reactions show that lactone **4** is thermally stable militates against the formation of the diene **17** and its subsequent rearrangement.[27,28] The finding that the copper catalyst appears to be intimately involved in the transformation of **4** into **6** leads us to suggest that the reaction proceeds via the spirocyclic lactone **20**, the product of a 4-*exo* radical cyclization onto the aromatic ring.[29] Once spirocyclization has taken place, presumably via the intermediacy of radical **19**, we envisage that lactone **20** suffers a rapid loss of CO_2 to produce the vinyl chloride **21**.[26] Finally double dehydrochlorination of **21** ultimately affords 1-chloronaphthalene (**6**).

Whatever the detailed mechanism[30] of this new benzannulation sequence, its ease of operation and potential generality will doubtless enable the synthesis of a large variety of aromatic systems from readily available intermediates. The application of this methodology to the synthesis of novel aromatic scaffolds[31] and target-oriented synthesis is now underway.

Experimental Section

A solution of the trichloroacetate **3** (640 mg, 2.4 mmol) in degassed 1,2-dichloroethane (10 mL) containing CuCl (11 mg, 0.11 mmol) and the ligand **2** (33 mg, 0.11 mmol) was sealed under nitrogen in a reaction vial and irradiated in a microwave reactor[18] for 2 h at 200 °C. On cooling the reaction to ambient temperature the solvent was removed in vacuo and the black residue purified by column chromatography (silica gel; eluent 10% EtOAc/petroleum ether) to afford 1-chloronaphthalene (**6**) (yield 327 mg, 84%).

Received: August 21, 2006
Revised: November 11, 2006
Published online: January 23, 2007

Keywords: cyclization · fused-ring systems · microwave irradiation · radical reactions · synthetic methods

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[13] Lactone **4** (^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, tetramethylsilane (TMS)): $\delta = 2.75$ (dd, $J = 15{,}11$ Hz, 1H), 3.15 (dd, $J = 16$, 5 Hz, 1H), 3.23 (dd, $J = 15$, 4 Hz, 1H), 3.35 (dd, $J = 16$, 4 Hz, 1H), 4.54–4.53 (m, 1H), 7.25–7.45 ppm (m, 4H); ^{13}C NMR (125 MHz, [D]$CHCl_3$, TMS): $\delta = 163.7$, 151.6, 132.3, 129.7, 126.1, 124.9, 120.0, 82.1, 54.9, 54.2, 37.9 ppm; IR (film): $\tilde{\nu}$1766 (s), 1487 (m),

1453 (m) 1217 (m), 1179 (m) cm^{-1}) readily undergoes hydrolytic ring opening upon exposure to moisture.
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