Tetrahedron Letters, Vol. 33, No. 44, pp. 6587-6590, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Induction of Radical Cyclizations with the 10-Methyl-9,10-dihydroacridine / $NaBH_4$ Photocatalytic System

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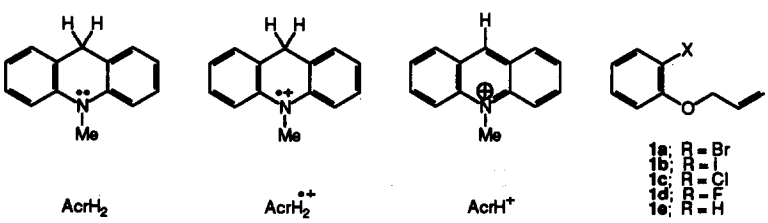
Abstract: *The radical cyclization of suitably unsaturated aromatic halides, such as 1-allyloxy-2-halobenzenes* (**1a-d**)*, can be induced with the 10-methyl-9,10-dihydroacridine / $NaBH_4$ photocatalytic system in DMF. The method is preparatively useful with the most reactive halides.*

The use of radical chemistry for the formation of carbon-carbon bonds in organic synthesis has increased tremendously within the last decade.[1,2] The intramolecular formation of carbon-carbon bonds via addition of carbon centered radicals to olefins often proceeds in excellent yields, with high regio- and stereoselectivity.[3] The tin hydride method of radical cyclization[4] offers many advantages and is probably the most frequently utilized amongst the various methods currently available. The known toxicity of organotin compounds, as well as difficulties frequently encountered during the separation of reaction products, complicates the use of tin hydrides in such transformations. For these reasons, the development of alternative methods for radical cyclizations is desirable.

Ishikawa and Fukuzumi recently reported an interesting system for the photodehalogenation of aliphatic and aromatic halides.[5] In this photocatalytic system, dehalogenation is achieved by irradiating a solution containing the halide, a catalytic amount of 10-methyl-9,10-dihydroacridine ($AcrH_2$) and an excess of $NaBH_4$ in CH_3CN / H_2O 9:1. It has been proposed that an aryl radical is an intermediate in this novel photodehalogenation. We therefore wished to test whether this photocatalytic system could be used to induce the radical cyclization of suitable substrates, such as 1-allyloxy-2-halobenzenes (**1a-d**),[6,7] and whether the method could be of preparative value.



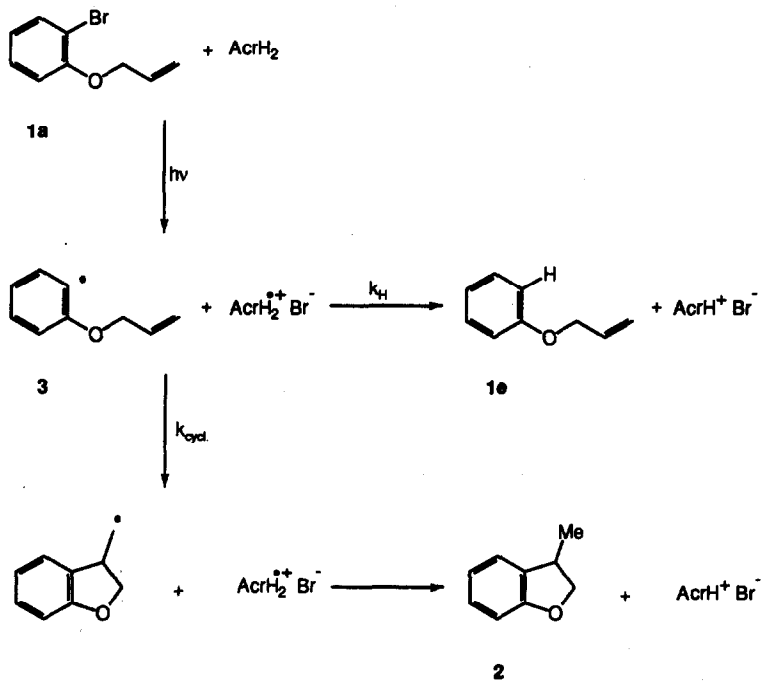
Initially, a solution containing equimolar amounts of substrate **1a** and $AcrH_2$ in CH_3CN without $NaBH_4$ was sealed under vacuum in a Pyrex NMR tube. The solution was irradiated in a Rayonet photochemical reactor using lamps with emission centered at 300 nm (Run 1, Table 1). Under these conditions, the yields of cyclized product **2** and reduction product **1e** (X = H) were approximately equal and remained low, even after 22 hours of irradiation.

Table 1. Reaction Conditions and Yields.

Run	Substrate	Concentration of substrate (mol l^{-1})	Concentration of $AcrH_2$ (mol l^{-1})	Concentration of $NaBH_4$ (mol l^{-1})	Solvent	Yield of **2**	Yield of **1e** (X = H)
1	**1a**	0.1	0.1	-	CH_3CN	14[a]	18[a]
2	**1a**	0.05	5×10^{-4}	0.5	CH_3CN/H_2O	38[a]	6[a]
3	**1a**	0.05	5×10^{-3}	0.25	DMF	65[b]	7[b]
4	**1b**	"	"	"	"	82[b] (76)[c]	2[b]
5	**1c**	"	"	"	"	48[b]	6[b]
6	**1d**	"	"	"	"	21[b]	<2[b]

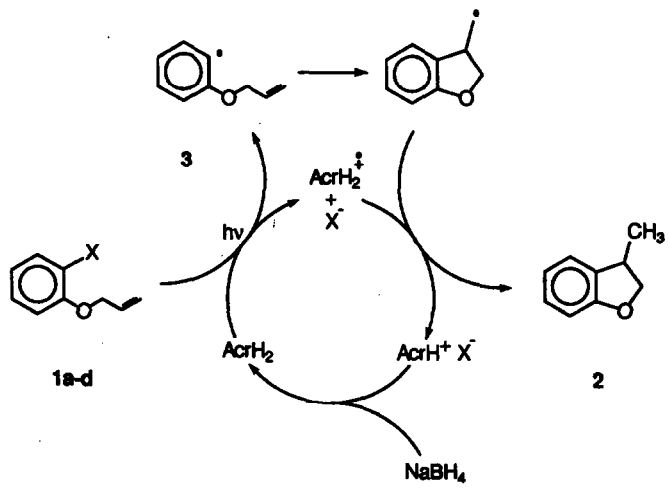
[a] yield determined by ^1H NMR analysis; [b] yield determined by HPLC analysis; [c] isolated yield.[8]

The low yields and the high proportion of reduction product **1e** observed in run 1 (**1e/2** = 1.3) have the same origin. Use of a relatively high concentration of $AcrH_2$ in the absence of $NaBH_4$ generates a high concentration of $AcrH^+$ as a by-product. Accumulation of this by-product inhibits the reaction, presumably by competitive absorption of the excitation light or by quenching of the triplet excited state of $AcrH_2$ by transfer of energy or an electron. In addition, the reduction of aryl radical **3** ($k_H[AcrH_2^{\bullet+}]$) competes more efficiently with cyclization ($k_{cycl.}$) in the presence of a high concentration of hydrogen donor ($AcrH_2^{\bullet+}$) (Scheme 1). As a result, the proportion of the reduction product **1e** is increased.



Scheme 1: Radical reduction versus cyclization of 1-allyloxy-2-bromobenzene (**1a**).

The *in situ* reduction of $AcrH^+$ by addition of an excess of $NaBH_4$ to the reaction mixture regenerates $AcrH_2$ and completes the catalytic cycle (Scheme 2). Only a small amount of $AcrH_2$ was therefore used in subsequent runs. As expected, the proportion of reduction product **1e** was smaller in run 2 (**1e/2** = 0.16). The yields remained low when the reaction was carried out in CH_3CN / H_2O 9:1. This can be attributed to the degradation of $NaBH_4$ in the presence of water during prolonged irradiation. This problem was overcome by using DMF as the solvent (Runs 3-6, Table 1). Degradation of $NaBH_4$ was not observed in DMF, and all reactions could be carried out until most of the starting material had disappeared. The yields of **2** varied depending on the nature of the halide; the maximum occurred in the case of the iodide **1b** (Run 4), which has the weakest carbon-halogen bond. Less reactive halides required longer irradiation times and gave lower yields. These lower yields can be attributed in part to the slow degradation of the reaction products during prolonged irradiation. The reactivity of the fluoride **1d** (Run 6) in spite of a strong carbon-halogen bond illustrates the generality of this photocatalytic system. These observations show that the photocatalytic cyclization of reactive 1-allyloxy-2-halobenzenes, as depicted in scheme 2, can be preparatively useful.[7]



Scheme 2: Photocatalytic mechanism for the radical cyclization of 1-allyloxy-2-halobenzenes (**1a-d**)

Acknowledgments. The authors are grateful to the Natural Sciences and Engineering Council of Canada and the Comité d'Attribution des Fonds Internes de Recherche (Université de Montréal) for financial support of this work.

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6. 1-Allyloxy-2-halobenzenes (**1a-d**) were prepared from the corresponding 2-halophenols and allyl bromide in DMF in the presence of sodium hydride: **1a**: (83%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, J = 1.6 and 7.8 Hz, 1H); 7.24 (ddd, J = 1.6, 7.4 and 8.3 Hz, 1H); 6.89 (dd, J = 1.4 and 8.3 Hz, 1H); 6.84 (ddd, J = 1.4, 7.4 and 7.8 Hz); 6.07 (tdd, J = 5.1, 10.5 and 17.3 Hz, 1H); 5.46 (qd, J = 1.6 and 17.3 Hz, 1H); 5.38 (qd, J = 1.6 and 10.5 Hz, 1H); 4.61 (td, J = 1.6 and 5.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9; 133.4; 132.6; 128.3; 122.0; 117.7; 113.6; 112.3 and 69.6; CIMS *m/z* (relative intensity) 213 (MH^+, 100); 134 (MH^+-Br, 84). **1b**: (89%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, J = 1.6 and 7.8 Hz, 1H); 7.26 (ddd, J = 1.6, 7.4 and 8.2 Hz, 1H); 6.79 (dd, J = 1.4 and 8.2 Hz, 1H); 6.70 (ddd, J = 1.4, 7.4 and 7.8 Hz); 6.05 (tdd, J = 4.8, 10.6 and 17.3 Hz, 1H); 5.52 (qd, J = 1.6 and 17.3 Hz, 1H); 5.30 (qd, J = 1.6 and 10.6 Hz, 1H); 4.58 (td, J = 1.6 and 4.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0; 139.4; 132.5; 129.3; 122.6; 117.5; 112.4; 86.6 and 69.6; CIMS *m/z* (relative intensity) 260 (MH^+, 60); 134 (MH^+-I, 100). **1c**: (63%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (dd, J = 1.7 and 7.7 Hz, 1H); 7.19 (ddd, J = 1.7, 7.5 and 8.3 Hz, 1H); 6.92 (dd, J = 1.4 and 8.3 Hz, 1H); 6.89 (ddd, J = 1.4, 7.5 and 7.7 Hz); 6.07 (tdd, J = 5.2, 10.5 and 17.3 Hz, 1H); 5.46 (qd, J = 1.6 and 17.3 Hz, 1H); 5.30 (qd, J = 1.6 and 10.5 Hz, 1H); 4.61 (td, J = 1.6 and 5.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0; 132.6; 130.3; 127.6; 123.0; 121.5; 117.8; 113.7 and 69.6; CIMS *m/z* (relative intensity) 169 (MH^+, 100). **1d**: (58%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87-7.10 (m, 4H); 6.05 (tdd, J = 5.3, 10.5 and 17.2 Hz, 1H); 5.42 (qd, J = 1.4 and 17.2 Hz, 1H); 5.29 (qd, J = 1.4 and 10.5 Hz, 1H); 4.59 (td, J = 1.4 and 5.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8 (d, J = 246 Hz); 146.6 (d, J = 10.4 Hz); 132.8; 124.1 (d, J = 4.0 Hz); 121.2 (d, J = 7.0 Hz); 118.0; 116.2 (d, J = 18.6 Hz); 115.4 and 70.1; CIMS *m/z* (relative intensity) 153 (MH^+, 100).

7. 1-Allyloxy-2-halobenzenes (**1a-d**) were used as substrates with various methods of radical cyclizations: a) Beckwith, A. L. J.; Gara, W. B.; *J. Chem. Soc., Perkin Trans II* **1975**, (7), 795-802. b) Beckwith, A. L. J.; Goh, S. W.; *J. Chem. Soc., Chem. Commun.* **1983**, 905-906 c) Abeywickrema, A. N.; Beckwith, A. L. J.; *Tetrahedron Lett.* **1986**, *27*(1), 109-112 d) Bhandal, H.; Patel, V. F.; Pattenden, G.; Russel, J. J.; *J. Chem. Soc., Perkin Trans I* **1990**, (10), 2691-2701. e) Chatgilialoglu, C.; Dickhaut, J.; Giese, B.; *J. Org. Chem.* **1991**, *56*(22), 6399-6403.

8. **Typical procedure of radical cyclization with the $AcrH_2$ / $NaBH_4$ system**: A solution containing 0.59 g (2.3 mmoles) of 1-allyloxy-2-iodobenzene (**1b**), 0.044 g (0.23 mmole) of 10-methyl-9,10-dihydroacridine and 0.43 g (11.4 mmoles) of $NaBH_4$ in 45 mL of DMF is prepared in a 4 cm x 11 cm cylindrical Pyrex flask, equipped with an internal cold finger to prevent overheating of the solution. The solution is deoxygenated with continuous argon bubbling and irradiated in a Rayonet photochemical reactor using lamps with emission centered at 300 nm. Photolysis is stopped when HPLC analysis shows that less than 5% of the starting compound remains. The reaction mixture is diluted with water and extracted with ether. After the usual work-up, the residue is purified by flash chromatography (hexanes/benzene 90:10). 3-Methyl-2,3-dihydrobenzofuran (**2**) was isolated as a clear oil (0.23 g; 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10-7.18 (m, 2H); 6.88 (dt, J = 1.0 and 7.4 Hz, 1H); 6.80 (d, J = 7.9 Hz, 1H); 4.69 (dd, J = 8.6 and 8.8, 1H); 4.08 (dd, J = 7.5 and 8.6 Hz, 1H); 3.57 (qdd, J = 6.9, 7.5 and 8.8 Hz, 1H); 1.34 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7; 132.2; 127.9; 123.7; 120.4; 109.4; 78.4; 36.5 and 19.3; CIMS *m/z* (relative intensity) 135 (MH^+, 100).

(Received in USA 6 July 1992; accepted 8 August 1992)