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Quantitating the Effect of an Ortho Substituent on Cyclization and Intramolecular Hydrogen-Transfer Reactions of Aryl Radicals

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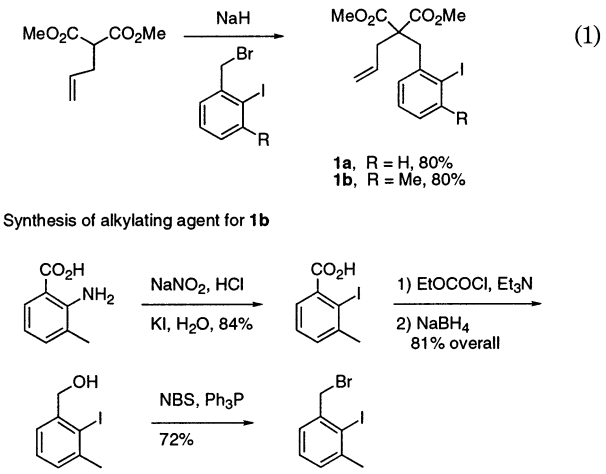
Abstract: Reduction of allyl 2-iodobenzyl malonates with triphenyltin hydrides generates aryl radicals that partition between 6-*exo* cyclization, 7-*endo* cyclization, and 1,5-hydrogen atom transfer. Rate constants for all of these processes are high ($>10^8$ M^{-1} s^{-1}), and the rates are only marginally reduced (<33%) by the introduction of methyl group ortho to the reacting radical.

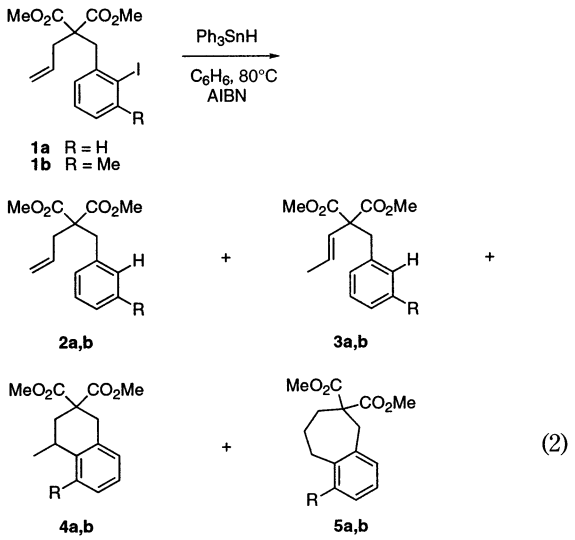
In the context of developing a tandem radical/ionic cyclization strategy[1] to the penitrem family of natural products,[2] we needed to know the effect of an ortho substituent on the intramolecular reactions of an aryl radical. Aryl radical cyclization and intramolecular hydrogen transfer reactions are well-known,[3] but the vast majority of examples are reactions of aryl radicals bearing hydrogen as an ortho substituent. Limited evidence suggested that larger ortho substituents could significantly retard the rate of a 5-*exo* cyclization.[4] Herein, we report competition kinetics[5] to determine the rate constants for 6-*exo* cyclization, 7-*endo* cyclization, and 1,5-hydrogen-transfer reactions of representative aryl radicals with and without ortho substituents. Surprisingly, the replacement of an ortho hydrogen by a methyl group only has a small effect on the rates of any of these reactions.

Cyclization precursors **1a** (R = H) and **1b** (R = Me) were synthesized by standard malonate alkylations (eq 1). The alkylating agent needed to construct **1b** was synthesized in good overall yield as shown in the lower part of eq 1. Full details for all of these reactions are contained in the Supporting Information.

Products from the reaction of **1a**,**b** were isolated and characterized in preparative reactions (eq 2). Cyclization of **1a** with 1.5 equiv of Ph_3SnH (0.05 M) at 80 °C in benzene followed by DBU workup[6] gave a mixture of four products in quantitative yield. These products were direct reduction products **2a** (15%) and **3a** (40%), 6-*exo* cyclization product **4a** (32%), and 7-*endo* cyclization product **5a** (13%). Though difficult to separate by silica chromatography, the products were readily resolved by GC to give the indicated ratios. Reduced products **2a** and **3a** were identified in the mixture by comparison with authentic samples (see the Supporting Information). Exposure of the mixture to ozone for 30 min to cleave the alkenes followed by chromatography provided a mixture of **4a** and **5a** along with benzyl dimethyl malonate (arising from ozonolysis of **3a** and deformylation). This mixture could not be separated, but selective decarbomethoxylation of the monoalkylated malonate[7] followed by chromatography gave a mixture of cyclized products **4a** and **5a** in 23% isolated yield. Careful chromatography of this mixture gave fractions enriched in the 6-*exo* (**4a**) and 7-*endo* (**5a**) products for spectroscopic characterization. Four analogous products **2b**−**5b** were formed in the cyclization of **1b**, and they were analyzed and characterized in a similar manner (see the Supporting Information).



(1)



(2)

The presence of migrated product **3a** indicated that 1,5-hydrogen transfer[8] is occurring in competition with

(1) (a) Nagashima. T. Ph.D. Thesis, University of Pittsburgh, 1998. (b) Rivkin, A. Ph.D. Thesis, University of Pittsburgh, 2001. (c) Rivkin, A.; Nagashima, T.; Curran, D. P. Submitted for publication.

(2) Leading reference: Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11254−11255.

(3) (a) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Organic Reactions*; Wiley: New York, 1996; Vol. 48. (b) Abeywickrema, A. N.; Beckwith, A. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 464−465. (c) Beckwith, A. L. J.; Meijs, G. F. *J. Org. Chem.* **1987**, *52*, 1922−1930.

(4) Hoffmann, H. M. R.; Schmidt, B.; Wolff, S. *Tetrahedron* **1989**, *45*, 6113−6126.

(5) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151−1176.

(6) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140−3157.

(7) Zhang, Q.; Curran, D. P. *Adv. Synth. Catal.*, in press.

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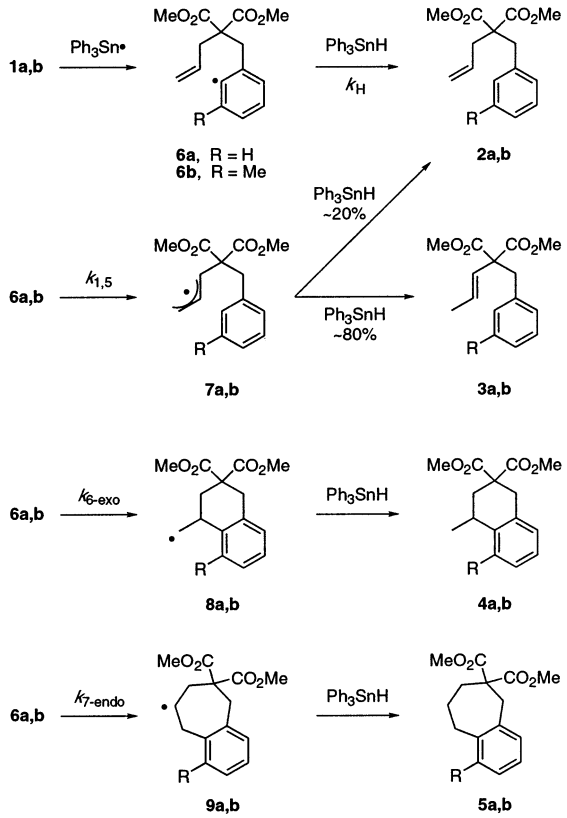
SCHEME 1



cyclization. Accordingly, we formulated the mechanism in Scheme 1 as a framework for the kinetic experiments. Halogen abstraction from **1a** gives aryl radical **6a**, which partitions between three pathways: 1,5-hydrogen atom transfer ($k_{1,5}$) to give allyl radical **7a**, 6-*exo* cyclization ($k_{6\text{-}exo}$) to give radical **8a**, and 7-*endo* cyclization ($k_{7\text{-}endo}$) to give **9a**.[9] Cyclized radicals **8a** and **9a** abstract hydrogen from tin hydride to give their respective products **4a** and **5a**. Allyl radical **7a** can abstract hydrogen at the terminus to give **3a** or at an internal position to give **2a**. Compound **2a** is also the product of direct bimolecular reduction of radical **6a** by tin hydride. This convolution of the clock reaction with a secondary reaction means that rate constants cannot be estimated at single concentration, but conducting experiments at varying concentrations allows the deconvolution of the clock reaction from the 1,5-hydrogen transfer reaction.

Reductions of both **1a** and **1b** with triphenyltin hydride were conducted at tin hydride concentrations increasing from 0.01 M to neat (~3.9 M). Reactions were conducted at 80 °C, and product ratios were measured by gas chromatography. The ratios were corroborated in several cases by ^{1}H NMR spectroscopy, so raw ratios were used without correction. In all cases, GC analysis revealed only four non-tin containing products, so the combined ratios were normalized to 100%.

TABLE 1. GC Product Ratios in Cyclization of 1a,b with Ph_3SnH

	substrate	Ph_3SnH [M]	% terminal **2a,b**[a]	% internal **3a,b**	% 6-*exo* **4a,b**	% 7-*endo* **5a,b**
1	**1a**	0.05	15 (7/8)	40	32	13
2	**1a**	0.11	14 (5/9)	46	30	10
3	**1a**	0.21	17 (8/9)	43	29	11
4	**1a**	1.01	36 (29/7)	33	22	9
5	**1a**	3.91	55 (50/5)	23	16	6
6	**1b**	0.01	12 (4/8)	41	33	14
7	**1b**	0.05	14 (5/9)	45	30	11
8	**1b**	0.11	16 (7/9)	45	29	10
9	**1b**	0.21	19 (11/8)	42	29	10
10	**1b**	0.25	22 (14/8)	40	27	11
11	**1b**	1.02	42 (36/6)	29	21	8
12	**1b**	3.91	64 (60/4)	20	10	6

[a] The yield of **2a**,**b** formed by direct reduction (clock reaction, k_H) to **2a**,**b** formed by 1,5-hydrogen transfer ($k_{1,5}$) followed by reduction. The yield of **2a**,**b** formed by 1,5-hydrogen transfer was calculated by multiplying the yield of **3a**,**b** by 0.2.

TABLE 2. Calculated Rate Constants (M^{-1} s^{-1}) for Cyclization and Hydrogen Transfer Reactions of Radicals 6a,b

radical	$k_{1,5}$	$k_{6\text{-}exo}$	$k_{7\text{-}endo}$
6a	12×10^8	6.5×10^8	2.1×10^8
6b	8.3×10^8	4.5×10^8	1.5×10^8

Table 1 shows the raw data from these sets of experiments. Plots of these data (not shown) demonstrate that directly reduced product **2** is formed by both pathways in Scheme 1 (calculated rate constants for all of the processes in Scheme 1 vary with tin hydride concentration, which is not possible). According to Scheme 1, the ratio of the migrated product **3** to the reduced product **2** arising from 1,5-hydrogen transfer must be constant since these are competing intermolecular reactions for the same radical. By trial and error data analysis, we could show that this ratio is about 0.2 for both radicals **6a** and **6b**. We thus partitioned the yield of product **2** into its two contributing pathways, direct reduction of **6** by tin hydride and indirect formation by 1,5-hydrogen transfer to **7** and tin hydride reduction; these partitioned values are shown in parentheses in Table 1. Experiments at the lowest concentrations were omitted, and rate constants for all the intramolecular reactions were then calculated as usual[5] by using the value 1×10^9 M^{-1} s^{-1} for k_H from Ph_3SnH.[10,11] The calculated rate constants are shown in Table 2.

The accuracy of these rate constants is not high because both the clock rate constant for hydrogen transfer and the amount of the directly reduced products are estimated numbers. Nonetheless, the absolute values can be used as good ballpark estimates for comparison with other aryl radical rate constants. This study targets

(8) Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051−6059.

(9) The 6-*exo*/7-*endo* ratios are roughly constant at higher concentrations, suggested that most of the 7-*endo* product arises by 7-*endo* cyclization. However, at lower concentrations, the proportion of 7-*endo* product appears to increase, suggesting that ring expansion (neophyl rearragement) of the 6-exo product may be occurring to some extent. See: Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.* **1987**, *52*, 4072−4078.

(10) (a) Chatgilialoglu, C.; Newcomb, M. In *Advances in Organometallic Chemistry*; West, R., Hill, A. F., Eds.; Academic Press: San Diego, 1999; Vol. 44. (b) Garden, S. J.; Avila, D. V.; Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem.* **1996**, *61*, 805−809.

(11) The value is estimated. Chatgilialoglu and Newcomb recommend 7.8×10^8 M^{-1} s^{-1} for the rate constant for reaction of tributyltin hydride with phenyl radical at ambient temperature (ref 10a). We rounded this up to account for anticipated small increases due to the phenyl groups and the higher temperature of our experiments.

comparison of the rates constants with and without the ortho substituent. To do this, we assume that the rate constant for direct hydrogen transfer (k_H) is not affected by the presence of the ortho substituent. Support for this assumption comes from the high rate constants for reaction of tin hydrides with phenyl (and vinyl) radicals.[10]

Radicals **6a** and **6b** have strikingly similar relative and absolute reactivities. The relative rates for 1,5-hydrogen transfer, 6-*exo* cyclization and 7-*endo* cyclization are roughly 6/3/1 in both cases. The calculated absolute rate constants for all three reactions, 1,5-hydrogen transfer, 6-*exo* cyclization and 7-*endo* cyclization are marginally higher (less than a factor of 1.5) for radical **6a** bearing the ortho hydrogen than for radical **6b** bearing the ortho methyl group. These small differences are probably outside of the error of the measurements and calculations. But such small differences are of little importance for synthetic planning, so we conclude that the effect of the ortho methyl group on preparative reactions of this type will be negligible.

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Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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