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Kinetics of Bromine−Magnesium Exchange Reactions in Heteroaryl Bromides

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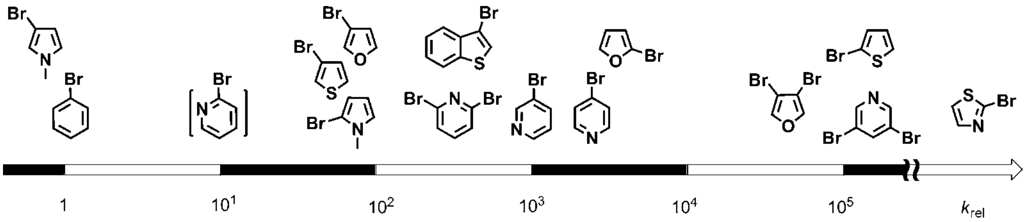
ABSTRACT



Competition experiments are reported which compare the relative reactivities of bromoheteroarenes toward *i*-PrMgCl·LiCl in THF at 0 °C.

Bromine−magnesium exchange reactions of heteroaryl bromides provide an efficient entry to a wide variety of five- and six-membered functionalized heteroaryl Grignard reagents, which can be used for the selective synthesis of polyfunctionalized heterocyclic compounds, such as thiazole, thiophene, furan, pyrrole, and pyridine derivatives.[1,2] The resulting heteroarenes are ubiquitous in natural products[3] and physiologically active compounds.[4] It has been shown that the mixed magnesium−lithium complex *i*-PrMgCl·LiCl has a significantly increased reactivity in bromine−magnesium exchange reactions compared to *i*-PrMgCl or *i*-Pr_2Mg.[5] In extension of our recent investigations on the kinetics of bromine−magnesium exchange reactions in substituted bromobenzenes,[6] we have now studied bromine−magnesium exchange reactions of heteroaryl bromides in order to assist the targeted use of these reactions for the synthesis of polyfunctional heterocyclic compounds.

The relative exchange rates were determined by treating mixtures of bromoheteroarenes and bromobenzenes or of two

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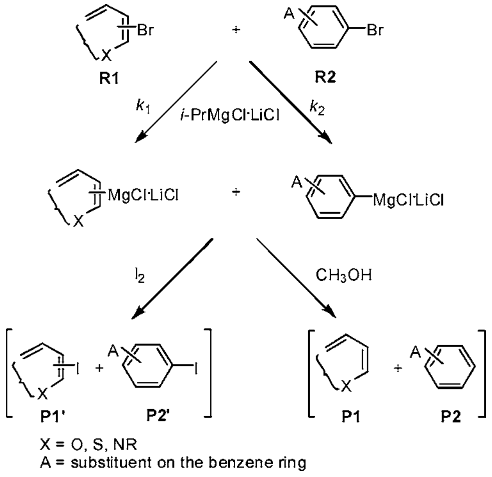
different bromoheteroarenes with a substoichiometric amount of *i*-PrMgCl•LiCl (typically 0.33 to 0.5 equiv) in THF at 0 °C. The resulting mixtures of aryl−magnesium reagents were then quenched either with iodine or with methanol to give the iodoarenes **P1′**/**P2′** or the debrominated arenes **P1**/**P2**, respectively (Scheme 1).

Scheme 1. Determination of Relative Br−Mg Exchange Rates



As in previous work,[6a] the product ratio was found to be independent of the reaction time in most cases, indicating kinetic reaction control. Exceptions will be discussed below. The relative reactivities of **R1** and **R2** toward *i*-PrMgCl•LiCl can be calculated by eq 1,[7] which considers the change of the ratio [**R1**]/[**R2**] during the course of the reaction.

$$\kappa = \frac{k_1}{k_2} = \frac{\log([\mathbf{R1}]_0/[\mathbf{R1}]_t)}{\log([\mathbf{R2}]_0/[\mathbf{R2}]_t)} \qquad (1)$$

With $[\mathbf{R1}]_0 = [\mathbf{R1}]_t + [\mathbf{P1}]_t$ and $[\mathbf{R2}]_0 = [\mathbf{R2}]_t + [\mathbf{P2}]_t$, eq 1 can be rewritten as:

$$\kappa = \frac{\log(1 + [\mathbf{P1}]_t/[\mathbf{R1}]_t)}{\log(1 + [\mathbf{P2}]_t/[\mathbf{R2}]_t)} \qquad (2)$$

For the calculation of κ by eq 2, the ratios $[\mathbf{P1}]_t/[\mathbf{R1}]_t$ and $[\mathbf{P2}]_t/[\mathbf{R2}]_t$ were determined by GC analysis, as described in the Supporting Information.

Each of the 13 heteroaryl bromides listed in Figure 1 was subjected to competition experiments with several bromoarenes, to give the 24 competition constants κ summarized in Figure 1, from which the k_{rel} values listed in the left column of Figure 1 were obtained by a least-squares optimization as described previously.[8] Though the reproducibility of the competition constants was worse than in the case of the substituted bromobenzenes, the fair agreement between the experimental values of κ and those

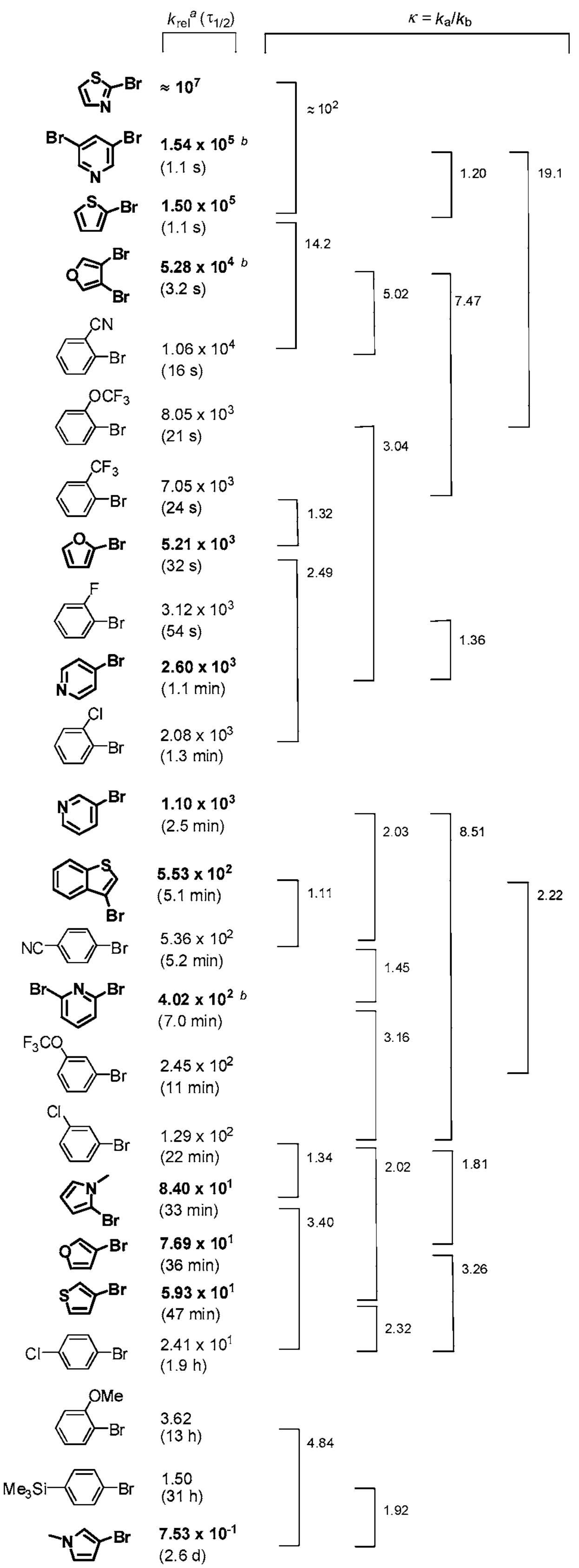


Figure 1. Relative reactivities of bromoarenes toward *i*-PrMgCl•LiCl in THF at 0 °C and $\tau_{1/2}$ for 1 M solutions (bromobenzene: k_{rel} = 1.0). Footnotes: (a) See ref 8. (b) k_{rel} not statistically corrected.

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[7] Huisgen, R. *Angew. Chem.* **1970**, *82*, 783–794; *Angew. Chem., Int. Ed.* **1970**, *9*, 751−762.

calculated from the averaged k_{rel} values shows the internal consistency of the data.

2-Bromothiazole is so reactive that the corresponding competition constant κ depended on the rate of mixing; therefore, it was not employed for the calculation of k_{rel} by the least-squares optimization.

Attempts to determine the relative reactivity of 2-bromopyridine by comparison with 4-chlorobromobenzene showed that the product ratio was strongly dependent on the reaction time. While at short reaction times 4-chlorophenylmagnesium halide was the major component, at longer reaction times, 2-pyridylmagnesium halide was the major product. The reason for this dependence is not clear, because independently synthesized 4-chlorophenylmagnesium halide did not react with 2-bromopyridine under the reaction conditions. Possibly, coordination of arylmagnesium halide to the pyridine-nitrogen activates 2-bromopyridine; as a result the exchange rate of 2-bromopyridine might increase with the degree of conversion.

In previous work,[6b] second-order rate constants for the reactions of two differently substituted bromobenzenes have been determined, and it was reported that multiplication with 6.0×10^{-6} M^{-1} s^{-1} converts the k_{rel} values (with $k_{rel} = 1.0$ for bromobenzene) into absolute second-order rate constants. With the relationship $\tau_{1/2} = 1/kc_0$ (k = second-order rate constant, c_0 = initial concentration), we have calculated the half-reaction times listed in Figure 1 for the bromine−magnesium exchange in THF solutions which are 1 M in bromoarene and 1 M in *i*-PrMgCl•LiCl.

To determine the effect of LiCl on the exchange rates quantitatively, we have studied the kinetics of the reaction of 3-bromobenzo[*b*]thiophene with *i*-PrMgCl in the absence of LiCl. From $k_2 = 1.78 \times 10^{-4}$ M^{-1} s^{-1} one can derive that the reaction with *i*-PrMgCl is approximately 19 times slower than that with *i*-PrMgCl•LiCl, and the half-reaction time of a solution that is 1 M in *i*-PrMgCl and 3-bromobenzo[*b*]thiophene is 1.5 h. While in this case the use of LiCl-activated *i*-PrMgCl is still favorable for achieving complete conversion (>98%) within 4 h, the LiCl additive does not appear to be necessary for the magnesiation of the upper four compounds of Figure 1.

As shown in Figures 1 and 2, 2-bromothiazole is by far the most reactive bromoarene investigated in this study. With an estimated half-reaction time of approximately 10^{-2} s it becomes clear why the reactivity of this compound determined by competition experiments is not well reproducible and the competition constant κ depends on the rate of mixing.[9]

Figure 2 illustrates that the 2-bromo-substituted five-membered heteroarenes, thiophene, furan, and pyrrole, are considerably more reactive than the corresponding 3-bromo derivatives. While 3-bromofuran and 3-bromothiophene react almost 10^2 times faster than bromobenzene, 3-bromo-*N*-methylpyrrole is even slightly less reactive than bromobenzene. Among the considerably more reactive 2-bromo-substituted derivatives, 2-bromothiophene sticks out with a k_{rel} value of more than 10^5 compared to bromobenzene. The 9-fold reactivity increase from 3-bromothiophene to 3-bromobenzo[*b*]thiophene corresponds to the previously reported annelation effect in the benzene series (1-bromonaphthalene is 5.5 times more reactive than bromobenzene).[6b]

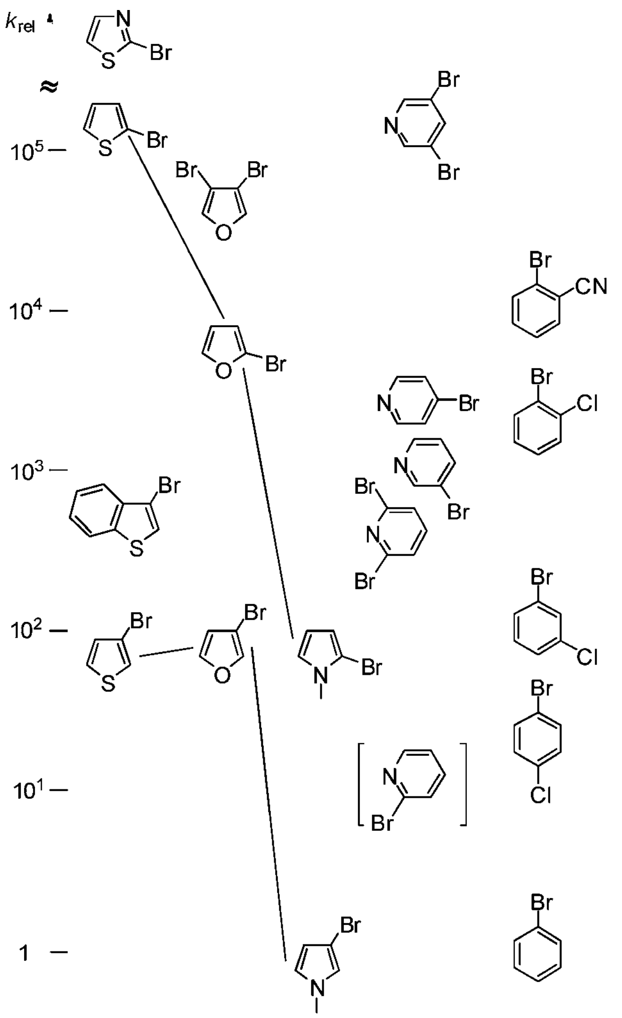
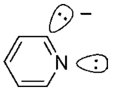


Figure 2. Relative reactivities of bromoheteroarenes toward *i*-PrMgCl•LiCl (0 °C, THF).

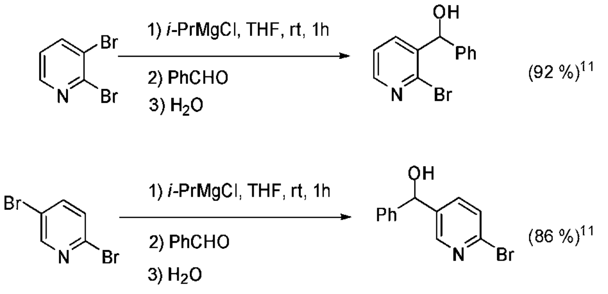
While 2-bromothiophene, 2-bromofuran, and 2-bromopyrrole are more reactive than the corresponding 3-isomers, 2-bromopyridine is considerably less reactive than the 3- and 4-bromopyridines. The reactivity order 2-bromopyridine ≪ 3-bromopyridine < 4-bromopyridine reflects the equilibrium mixture of deprotonated pyridines in the gas phase, which contains 70−80% of 4-deprotonated, 20−30% of 3-deprotonated, and 0% of 2-deprotonated pyridine.[10a] As discussed previously, repulsion between lone pairs may account for this finding.[10]



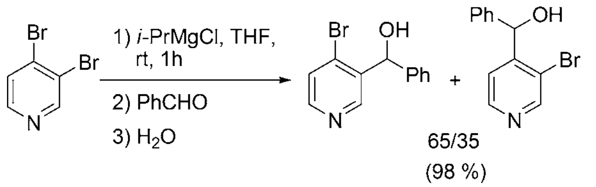
2,6-Dibromopyridine as well as the other dibromo-substituted heteroarenes react much faster than the monobrominated derivatives, in line with the previously reported accelerating inductive effect of halogens in bromobenzenes.[6]

The relative reactivities shown in Figure 2 can be used to predict the regioselectivities of the bromine−magnesium exchange in multiply brominated substrates. Thus, Quéguiner's report that 2,3- and 2,5-dibromopyridines react selectively in the 3- and 5-position, respectively (Scheme 2),[11] is in line with the 10^2 times higher k_{rel} value of 3-bromopyridine compared to 2-bromopyridine.

Scheme 2. Regioselective Grignard Reactions of Dibromopyridines As Described by Quéguiner in Ref 11



Furthermore, the product ratio reported for the functionalization of 3,4-dibromopyridine (eq 3)[11] is in agreement with the similarity of the k_{rel} values of 3-bromopyridine and 4-bromopyridine, though the k_{rel} values of Figure 1 as well as the relative gas phase acidities of these two positions[10a] suggest a slightly preferred exchange of the 4-bromine atom.



(3)

Analogous regioselectivities hold for the bromine−lithium exchange, as shown by the selective lithiation of 2,5-dibromopyridine in the 5-position by *n*-butyllithium.[10] However, because of subsequent isomerizations of lithiated halogenopyridines, the site of the initial bromine−lithium exchange is often not clear in these systems.[12]

In conclusion, competition experiments allowed us to derive the relative reactivities of heteroaryl bromides toward *i*-PrMgCl·LiCl in THF at 0 °C. It is found that most heteroarenes undergo the bromine−magnesium exchange reaction considerably faster than bromobenzene. While in the series of the five-membered heteroarenes furan, pyrrole, and thiophene, the 2-bromo derivatives are considerably more reactive than the 3-substituted isomers, the relative reactivities are opposite in the pyridine series, and 2-bromopyridine is much less reactive than 3- and 4-bromopyridine. Comparison with literature data on the reactivities of various dibromopyridines showed that the regioselectivities of the Br−Mg exchange in dibromopyridines can be predicted on the basis of the k_{rel} values listed in Figure 1. The most reactive compounds of this series, 3,4-dibromofuran, 2-bromothiophene, 3,5-dibromopyridine, and 2-bromothiazole, are so reactive that the 19 times less active *i*-PrMgCl (without LiCl) appears to be appropriate for the Br−Mg exchange reaction.

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Supporting Information Available: Experimental procedure and data for the determination of the relative exchange rates κ and determination of absolute rate constants. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) To obtain a consistent set of relative reactivities, the competition constants obtained in this work and the 58 competition constants reported previously have jointly been subjected to the least-squares minimization described in ref 6b. In this way, the seemingly separate blocks of k_{rel} in Figure 1 were tightly linked with each other. The consistency of competition constants derived by quenching with methanol or iodine proves that the method of quenching does not affect the results.

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