



RADICAL AROMATIC SUBSTITUTION VIA ATOM-TRANSFER ADDITION

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Abstract: New methodology for radical aromatic substitution has been developed involving the addition of electron-deficient radicals to unprotected pyrroles and indole. This non-oxidative process is presumed to be occurring via atom-transfer addition of suitable organoiodides and bromides with subsequent non-radical elimination of HI or HBr, respectively. The process also occurs under stannane-free conditions. © 1999 Elsevier Science Ltd. All rights reserved.

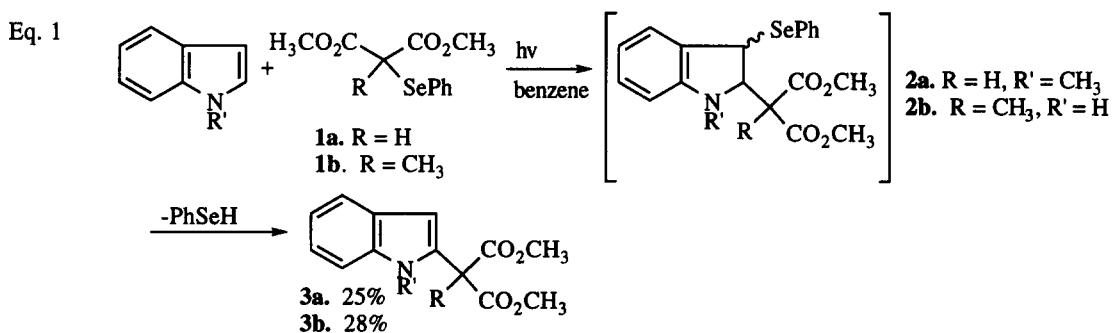
The process of radical aromatic substitution for hydrogen has long been known as a means of appending substituents to aromatic rings, but has seen modest use as a general synthetic tool, due to the limitations of the existing methodology. This is a process of obvious value, given the ubiquitous nature of aromatic and heteroaromatic ring systems in important synthetic targets. The most generally useful current methodology for radical aromatic substitution involves a non-chain sequence of radical addition followed by oxidation, typically with Fe, Ce or Mn salts, and subsequent proton loss. For example, acetone,¹ nitromethane,² or malonate esters³ can be added to benzene or substituted benzenes in this fashion. Malonate esters can only be used if substituted on the reactive carbon with one non-hydrogen functionality in order to inhibit overoxidation leading to decomposition.^{3,4} This reaction is characterized by mediocre yields in cases where electron donating groups are absent from the aromatic ring, and poor regioselectivity, with mixtures consisting of *o*, *m*, and *p* isomers obtained. Methodology of this type has also seen some use for the synthesis of aromatic heterocycles. While it is reasonably effective when using sulfur and oxygen heterocycles, nitrogen heterocycles such as indole or pyrrole require electron-withdrawing substituents in order to avoid oxidative decomposition⁵, thus further limiting its application.

The most general methodology for transformations of this type, which will provide the benchmark for comparison with our research, is recent oxidative substitution methodology developed by Baciocchi.⁶ This methodology uses an alkyl iodide as a radical precursor, as well as H₂O₂, DMSO and Fe(II), or alternatively, Et₃B and O₂. While this methodology works reasonably well with most simple nitrogen heterocycles, it is still dependent upon the use of oxidizing conditions, and in examples where lower yields are observed this may have been problematic. There are also problems with overalkylation, with a 15-20 fold excess of pyrrole required in order to minimize formation of a product arising from substitution of 2 equivalents of the radical.

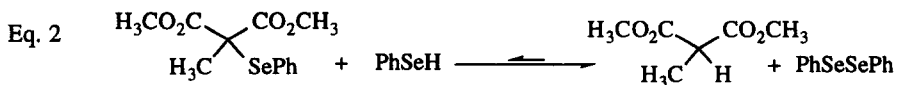
We envisioned that a sequence of events involving radical atom transfer addition of an organoselenide or organohalide, followed by spontaneous loss of HSePh, HBr, or HI, respectively, would lead to net substitution at the arene. This process would effectively create a carbon-arene bond concurrent with addition of the leaving group necessary for subsequent elimination and regeneration of aromaticity. Tandem reactions involving an

atom-transfer addition reaction accompanied by an exothermic non-radical reaction utilizing the transferred halogen atom are quite rare, and it has been noted that the second, non-radical step may be used to drive thermoneutral or endothermic radical processes to completion.⁷

Phenylselenomalonates were initially chosen for this purpose, given our concerns that the HI or HBr generated in the course of this reaction with the corresponding organohalides might prove deleterious to the reaction. Photolysis of phenylselenomalonates in the presence of an excess of indole led to the desired substitution products in poor yield after 48 h. (Eq. 1) Two isomeric products, corresponding to the stereoisomers of the proposed initial addition product **2a**, were observed at long retention times in the GC/MS (*m/e* 404, *M*⁺). Unfortunately, we were unable to isolate and more fully characterize **2a** prior to elimination of PhSeH. Comparably poor yields were obtained for the reaction of phenylselenomalonates with *N*-methylindole and benzothiophene substrates. While product yields were poor, the reaction proceeded quite cleanly, with significant quantities of unreacted selenide and indole present in the crude reaction mixture, even upon photolyses of a week or longer, indicating that some inhibitor of the radical chain reaction was being generated in the reaction mixture.



No PhSeH was detected in the crude reaction mixture, but significant quantities of PhSeSePh were observed. The PhSeH which is liberated in the course of completed substitution reactions apparently reacts with unreacted phenylselenomalonate to generate the diselenide and malonate.⁸ (Eq. 2) The same products were obtained by adding PhSeH to dimethyl phenylselenomethylmalonate in the absence of indole or photolysis. Previous experiments have shown that while a trace of PhSeSePh does not adversely effect phenylselenide transfer radical addition reactions, larger quantities do act as a radical chain suppressant.⁹



Recognizing the inherent limitations of phenylselenides for our desired transformation, we turned our attention to organohalides. Curran has shown that a substoichiometric quantity of Bu₃SnSnBu₃ is required in iodine-transfer radical addition reactions in order to consume I₂, a radical chain suppressant which is generated as a byproduct of these reactions.¹⁰ We also chose to add propylene oxide as an HI trap. The use of NEt₃ or borohydride exchange resins for this purpose in similar reactions has also been reported.⁷ Initial reactions of ethyl iodoacetate with an excess of pyrrole in the presence of propylene oxide and Bu₃SnSnBu₃ led to the desired substitution product **4** in 43% yield, in addition to an undetermined quantity of ethyl phenylacetate (Eq. 3), indicating reactivity with the benzene solvent under the reaction conditions. After surveying several potential solvents, we found that the less toxic solvent methyl *t*-butyl ether (MTBE) provided **4** in improved (64%) yield.

We were also interested in developing this methodology as a stannane-free radical process, given the well documented challenges entailed in the removal of trialkyltin halide byproducts,¹¹ and found that the addition of $\text{Na}_2\text{S}_2\text{O}_3$ as an I_2 reductant in the presence of the phase-transfer catalyst $\text{Bu}_4\text{N}^+\text{Br}^-$ to aid in thiosulfate solubility provided an effective alternative to the use of distannanes. After completion of this work, the use of AIBN for this purpose was reported.^{7a} Under these conditions, a 90% yield of substitution product **4** was obtained after simple Kugelrohr distillation of the crude reaction mixture. (Eq. 4) In contrast, the Baciocchi⁶ oxidative methodology generates a 59% yield of the corresponding methyl ester. The addition of other alkyl iodides and bromides to indole or pyrrole under these conditions is shown in Table I.¹² All yields shown are for products isolated by flash chromatography (except where noted) which were pure by TLC and ^1H and ^{13}C NMR.

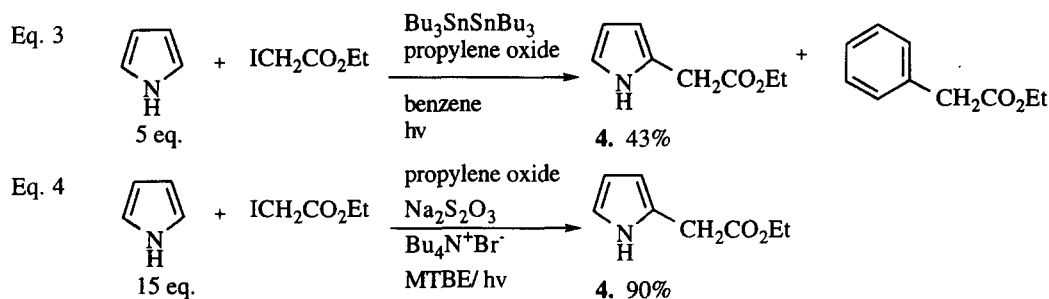


Table I.

Heterocycle	Halide	Product	Yield
15 eq. pyrrole	ICH_2CN		85% (Kugelrohr distillation)
15 eq. pyrrole	$\text{ICH}_2\text{CONH}_2$		82%
15 eq. pyrrole			84%
	$\text{ICH}_2\text{CO}_2\text{Et}$ 3 eq.		22%
5 eq. indole	$\text{ICH}_2\text{CO}_2\text{Et}$		36%
5 eq. indole			65%

Regioselectivities in all cases but one were outstanding with barely detectable (by GC/MS) and non-isolable quantities of other isomeric products being formed. At least 5 isomeric products were obtained in the course of the reaction between ethyl iodoacetate and indole. The yield shown is that for the pure major isomer.

Significant quantities of a substance with the molecular weight of the HI addition product to propylene oxide (m/e 186, M^+) were detected in the GC/MS of the crude reaction mixtures when organoiodides were utilized, providing evidence that the propylene oxide was fulfilling its proposed role.

This methodology, like the Baciocchi oxidative substitution reactions, required a significant excess of the heteroaromatic substrate in order to maximize the product yield by suppressing the formation of dialkylated products, which were characterized solely by their molecular ions in the GC/MS. The reaction was attempted with 2,4-dimethyl pyrrole in order to assess the feasibility of carrying out this reaction with the heteroaromatic as limiting reagent when the presumed position of the unwanted second radical addition was blocked. No dialkylation products were obtained in this case. Whether the poor yield obtained was the result of the diminished rate of radical attack on the more highly substituted pyrrole, abstraction of a methyl hydrogen, or some other factor is not known.

In conclusion, we have illustrated a new approach to radical aromatic substitution on heteroaromatics which should prove at least complementary to existing methodology for this purpose, and may offer unique opportunities for radical transformations involving reagents which prove highly sensitive to oxidative conditions. The fact that these atom-transfer radical transformations can be carried out under a novel set of stannane-free conditions is also noteworthy. Further studies of the scope and limitations of this approach are underway.

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