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Synthesis of Multisubstituted Pyrroles from Doubly Activated Cyclopropanes Using an Iron-Mediated Oxidation Domino Reaction

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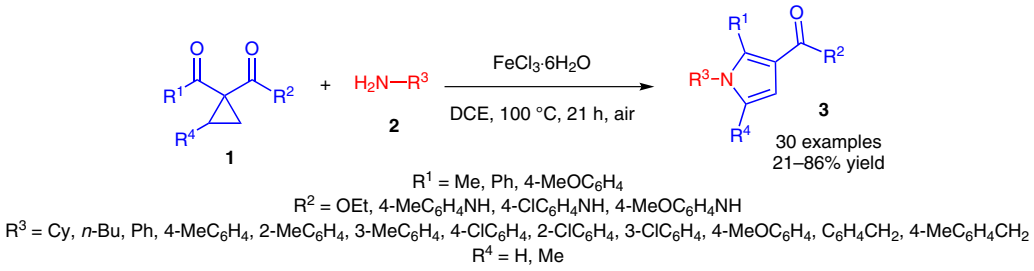
Iron-Mediated Synthesis of Pyrroles from Cyclopropanes



R^1 = Me, Ph, 4-$MeOC_6H_4$
R^2 = OEt, 4-MeC_6H_4NH, 4-ClC_6H_4NH, 4-$MeOC_6H_4NH$
R^3 = Cy, *n*-Bu, Ph, 4-MeC_6H_4, 2-MeC_6H_4, 3-MeC_6H_4, 4-ClC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-$MeOC_6H_4$, $C_6H_4CH_2$, 4-$MeC_6H_4CH_2$
R^4 = H, Me

Significance: The synthesis of highly substituted pyrroles **3** from cyclopropanes **1** and amines **2** via an iron-mediated sequential ring opening–cyclization–dehydrogenation reaction is reported. The conditions were optimized using different solvents, reaction times, and iron catalysts. The scope was studied and cyclopropanes **1** bearing methyl and aryl substituents at R^1 were tested with the latter giving better yields. EWG- and EDG-substituted aryl amines as well as R^2 = OEt were well tolerated. Also, a methyl group in the cyclopropane (R^4 = Me) was suitable, furnishing 1,2,3,5-substituted pyrrole **3** in good yield. A series of aromatic and aliphatic amines were screened as well: aliphatic amines furnished pyrroles **3** in low yields, while aromatic amines gave better results, although the yields decrease according to the position of the phenyl substituent. A reaction mechanism involving a radical process was suggested based on radical trapping experiments.

Comment: Cyclopropane derivatives can be used as precursors to synthesize a variety of useful heterocyclic motifs (C. A. Carson, M. A. Kerr *Chem. Soc. Rev.* **2009**, *38*, 3051; J. R. Green, V. Snieckus *Synlett* **2014**, *25*, 2258). The present work reports an efficient synthesis of tri- and tetrasubstituted pyrroles in moderate to good yields from readily available cyclopropanes and amines. The reaction shows a broad substrate scope; both EWG and EDG in **1** and **2** affording pyrroles **3** in comparable yields. While anilines with different patterns of substitution furnished **3** in good yields, a large excess of amine was required when benzylamines were used. The readily available cyclopropanes can be easily prepared in high yields by the reaction of a dicarbonyl compound with 1,2-dibromoethane (Z. Zhang et al. *Angew. Chem. Int. Ed.* **2007**, *46*, 1726).

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