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Iodine-Mediated Electrophilic Cyclization of 2-Alkynyl-1-methylene Azide Aromatics Leading to Highly Substituted Isoquinolines and Its Application to the Synthesis of Norchelerythrine

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Category

Synthesis of Heterocycles

Key words

isoquinolines

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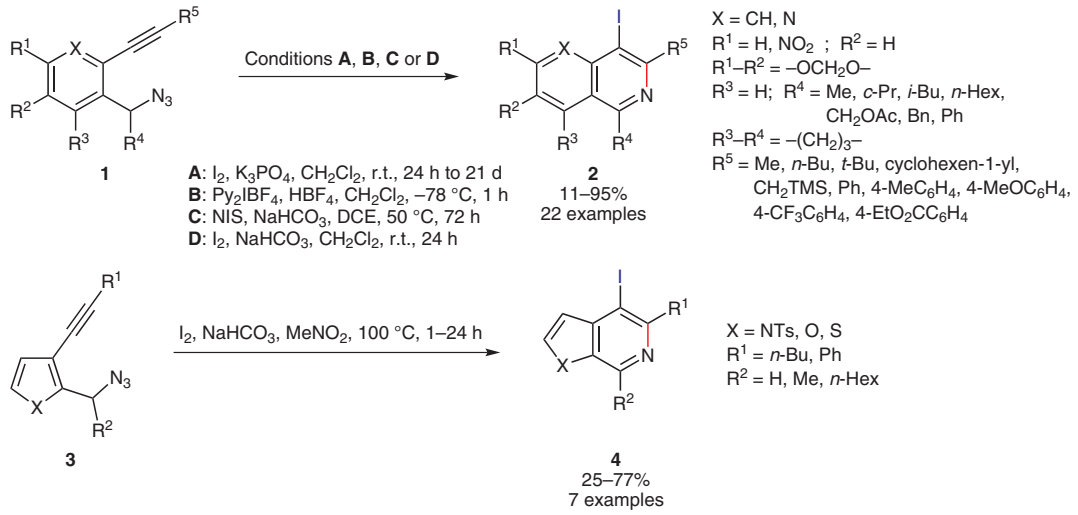
azides

Synthesis of Isoquinolines by I_2-Mediated Electrophilic Heteroannulation



Significance: Reported here is the synthesis of highly substituted isoquinolines **2** via the iodine-mediated electrophilic cyclization of 2-alkynyl-1-methylene azido arenes **1**. Several sets of conditions were identified using different iodonium sources, depending on the reactivity of the substrate. Both electron-donating and -withdrawing groups are equally tolerated on the aromatic ring, although electron-neutral and -donating groups are clearly favored at the alkyne terminus. The reaction was extended to include heterocyclic substrates including pyridines, pyrroles, furans and thiophenes **3**, to give the corresponding isoquinolines in poor to excellent yield. The utility of this methodology was further demonstrated by the short synthesis of the potent antitumor agent norchelerythrine. A plausible mechanism involving formation of an iodonium species that is intercepted by the azido group, followed by aromatization on loss of N_2 is suggested.

Comment: Isoquinolines are common motifs both in natural products and pharmaceuticals (see Book below). Classical methods for the synthesis of isoquinolines such as the Pomeranz–Fritsch reaction often involve harsh conditions and exhibit poor functional group tolerance. Although recent transition-metal-catalyzed conditions developed by Larock and co-workers (*J. Org. Chem.* **2003**, *68*, 920; *J. Org. Chem.* **2003**, *68*, 980) allow efficient synthesis of 3,4-disubstituted isoquinolines, C-1 substituted derivatives are not available by this methodology. The current method represents a general and flexible approach to highly substituted isoquinolines bearing an iodo group at the 4-position suitable for further functionalization. Functional group tolerance is high by virtue of the availability of three distinct sets of conditions employing acidic, basic or neutral media.

Book: M. Álvarez, J. A. Joule, In *Science of Synthesis*, Vol. 15; D. Black, Ed.; Georg Thieme Verlag: Stuttgart, New York, **2004**, 661-838.

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