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AN INTRAMOLECULAR PASSERINI REACTION: SYNTHESIS OF HYDRASTINE.

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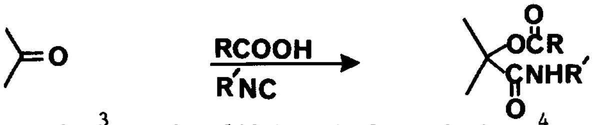
Summary: An intramolecular Passerini reaction between 3,4-methylenedioxyphenethylisocyanide and opianic acid is applied in a total synthesis of hydrastine, a phthalideisoquinoline alkaloid.

In a reaction which today bears his name, Passerini observed[1] isonitriles combine with carbonyl compounds and carboxylic acids in a three-component addition to afford α-acyloxycarbonamides (eq 1). The over-all process transforms a formally divalent carbon to a tetravalent carbon by α-addition of both an electrophile and nucleophile, creates a new carbon-carbon bond, and establishes a function group combination which can be exploited for further chemistry. Intrigued by the synthetic potential of the Passerini reaction, we accordingly initiated studies of an intramolecular variant[2] which we describe here.

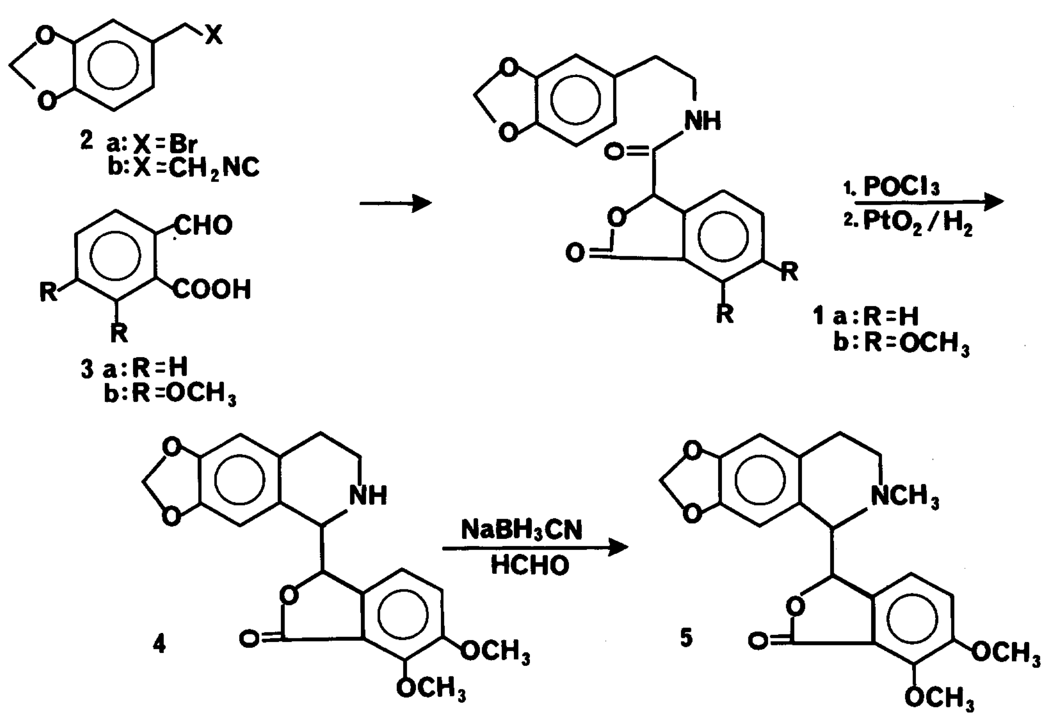


(1)

Our analysis of approaches[3] to phthalideisoquinoline alkaloids[4] focussed on the frequently troublesome preparation of the key lactonic amide intermediate 1 which is readily converted to tetrahydroisoquinoline by Bischler-Napieralski cyclization and reduction. We recognized that lactonic amides of type 1 are also accessible from phenethylisocyanides by a Passerini reaction if the carbonyl and carboxylic acid components are appropriately situated for intramolecular participation. The application of this strategy to phthalideisoquinolines is shown below in an efficient total synthesis of hydrastine.

Alkylation[5] of α-lithiomethylisocyanide with piperonyl bromide 2a at -78° for 1 hr then warming to 0° gave 2b (88%) as a colorless oil[6] [nmr ($CDCl_3$,δ): 2.84 (t,2H), 3.53(t, 2H), 5.90 s, 2H), 6.56 - 6.80 (m, 3H); ir (νmax) 2140 cm^{-1}]. Isonitrile 2b (1.5 mmol) in 10 ml anhydrous methylene chloride was added dropwise to an equal molar amount of 2-carboxybenzaldehyde 3a in 6 ml methylene chloride and stirred for 3 h. Chromatographic isolation furnished 1a (78%), mp 111-12° (MeOH) [nmr ($CDCl_3$,δ): 2.63 (t,2H), 3.32 - 3.62 (m, 2H), 5.86 (s, 2H), 6.13 (s, 1H), 6.34 - 6.78 (m, 3H), 7.06 -8.22 (m, 4H); ir (νmax) 3420, 1745, 1690 cm^{-1}].

Reaction of 2b with opianic acid[7] 3b under identical conditions yielded 1b (71%), mp. 147-8° (lit.[8]148°). The synthesis of hydrastine was completed by cyclization with phosphorus oxychloride in acetonitrile and reduction over Adams' catalyst to give norhydrastine[8] 4. N-methylation with sodium cyanoborohydride and formalin afforded (±)-hydrastine 5 (58% from 1b) as an approximately equal mixture of interconvertable[4] α-and β-isomers identical with authentic material.



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References and Notes

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