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Synthesis of 5,6-Dihydro-4*H*-pyrido[3,2,1-*jk*]carbazoles *via* Intermolecular [4+2] Cycloaddition

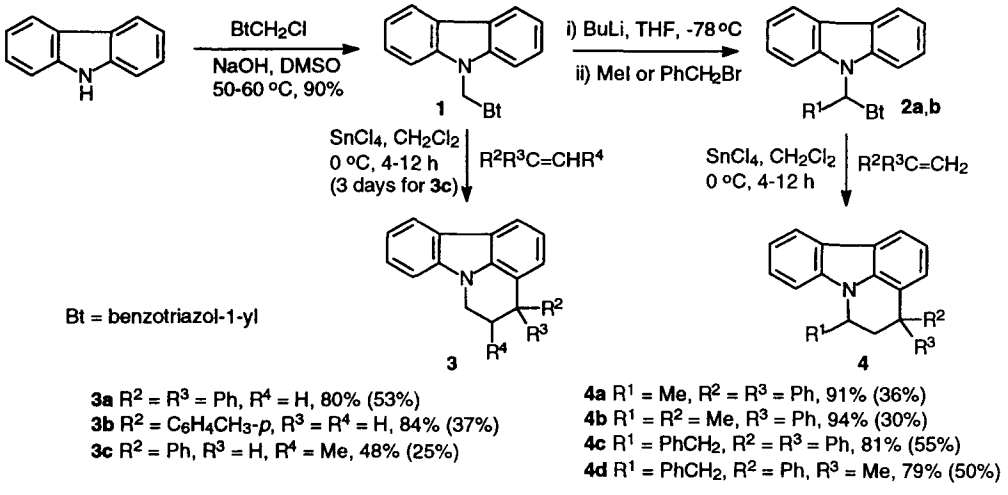
Alan R. Katritzky,* Guifen Zhang, Ming Qi, and Linghong Xie

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, FL 32611-7200

Abstract: 4-, 4,5- and 4,6-Substituted 5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazoles are synthesized regioselectively from carbazole by a novel, two step sequence. © 1997 Elsevier Science Ltd.

Many substituted carbazoles are natural products and/or biologically active, and the development of new synthetic methodologies for carbazoles and fused-ring derivatives has received considerable attention, with numerous routes reported.[1,2] The relatively few methods available for the synthesis of 5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazoles include (i) intramolecular Diels-Alder reactions of 3-vinylindoles,[3,4] (ii) Fisher indole syntheses starting from tetrahydroquinolines,[5] (iii) photolytic cyclization of *N*-aryltetrahydroquinolines,[6] and (iv) Lewis acid catalysed dimerization of *N*-vinylcarbazoles.[7] These four routes are all multistep and often utilize severe reaction conditions and/or lack generality. Recently, we demonstrated that various *N*-(*N*-arylaminomethyl)benzotriazoles, as masked iminium cations, react readily with alkenes to form a new six-membered ring.[8,9] Herein, we adopt an analogous approach for the construction of the pyridine ring in novel two step syntheses of 4-mono-, 4,4-di-, 4,5-di-, and 4,6-di-substituted 5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazoles from carbazole itself.

1-(Carbazol-9-ylmethyl)benzotriazole **1** was prepared as before[10] from carbazole on a large scale and in good yield. We now show that compound **1** reacts with both terminal and internal alkenes in the presence of tin chloride ($SnCl_4$, 1 equiv) to afford 4- and 4,5-substituted 5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazoles **3a-c** regioselectively under moderate conditions (Scheme 1).[11] To obtain analogs **4a-d** containing an additional substitutent adjacent to the nitrogen atom, compound **1** was lithiated and then reacted with alkyl halides to produce 1-[(carbazol-9-yl)alkyl]benzotriazoles **2a,b**.[10] Intermediates **2a,b**, without isolation, were reacted with alkenes under the same conditions to give 4,6-substituted 5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazoles **4a-d** regioselectively. The results are summarized in Scheme 1. We experienced difficulties in the purification of carbazoles **3** and **4** (as did previous researchers[4,6]); however, we were able to isolate the pure compounds **3a-c** and **4a-d** (all are novel and gave satisfactory ^1H and ^{13}C NMR spectra, and microanalyses or HRMS) in moderate yields by a neutral alumina column. Scheme 1 reports both crude yields (calculated from the amount obtained and the purity according to GC or ^1H NMR) and isolated yields (in blackets, all starting from compound **1**). The crude products from our reactions were all > 80% pure by GC or NMR.



3a $R^2 = R^3 = Ph$, $R^4 = H$, 80% (53%)
3b $R^2 = C_6H_4CH_3$-*p*, $R^3 = R^4 = H$, 84% (37%)
3c $R^2 = Ph$, $R^3 = H$, $R^4 = Me$, 48% (25%)

4a $R^1 = Me$, $R^2 = R^3 = Ph$, 91% (36%)
4b $R^1 = R^2 = Me$, $R^3 = Ph$, 94% (30%)
4c $R^1 = PhCH_2$, $R^2 = R^3 = Ph$, 81% (55%)
4d $R^1 = PhCH_2$, $R^2 = Ph$, $R^3 = Me$, 79% (50%)

Scheme 1

In conclusion, we have developed a new intermolecular [4+2] cycloaddition reaction for the synthesis of 5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazoles. This methodology employs readily available starting materials and uses a simple procedure.

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11. A representative experimental procedure is as follows: compound **1**, alkene and stannic chloride were mixed in CH_2Cl_2 at 0 °C and stirred for 4-12 h. After a basic (5% NaOH) aqueous work-up and extraction, the crude product was checked by NMR and GC/MS; the pure compound was isolated by a neutral alumina column. In the cases of **4a,b** (reactive alkenes as substrates), $ZnBr_2$ (2 equiv) was used instead of $SnCl_4$, and products were isolated by silica gel columns. The ratios of diastereomers **4b** (1:1) and **4d** (66:34) are determined by GC and ^1H NMR. Compound **3c** is a single *trans*-isomer (*cf.* ref 9).

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