

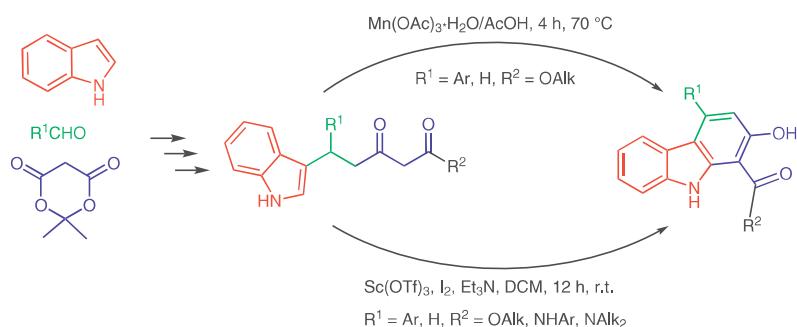
Transition-Metal-Promoted Oxidative Cyclization To Give 1,2,4-Trisubstituted Carbazole Scaffolds

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Abstract Herein, we describe the synthesis of a 1,2,4-trisubstituted carbazole core from 5-(1*H*-indol-3-yl)-3-oxopentanoic acid esters or amides. For oxidative cyclization, we tested two different approaches. First, we used manganese triacetate as a conventional moderate oxidizer to ensure the radical course of the reaction. Second, we examined the use of a more complex oxidizing agent $\text{I}_2/\text{Me}(\text{OTf})_3$. In both cases, formation of a fused-ring carbazole system with a 2-hydroxyl and 1-carboxylic substituent were observed. In connection with the formation of an unexpected reaction intermediate, mechanistic aspects of the process were discussed.

Key words carbazole, oxidative cyclization, indole, 3-oxoester, transition metals

In many biologically active compounds, the carbazole system and structurally similar surrogates containing one saturated six-membered ring, play important roles as a scaffold. This structural motif can be found in various alkaloids,¹ such as pyrayaquinones,² murrayafolines;³ in active compounds against human papillomavirus infections;⁴ in HIV-integrase inhibitors;⁵ α - and β -adrenoreceptor ligands;⁶ in antagonists of the prostaglandin receptor;⁷ and in antitumor agents such as aspidosperma alkaloids exemplified by vincristine and vinblastine;⁸ and the antiemetic ondansetron.⁹

Given the broad application of compounds containing the carbazole group, a significant number of synthesis methods to access this scaffold have been developed. A frequently used approach requires the formation of a five-membered heterocyclic ring for the synthesis of carbazole derivatives; thus, the most popular approaches are variations of the Fischer indole synthesis with the hydrazine derivative as a key intermediate,^{6,10} the closing of the pyrrole ring through the palladium-mediated Heck reaction,¹¹ and

the formation of the central ring via oxidative coupling (Figure 1).¹² A less explored approach is the formation of the A ring on the existing indole moiety during the synthesis of carbazole-like compounds.

In 1994, Chuang et al. described oxidative radical cyclization using manganese(III) acetate and *N*-aroylindoles with the subsequent insertion of the malonic moiety into the newly formed ring.¹³ Based on these results, Kerr et al. used *N*-acyl indoles containing a 1,3-dicarbonyl moiety at the end of the alkyl side chain to perform oxidative radical cyclization, leading to the formation of mersicarpine and tronocarpine alkaloids, also with manganese(III) acetate as an oxidizer.¹⁴ Malonyl derivatives of indole were oxidized by the $\text{Mn}(\text{acac})_3$ complex or under rare-metal-free conditions using oxygen under UV irradiation in the presence of CaI_2 .¹⁵ Stephenson performed the cyclization of *N*-alkyl indoles using a photocatalyzed process in the presence of a ruthenium complex.¹⁶ Moreover, 3-substituted and *N*-carboethoxy protected indoles were cyclized to (+)-subincanadine F alkaloid using cerium(IV) ammonium nitrate (CAN) as an oxidizer.¹⁷ Another approach for the cyclization of the third ring assumed the formation of carbenes as reactive intermediates via rhodium-catalyzed decomposition of α -diazo- β -keto esters.¹⁸ France et al. described a modification of this method, in which the α -diazo moiety was converted into the cyclopropyl ring. This ring then underwent cyclopropane ring opening when reacted with In(III) Lewis acid catalyst, followed by subsequent Friedel-Crafts alkylation of the indole ring, leading to a new six-membered ring.¹⁹

In this study, we present an alternative approach for the development of carbazoles and tetrahydro-carbazoles. We focused our research efforts on the cyclization of 5-(1*H*-indol-3-yl)-3-oxopentanoic acid derivatives **4aa–ad** and 5-(1*H*-indol-3-yl)-5-aryl-3-oxopentanoic acids derivatives **4ba–cb**, which were easily accessible from acyl Meldrum's acids **3a–c** (Scheme 1).²⁰ In the case of **4aa–ad** with $\text{R}^1 = \text{H}$,