Abstract

Given the ambident reactivity of oxindoles in terms of N- versus C-alkylation, realization of the three points of diversity available to (presumably benzenoid substituted) benzylidene oxindoles is normally achieved via a sequence involving initial N-alkylation of the corresponding isatin precursor, reductive deoxygenation to the N-alkylated oxindole, and finally aldol condensation to the desired target. Since benzenoid substituted isatins are generally more readily available than the corresponding oxindoles, an alternate but much less examined manifold involves reduction of the isatin to an oxindole, aldolization at the C-3 position followed by N-alkylation of the resultant benzylidene oxindole. Since benzylidene oxindoles have potential beyond that of kinase inhibitors (which have a strict requirement of a free N-H moiety) one of the goals of our research program has been to develop a method for N-alkylation of benzylidene oxindoles for a variety of pharmaceutical as well as imaging purposes. An overarching stratagem of this design concept was to achieve this goal through a libraries from libraries approach, wherein sub-libraries of precursor compounds can be prepared and screened for alternative applications before subjecting these compounds to further elaboration for subsequent screens in terms of other applications. The key reaction process detailed herein involving the N-alkylation of benzylidene oxindoles is a reaction that has seen only limited usage and sometimes only as the first step in a multi-step sequence (without isolation or characterization of the initial alkylated product). This study demonstrates the effectiveness of KF/alumina as a base for this purpose and the application of the methodology for the introduction of linker groups for use as potential imaging agents.