Efficient Metal-free and Chemoselective NHC catalyzed N1/C3-Functionalization of Diverse Isatins as Pharmaceutical Ingredients

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An eco-friendly N-Heterocyclic Carbene (NHC) organocatalysis can control the N1-functionalization (aza-Michael addition) and C3-functionalization (Morita–Baylis–Hillman reaction, MBH) of isatins in the absence of (1) protecting group, (2) stoichiometric reagent, and (3) heat energy. The challengeable N1-functionalization of N-unsubstituted (NUS) isatins into N-substituted (NS) isatins was realized through 10 mol % NHC and 10 mol % 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalysts within 10 min with up to 98 % isolation yield. The subsequent MBH adducts of as-synthesized NS-isatins (N1/C3-functionalization) was perfectly acquired in our designed organocatalysis within 30 min with the superiority to C3/N1-functionalization (MBH/aza-Michael). For guiding the applying to versatile druggble isatin library, the NHC catalysis was compared with reported functionalization of isatins in the view of green chemistry principles including solvent scoring of ACS GCI pharmaceutical roundtable, E-factor, atom economy and so on.