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Article

Gold-catalyzed addition reaction between creatinine and isatin: A sustainable and green chemistry approach for the diastereoselective synthesis of 3-substituted-3-hydroxyisatins

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ABSTRACT

The aldolization of various isatins with creatinine under gold catalysis in water has been developed. The reaction is operationally simple as the products can be isolated by simple filtration without requiring tedious solvent extraction and column chromatographic techniques. The generality of this methodology is showcased through the reactions of a wide range of isatin derivatives with creatinine to afford the respective aldol products in excellent yields with complete *syn*-selectivity. The scope of this chemistry is further extended to a tandem reaction involving isatins, creatinine and malononitrile to afford multicomponent products in excellent yields with complete *anti*-selectivity. The antioxidant potency of the synthesized compound was assessed by a spectrophotometric method, which revealed that three compounds containing halogen atoms (**2c**, **2d** and **2e**) were the most active compared with the standard.

1. Introduction

The structural motif of 3-substituted-3-hydroxyisatin is present in several bioactive natural products as well as clinical drugs such as paratunamide A, CPC-1 and sporidesmin (Fig. 1) [1–3]. The medicinal properties of these compounds are derived from the C3 substituent and the absolute configuration of the chiral center [4]. The development of efficient and practical methods to prepare such compounds is of paramount importance and it is an active area of research in asymmetric catalysis [5–7]. One of the simplest preparative procedures for 3-substituted-3-hydroxyisatins is the catalytic addition of nucleophiles to readily available isatins, which grants access to appealing molecular scaffolds possessing quaternary carbon centers [8,9]. Furthermore, organic reactions employing water as a medium hold great promise from a green chemistry perspective [10]. For example, Dash *et al.* [11,12] have previously reported the water-catalyzed diastereoselective aldol reaction of thiazolidinediones with isatin and other aldehydes. As part of our ongoing interest in developing new methodologies for the synthesis of heterocycles [13–24], coupled with the reality that creatinine is present in numerous natural products [25], we envisaged the replacement of thiazolidinediones with structurally relevant creatinine in the aldolization of isatins. In 2010, Crooks *et al.* [26–29] reported the diastereoselective aldol addition of isatins with creatinine. However, this methodology

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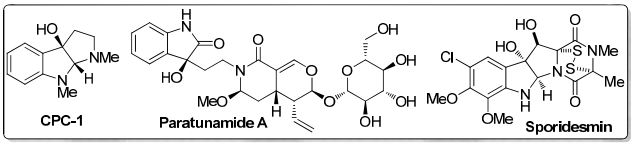

Fig. 1. Natural products containing a 3-hydroxyisatin scaffold.

suffers from the need to use $NaOOCH_3$ (NaOAc) and CH_3COOH (AcOH) in stoichiometric quantities, which prompted us to revisit this transformation with particular emphasis on performing the reaction under gold catalysis in water without compromising the diastereoselectivity. Herein, we report our study on the gold(III)-catalyzed diastereoselective aldol addition of isatins with creatinine under aqueous condition leading to 3-hydroxyisatin derivatives. In view of the extensive biological properties of 3-hydroxyisatins, all the compounds were screened for their free radical scavenging activity. The gold-catalyzed protocol was also extended to a three-component reaction between isatins, malononitrile and creatinine through a tandem condensation / conjugate addition.

2. Experimental

2.1. Materials, methods and instruments

Solvents and reagents were purchased from SRL chemicals, India Pvt. Ltd, India and were used without further purification. Melting points (m.p.) were determined in open capillary tubes and are uncorrected. Infrared (IR) spectra were recorded on a Jasco FT-IR spectrophotometer as KBr pellets. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ or DMSO-d_6 solutions on a Bruker spectrometer at 400 and 100 MHz, respectively. The proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) as internal standard and are expressed in parts per million (ppm). The spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet). The coupling constants (J) are given in hertz. Mass spectra were recorded on a PE-SCIEX API 3000 mass spectrometer. Elemental analyses were recorded using a ThermoFinnigan FLASH EA 1112CHN analyzer. All compounds gave C, H and N analysis within ±0.5% of the theoretical values. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany) using analytical grade solvents and visualized with iodine spray (10% (w/w) I_2 in silica gel) or UV light (λ = 254 and 365 nm). The absorbance was measured at 517 nm using a Systronics 118 model spectrophotometer.

*2.2. General procedure for the synthesis of compounds **2a**–**2p***

Water (15 mL) was added to a mixture of 1.0 mmol of isatin derivative, 1.2 mmol of creatinine (for **2p**, 2.3 mmol of creatinine) and 1 mol% of $HAuCl_4$ and the resulting suspension was heated to reflux for 30 min. The clear reaction mixture was cooled to 15–20 °C. The precipitated aldol product was filtered and washed with copious amount of water and then with methanol and ethyl acetate (EtOAc). The obtained product was thoroughly dried under vacuum to afford the pure product **2a**–**2p**.

3-Hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one (**2a**): Yellow solid; m.p. = 225–227 °C; IR (KBr): 3557, 3384, 3242, 2795, 1718, 1689, 1672, 1242, 755 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.14 (s, 3H, $-CH_3$), 4.04 (s, 1H, CH), 6.31 (brs, 1H, OH), 6.70–6.74 (d, J = 7.6 Hz, 1H, $-C_7H$), 6.81–6.88 (t, J = 7.6 Hz, 1H, $-C_6H$), 7.06–7.07 (d, J = 7.6 Hz, 1H, $-C_4H$), 7.17–7.20 (t, J = 7.8 Hz, 1H, $-C_5H$), 7.51 (brs, 2H, NH_2), 10.23 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 32.6, 69.4, 76.3, 109.5, 121.1, 123.9, 127.9, 129.3, 142.6, 171.8, 175.7, 182.3. MS (ESI): m/z = 261 $[M+H]^+$; Anal. Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.38%; H, 4.65%; N, 21.53%. Found C, 55.55%; H, 4.61%; N, 21.45%.

5-Fluoro-3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one (**2b**): Pale yellow solid; m.p. = 250–252 °C; IR (KBr): 3358, 3174, 3047, 2697, 1731, 1701, 1645, 1435, 806 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.14 (s, 3H, CH_3), 4.07 (s, 1H, CH), 6.52 (bs, 1H, OH), 6.70–6.75 (m, 1H, $-C_7H$), 6.80–6.84 (dd, J = 8.1 Hz, J = 2.37 Hz 1H, $-C_4H$), 6.99–7.06 (m, 1H, $-C_6H$), 7.51 (brs, 2H, NH_2), 10.28 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 32.2, 69.8, 76.5, 111.0, 124.2, 126.0, 129.9, 130.4, 141.9, 172.7, 175.8, 182.1. MS (ESI): m/z = 279 $[M+H]^+$; Anal. Calcd. for $C_{12}H_{11}FN_4O_3$: C, 51.80%; H, 3.98%; N, 20.14%. Found C, 52.09%; H, 3.92%; N, 20.05%.

5-Chloro-3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one (**2c**): Pale brown solid; m.p. = 267–269 °C; IR (KBr): 3384, 3177, 2782, 2672, 1731, 1707, 1618, 1586, 1083, 818 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.16 (s, 3H, CH_3), 4.07 (s, 1H, CH), 6.52 (brs, 1H, OH), 6.74–6.77 (d, J = 8.1 Hz, 1H, $-C_7H$), 6.99–7.00 (d, J = 2.4 Hz, 1H, $-C_4H$), 7.23–7.24 (dd, J = 8.1 Hz, J = 2.1 Hz, 1H, $-C_6H$), 7.55 (brs, 2H, NH_2), 10.39 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 32.8, 69.6, 76.3, 110.9, 123.9, 125.0, 129.1, 129.9, 141.6, 172.0, 175.3, 182.1. MS (ESI): m/z = 295 $[M+H]^+$, 297 $[M+H]^{2+}$; Anal. Calcd. for $C_{12}H_{11}ClN_4O_3$: C, 48.91%; H, 3.76%; N, 19.01%. Found C, 49.05%; H, 3.72%; N, 18.94%.

5-Bromo-3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one (**2d**): Brown solid; m.p. = 246–248 °C; IR (KBr): 3384, 3176, 2980, 2672, 1731, 1707, 1566, 1186, 818 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.16 (s, 3H, CH_3), 4.07 (s, 1H, CH), 6.53 (brs, 1H, OH), 6.70–6.73 (d, J = 8.1 Hz, 1H, $-C_6H$), 7.11 (s, 1H, $-C_4H$), 7.36–7.38 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H, $-C_7H$), 7.76 (brs, 2H, NH_2), 10.42 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 32.9, 69.6, 76.4, 111.5, 112.7, 126.6, 130.4, 132.0, 142.1, 172.1, 175.2, 182.1. MS (ESI): m/z = 339 $[M+H]^+$, 241 $[M+H]^{2+}$; Anal. Calcd. for $C_{12}H_{11}Br_4O_3$: C, 42.50%; H, 3.27%; N, 16.52%. Found C, 42.35%; H, 3.33%; N, 16.60%.

5-Iodo-3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one (**2e**): Dark brown solid; m.p. = 202–204 °C; IR (KBr): 3394, 3176, 2973, 2768, 1730, 1707, 1583, 1308, 1184, 817 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.17 (s, 3H, CH_3), 4.06 (s, 1H, CH). 6.44 (brs, 1H, OH), 6.66–6.71 (d, J = 8.4 Hz, 1H, $-C_6H$), 7.09 (s, 1H, $-C_4H$), 7.37–7.40 (dd, J = 8.2 Hz; J = 1.4 Hz, 1H, $-C_7H$), 7.13 (s, 1H, $-C_4H$), 7.44–7.49 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H, $-C_7H$); ^{13}C NMR (DMSO-d_6): δ 33.0, 69.8, 76.5, 111.5, 112.8, 126.9, 130.4, 132.2, 142.3, 172.5, 175.5, 182.6. MS (ESI): m/z = 387 $[M+H]^+$; Anal. Calcd. for $C_{12}H_{11}IN_4O_3$: C, 37.32%; H, 2.87%;