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ORIGINAL ARTICLE

Silicotungstic acid ($H_4SiW_{12}O_{40}$): An efficient Keggin heteropoly acid catalyst for the synthesis of oxindole derivatives

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Abstract Condensation of various isatins with heteroaromatics (indoles and pyrrole) has been carried out in the presence of catalytic amount of silicotungstic acid (STA) at room temperature to form their corresponding 3,3-bis(indolyl)- and 3,3-bis(2-pyrrolyl)oxindoles. The mechanistic aspects of the reaction have also been discussed.

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1. Introduction

Isatin (2,3-dioxindole) identified as an endogenous compound in humans that has a range of biological properties including actions in the brain and offering protection against certain type of infections (Pandeya et al., 2005). Various derivatives of isatin are key motifs of natural product structures for example Convolutamydine A is an alkaloid which is isolated from marine bryozoan *amathia convoluta* has exhibited potent activity in differentiation of HL-60 human promyelocytic leukemic cells (Kamano et al., 1995). A well-known category of isatins are oxindoles which possess anti-convulsant natures including antibacterial, anti-inflammatory, antiprotozoal and mechanism-specific antiproliferative properties and also patented as PR (progesterone receptors) agonists (Pajouhesh et al., 1983). They can also be used as laxatives (Garrido et al., 1975). Much attention has been devoted to the preparation of oxindole rings because their systems are the core structures of many pharmacological agents. For example, Spiro[indole-thiazolidinones] possess antifungal activities against pathogens (Dandia et al., 2006) and Spirotryprostatine B as a natural alkaloid, showed anti-mitotic properties to get it in great interest as an anti-cancer drug (Sebahar and Williams, 2000). Isatins possess a reactive carbonyl group at 3-position that readily made them good electrophilic candidates to undergo condensation reactions with indoles to form 3,3-bis(indolyl)oxindole derivatives. The synthesis of natural 3,3-bis(indolyl)oxindole (**3a**) was first reported by Seidel in 1950. 3,3-Bis(indolyl)indoline-2-ones (3,3-bis(indolyl)oxindoles) showed anti-cancer properties (Kamal et al., 2010). During recent years some methods have been reported for the condensation of some electron-rich heteroaromatics such as indoles and pyrroles with isatins using catalysts such as silica sulfuric acid (SSA) (Azizian et al., 2006), $KAl(SO_4)_2.12H_2O$ (Azizian et al., 2004), ceric ammonium nitrate (CAN) (Wang and Ji, 2006), phosphotungstic acid ($H_6P_2W_{18}O_{62}$) (Alimohammadi

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et al., 2008), montmorillonite K10 clay (Chakrabarty et al., 2005), KSF (Nikpasand et al., 2010), ionic liquids (Karimi et al., 2011 and Rad-Moghadam et al., 2010), $FeCl_3$ (Kamal et al., 2010) and I_2 (Paira et al., 2009) to prepare the corresponding, 3,3-bis(3-indolyl)- and, 3,3-bis(2-pyrrolyl)oxindoles. Some of these strategies have shortcomings such as cost, reaction time, operational parameters and yield. Due to these deficiencies and also the significance of this class of compounds, offering new and efficient methods for their synthesis is still in demand. Heteropoly acids (HPAs) have been pointed out lately as versatile, environmentally benign, water tolerate, stable and green heterogeneous and homogenous catalysts for a variety of organic reactions (Okuhara, 2002). They contain lewis and strong bronsted acidity (Nandhini et al., 2004). Solid HPAs have discrete ionic structures that contain heteropolyanion (polyoxometalate) units and countercations that are H^+ (Kozhevnikov, 1998). This special structure exhibits high proton mobility while heteropolyanions stabilize cationic intermediates (Izumi et al., 1992). The best known HPAs are the Keggin type $H_{8-n}XM_{12}O_{40}$, where X is he central atom, n is the oxidation state of X and M is the metal ion. In the Keggin type HPAs, protons take part in the formation of the crystal structure by linking the neighboring polyoxometalate units (Kozhevnikov, 1998). Also HPAs possess bronsted acidity, but found to be efficient in catalyzing some reactions that conventionally use lewis acids such as Friedel–Crafts alkylation (Kamakshi and Reddy, 2007). Silicotungstic acid $H_4W_{12}SiO_{40}$ is one of the well-known Keggin types of HPAs. It has been used as an acid catalyst in some transformations such as bis(indolyl)methane synthesis (Rafiee et al., 2011), alkylation of benzene with olefins (Sawant and Halligudi, 2005), production of acrolein from glycerol (Tsukuda et al., 2007), indole Michael addition (Murugan et al., 2005) and 1,2-dihydroquinones (Kamakshi and Reddy, 2007). We wish now to report a new usage of silicotungstic acid as an impressive, inexpensive and easily handling acid catalyst for the synthesis of 3,3-bisoxindole derivatives *via* the condensation reaction of various isatins with indoles and pyrrole at room temperature.

2. Materials and methods

Isatins, indoles, pyrrole, STA and solvents were purchased from Merck, Aldrich and Alfa Aesar and used without further purification. N-Benzylisatin is synthesized from isatin according to the reported procedure (Azizian et al., 2003). Melting points were determined using a Stuart Scientific SMP2 capillary apparatus and are uncorrected. IR spectra were recorded from KBr disks on a Shimadzu IR-435. ^1H NMR spectra were recorded with a Bruker drx 500 (500 MHz) machine. Mass spectra were obtained on a Platform II spectrometer from Micromass; EI mode at 70 eV. Preparative layer chromatography (PLC) was carried out on $20 \times 20\ cm^2$ plates, coated with a 1 mm layer of Merck silica gel PF_{254}, prepared by applying the silica as slurry and drying in air.

2.1. General synthetic procedure for the synthesis of **3a–l**, **6** and **7**

To a solution of isatins **1a–e** (1 mmol) and indoles **2a–d** or **4** (2 mmol) or pyrrole **5** (3 mmol) in CH_3OH (5 ml) silicotungstic acid (0.1 mmol) was added. The mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion, the solvent was evaporated and the resulting crude residue was purified by chromatography on silica gel (eluent: *n*-hexane–ethyl acetate, 1:1) to afford the pure products (Table 2 and Scheme 2).

Some selected data are as follows:

2.2. 3,3-Bis(3-methylindolyl)-oxindole (**6**)

m.p. 255–258 °C, IR (KBr): υ = 3325 (NH), 1712 (CO), 1618, 1475, 1198, 676 (N-H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.05 (s, 6H, $2CH_3$), 6.97 (d, *J* = 7.35 Hz, 1H, Ar-H), 7.07–7.35 (m, 9H, Ar-H), 7.55 (d, *J* = 7.55 Hz, 2H, Ar-H), 8.13 (br s, 2H, NH), 8.21 (br s, 1H, NH) ppm. MS *m/z* (%) 391 (M^+, 18), 376 (M^+-CH_3, 13), 348 (M^+-CO and NH, 15), 332 (M^+-HCO and NH and CH_3, 4), 261 (M^+-3-methylindolyl, 20), 232 (M^+-3-methylindolyl and CHO, 20), 130 (3-methylindolyl$^+$, 100).

2.3. 3,3-Bis(2-pyrrolyl)-oxindole (7)

m.p. 173–175 °C, IR (KBr): υ = 3351 (NH), 3261 (NH), 1710 (CO), 1618, 1462, 1078, 738 (N-H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.02 (br s, 2H, Ar-H), 6.13–6.14 (m, 2H, Ar-H), 6.75 (s, 2H, NH), 6.94 (d, *J* = 7.74 Hz, 1H, Ar-H), 7.14 (t, *J* = 7.56 Hz, 1H, Ar-H), 7.28 (br s, 1H, NH), 7.29 (t, *J* = 7.88 Hz, 1H, Ar-H), 7.49 (d, *J* = 7.45 Hz, 1H, Ar-H), 8.67 (br s, 2H, NH) ppm. MS *m/z* (%) 263 (M^+, 53), 220 (M^+-CO and NH, 25), 153 (M^+-HCO and NH and pyrrolyl, 17), 65 (pyrrolyl$^+$, 100).

3. Results and discussion

To investigate the solvent nature on the reaction rate, the model condensation of indole and isatin was performed in various solvents and conditions. According to the data presented in Table 1, it seems that the polarity of the solvent is necessary, as the reaction in *n*-Hexane, a non-polar solvent candidate, did not progress (entry 1). Using polar solvents like $CHCl_3$, EtOAc, MeOH and EtOH, the model reaction promoted obviously. These observations lead that the solubility of the substrates is essential in reaction promotion. The polarity, dipole moment, and hydrogen bonding of a solvent are

Table 1 Solvent optimization of the reaction of indole (2 mmol) with isatin (1 mmol) in the presence of STA (0.1 mmol).

Entry	Solvent	Condition	Yield (%)[a] (Time (min)[b])
1	*n*-Hexane	RT	10 (70)
2	$CHCl_3$	RT	35 (70)
3	EtOAc	RT	40 (70)
4	MeOH	RT	96 (10)
5	–	70 °C	70 (50)
6	MeOH	50 °C	96 (10)
7	$EtOH/H_2O$ (4:1)	RT	80 (30)
8	CH_3CN	RT	85 (30)

[a] Isolated yields.

[b] Times are given after maximum progression of the reaction (TLC).

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