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ORIGINAL PAPER

Application of SBA-Pr-NH_2 as a nanoporous base silica catalyst in the development of 2,2-Bis(1*H*-indol-3-yl) acenaphthen-1(2*H*)-ones syntheses

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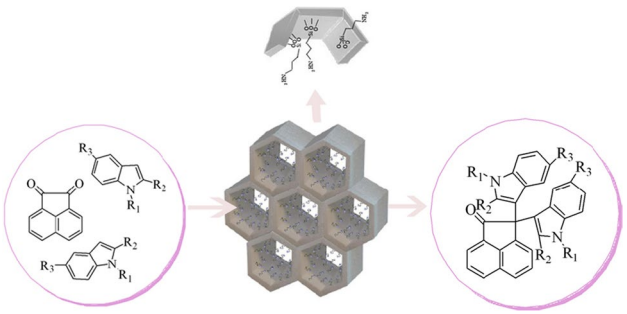
Abstract One-pot reaction for the synthesis of symmetrical 2,2-bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-one is reported by condensing acenaphthenequinone and indoles in the presence of catalytic amount of amino-functionalized silica (SBA-Pr-NH_2) under solvent-free conditions at 100 °C.

Graphical Abstract



Keywords Multi-component reaction · 2,2-Bis(1*H*-indol-3-yl)acenaphthen-1(2*H*)-ones · SBA-Pr-NH_2 · Nanoporous base silica · Indoles

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Introduction

Mesoporous solids such as amino-functionalized SBA-15 have unique features including high specific surface area, large pore volume, controllable and narrowly distributed pore sizes, biocompatibility, and low levels of toxicity [1, 2]. These ordered mesoporous materials have been reported to have potential applications in several areas such as adsorption [3], chromatography [4], drug delivery [5], and catalysis [6].

Indole frameworks have attracted attention of many chemists due to their pharmacological and biological activities [7–12]. Moreover, bisindolylalkanes (BIAs) are an important class of these bioactive compounds [13–19] whereas benzofuran-bisindole derivatives **1** have anti-hyperlipidemic activities [20]. Bisindole compound **2** inhibits the growth of both Gram-positive and Gram-negative bacteria [21], and bisindole derivatives of *Catharanthus* alkaloids have potential cytotoxic properties (Fig. 1) [22]. Also, a number of synthetic methods for preparation of bis(indolyl)alkane derivatives have been reported in the literature by the reaction of indole with various aldehydes and ketones [23–29].

Due to our interest in developing new synthesis in the field of nanocatalyst applications, herein we explore the catalytical activity of amino-functionalized silica (SBA-Pr-NH_2) as an eco-friendly, efficient and reusable catalyst (Fig. 2) to reduce reaction time and temperature in the synthesis of 2,2-bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-one derivatives. To date, condensation of acenaphthenequinone (**3**) and indoles (**4**) was performed under grinding condition [30] and in the presence of catalytic amount of ceric ammonium nitrate (CAN) [31] to produce 2,2-bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-ones.

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Experimental

General information

All chemicals were attained commercially and used without further purification. IR spectra were measured from KBr disk using a FT-IR Bruker Tensor 27 instrument. Melting points were established using the capillary tube method with an Electrothermal 9200 apparatus. The ^{1}H and ^{13}C NMR (100 and 500 MHz) was performed on a Bruker DPX using TMS as an internal standard. Gas chromatography–mass spectrometry (GC–MS) analysis was recorded on an Agilent 6890-5973 GC/MS detector.

SBA-15 nanoporous silica synthesis and functionalization

As previously reported [32, 33], pluronic P123 nonionic surfactant as a structure-directing agent and TEOS were utilized under acidic conditions for the synthesis of SBA-15. Moreover, the post-synthesis grafting method was utilized for surface modifications over the nanoporous silica with aminopropyl moieties [34].

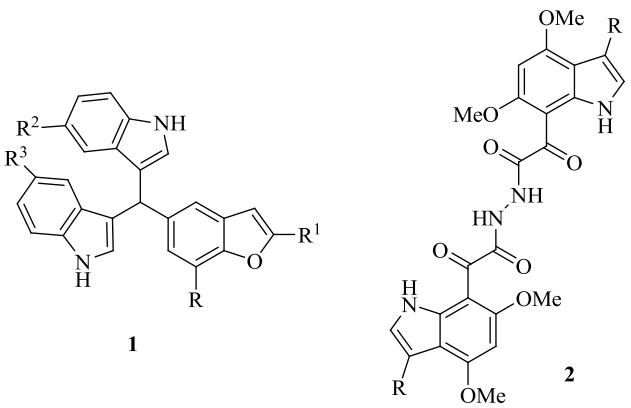


Fig. 1 Representative examples of bisindolylalkanes compounds

General procedure for the preparation of indole derivatives (4d-4 g)

Indoles (1 mmol), potassium carbonate (1.3 mmol), and the corresponding alkyl halide (1.1 mmol) were dissolved in DMF (5 ml) and heated under reflux at 100 °C. Upon completion of the reaction (monitored by TLC), the crude product was poured in iced water. The obtained solids were dissolved in ethyl acetate to give the crystal of pure products.

General procedure for the preparation of compound (5a-5i)

The SBA-Pr-NH_2 (0.02 g) was activated in vacuum at 100 °C and then after cooling to room temperature, acenaphthenequinone **3** (1 mmol) and indoles **4** (2 mmol) were added to it. The mixture was stirred under solvent-free condition at 100 °C for an appropriate time to produce 2,2-bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-one derivatives **5a**-**5i**. The completion of reaction was indicated by TLC, the resulting solid product was dissolved in hot ethyl acetate, filtered for removing the unsolvable catalyst and then the filtrate was cooled to give the pure yellow product. The spectroscopic and analytical data for compounds are offered in the following part. Finally, the recovered catalyst could then be reused after washing sequentially with diluted aqueous Et_3N solution, water, and acetone.

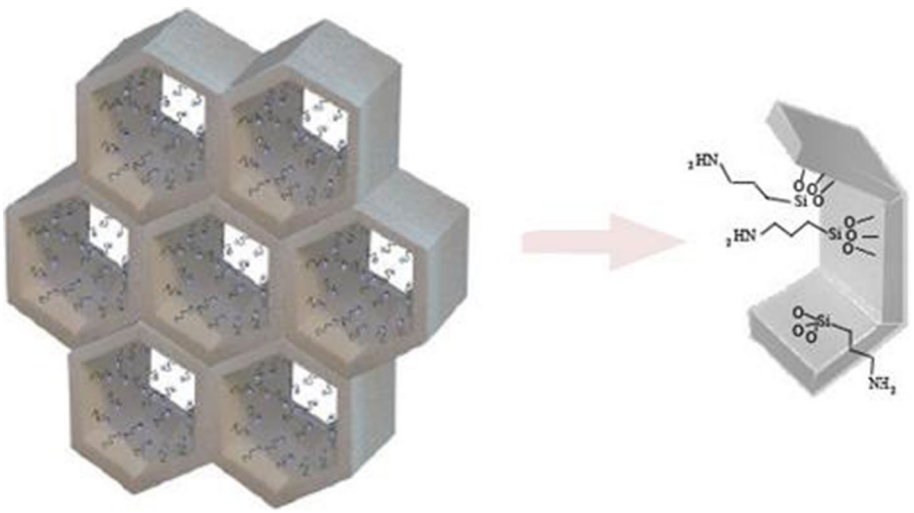
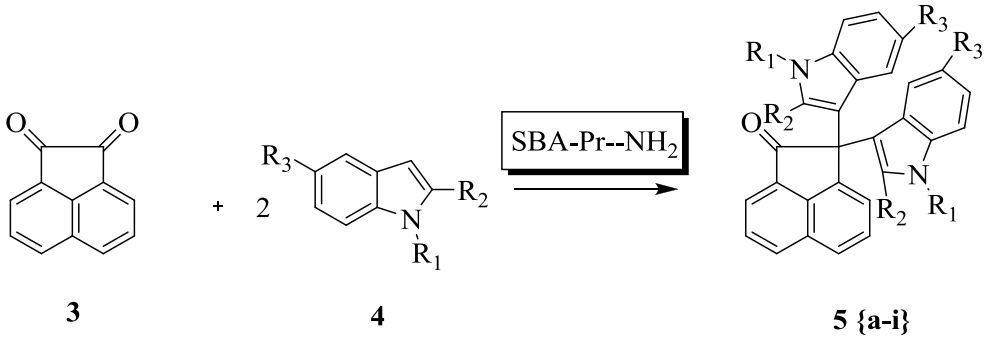


Fig. 2 Amino-functionalized silica (SBA-Pr-NH_2) as catalyst

Scheme 1 Synthesis of 2,2-bis(1*H*-indol-3-yl) acenaphthen-1(2*H*)-one derivatives (**5a-5i**) in the presence of SBA-Pr-NH_2



2,2-Bis(1-hexyl-1*H*-indol-3-yl)acenaphthylen-1(2*H*)-one (5e)

mp: 255–257 °C. IR [KBr, ν_{max} (cm^{-1})]: 3061, 2923, 2654, 1720 (C=O), 1597, 1275, 1013, 891, 777. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.01 (m, 6H, CH_3), 2.07–2.19 (m, 12H, CH_2), 2.50–2.60 (m, 4H, CH_2), 3.34 (m, 4H, CH_2), 6.78 (d, J = 7.6, 2H, Ar–H), 6.88 (t, J = 7.1, 3H, Ar–H), 6.98 (d, J = 6.9, 4H, Ar–H), 7.13 (td, 3H, Ar–H), 7.22 (m, 2H, Ar–H), 7.30 (s, 2H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2, 23.6, 27.1, 29.0, 30.5, 40.2, 60.3 (C-Spiro), 112.0, 112.6, 112.7, 125.7, 126.5, 129.2, 129.5, 129.5, 129.6, 129.8, 130.0, 130.2, 131.1, 133.4, 135.5, 135.9, 140.0, 139.5, 139.7, 189.7 (C=O). EI-MS: 566 (M^+), 442 (6), 332 (28), 299 (65), 282 (64), 270 (60), 254 (98), 182 (89), 154 ($C_{11}H_6O^{\bullet}$, 100), 126 ($C_{10}H_6^{\bullet}$, 90), 63 (24), 50 (15).

2,2-Bis(1-heptyl-1*H*-indol-3-yl) acenaphthylen-1(2*H*)-one (5f)

mp: 255–257 °C. IR [KBr, ν_{max} (cm^{-1})]: 3059, 2923, 1719 (C=O), 1598, 1306, 1013, 891, 831. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.50 (m, J = 1.7, 6H, CH_3), 2.98 (m, 16H, CH_2), 3.34 (m, 4H, CH_2), 3.51 (m, 4H, CH_2), 7.91–7.94 (m, 4H, Ar–H), 8.08 (d, J = 7.1, 6H, Ar–H), 8.44 (d, J = 8.3, 4H, Ar–H), 8.53–8.57 (m, 2H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 23.6, 27.4, 28.8, 30.2, 30.3, 42.2, 59.5 (C-Spiro), 112.2, 112.6, 112.8, 125.4, 126.4, 129.4, 129.6, 129.6, 129.7, 129.8, 129.9, 130.6, 131.1, 133.4, 135.6, 136.0, 139.0, 139.3, 139.5, 180.5 (C=O). EI-MS: 594 (M^+), 332 (12), 254 (10), 182 (68), 154 ($C_{11}H_6O^{\bullet}$, 100), 126 ($C_{10}H_6^{\bullet}$, 100), 74 (22), 50 (20).

2,2-Bis(1-octyl-1*H*-indol-3-yl)acenaphthylen-1(2*H*)-one (5 g)

mp: 258–260 °C. IR [KBr, ν_{max} (cm^{-1})]: 3059, 2923, 1719 (C=O), 1595, 1274, 1011, 890, 830. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.08 (m, 6H, CH_3), 2.42 (m, 20H, CH_2), 3.18 (m, 4H, CH_2), 3.45 (m, 4H, CH_2), 7.86–7.89 (m, 6H, Ar–H), 8.14 (d, J = 6.8, 5H, Ar–H), 8.30 (d, J = 8.3, 5H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 23.5, 27.4, 28.5, 30.3, 30.5, 42.4, 60.5 (C-Spiro), 110.2, 110.2, 112.6, 125.7, 126.8, 129.0, 129.2, 129.4, 129.6, 129.8, 129.8, 130.1, 130.7, 131.2, 133.4, 135.6, 136.1, 139.1, 139.5, 182.3 (C=O). EI-MS: 622 (M^+), 396 (10), 207 (12), 182 (100), 154 ($C_{11}H_6O^{\bullet}$, 100), 126 ($C_{10}H_6^{\bullet}$, 100), 74 (22), 50 (10).

2,2-Bis(5-methyl-1*H*-indol-3-yl) acenaphthylen-1(2*H*)-one (5 h)

mp: 261–263 °C. IR [KBr, ν_{max} (cm^{-1})]: 3424 (NH), 3059, 1720 (C=O), 1596, 1275, 1210, 1057, 892, 831, 777. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61 (s, 6H, CH_3), 7.85 (t, J = 7.6, 6H, Ar–H), 8.12 (d, J = 7.0, 5H, Ar–H), 8.29 (d, J = 8.3, 5H, Ar–H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.7, 63.2 (C-Spiro), 111.1, 112.3, 112.5, 125.1, 126.7, 128.6, 128.9, 129.2, 129.4, 129.7, 130.2, 130.4, 130.5, 131.6, 133.3, 135.7, 136.1, 139.5, 184.2 (C=O). EI-MS: 426 (M^+), 296 (18), 207 (22), 182 (100), 154 ($C_{11}H_6O^{\bullet}$, 100), 126 ($C_{10}H_6^{\bullet}$, 100), 98 (19), 63 (33), 50 (10).

2,2-Bis(5-chloro-1*H*-indol-3-yl) acenaphthylen-1(2*H*)-one (5i)

mp: 263–265 °C. IR [KBr, ν_{max} (cm^{-1})]: 3421 (NH), 3059, 1719 (C=O), 1596, 1275, 1012, 892, 830, 777. ^{1}H NMR

Table 1 The optimization of reaction condition in the synthesis of 2,2-bis(1*H*-indol-3-yl)acenaphthen-1(2*H*)-ones

Entry	Conditions	Temperature	Catalyst	Time (min)	Yield
1	Neat	r. t.	SBA-Pr-NH_2	40	Trace
2	Neat	40 °C	SBA-Pr-NH_2	30	45 %
3	Neat	80 °C	SBA-Pr-NH_2	20	71 %
4	**Neat**	**100 °C**	**SBA-Pr-NH_2**	**10**	**82 %**
5	Neat	120 °C	SBA-Pr-NH_2	10	71 %
6	Neat	100 °C	–	55	65 %
7	CH_3CN	100 °C	SBA-Pr-NH_2	40	50 %
8	H_2O	100 °C	SBA-Pr-NH_2	60	55 %
9	MeOH	100 °C	SBA-Pr-NH_2	40	58 %

Bold values indicate the best condition

Table 2 Synthesis of 2,2-bis(1*H*-indol-3-yl) acenaphthen-1(2*H*)-one derivatives

Entry	R_1	R_2	R_3	Product	Time (min)	Yield (%)	Mp (°C)	Mp [Lit]
1	H	H	H	**5a**	10	82	286–289	289–290 [30]
2	H	Me	H	**5b**	10	78	290–292	292–293 [30]
3	H	H	OMe	**5c**	10	69	>300	>300 [31]
4	Me-	H	H	**5d**	20	70	>300	>300 [30]
5	*n*-Hexyl	H	H	**5e**	30	65	255–257	New
6	*n*-heptyl	H	H	**5f**	40	63	255–257	New
7	*n*-octyl	H	H	**5g**	20	60	258–260	New
8	H	H	Me-	**5h**	10	88	261–263	New
9	H	H	Cl	**5i**	10	72	263–265	New

(300 MHz, $CDCl_3$): δ 7.85–7.90 (m, 6H, Ar–H), 8.13 (d, $J = 7.1$, 5H, Ar–H), 8.29 (d, $J = 8.4$, 5H, Ar–H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.3 (C-Spiro), 111.2, 112.4, 112.7, 125.2, 126.5, 128.4, 128.7, 129.2, 129.3, 129.7, 130.2, 130.4, 130.5, 131.6, 133.1, 135.6, 136.1, 139.2, 182.5 (C = O). EI-MS: 467 (M^+), 182 (29), 154 ($C_{11}H_6O^{\bullet}$, 100), 126 ($C_{10}H_6^{\bullet}$, 42), 98 (4), 74 (6), 63 (5), 50 (4).

Results and discussion

In the continuation of our interest in the synthesis of various compounds of biological importance [35, 36] using amino-functionalized silica (SBA-Pr-NH_2) as a heterogeneous nanocatalyst, herein we report the synthesis of some 2,2-bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-one derivatives under mild reaction condition. Thus, the reaction of acenaphthenequinone (**3**) and indoles (**4**) in the presence of catalyst at 100 °C has been shown to give the desired products in good yields (Scheme 1). The reaction was optimized using different reaction conditions for obtaining the best yield of compound **5a.** The results are summarized in Table 1. It was observed that solvent-free condition in the presence of 0.02 g catalyst at 100 °C provides the best result in terms of yield and time (entry 1). The product was obtained in a moderate yield (50–58 %) using other solvents such as MeCN, H_2O, and MeOH (entries 3–5). Then, to investigate the scope of the reaction further, a series of differently substituted 2,2-bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-ones were successfully prepared and the results were illustrated in Table 2. Corresponding products were synthesized successfully in good yields (60–88 %) under solvent-free condition in the presence of SBA-Pr-NH_2.

Finally, the reusability of the catalyst was investigated for the synthesis of the model compound **5a**. The filtered catalyst was washed sequentially with diluted aqueous Et_3N solution, water, and acetone to reuse without any noticeable loss in activity. As illustrated in Fig. 3, the process of recycling was fulfilled four times that were established to be 82, 78, 73, and 65 %, respectively.

The reaction was probably preceded as shown in Scheme 2. Acenaphthenequinone **3** may be subject to additional nucleophilic attack by indoles which is converted to 2-hydroxy(2-indo-3-lyl)acenaphthylen-1(2*H*)-one (**7**). This intermediate (**7**) then undergoes a nucleophilic substitution reaction via another molecule of indole to prepare 2,2-bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-ones by elimination of water. Thus, 2-hydroxy(2-indo-3-lyl)acenaphthylen-1(2*H*)-one **7** may be formed in situ as a key intermediate using catalytic amount of SBA-Pr-NH_2.

The synthesis of the *N*-alkylated indoles was performed by reaction of the indole with different alkyl halides in DMF in the presence of K_2CO_3 (Scheme 3) [37].

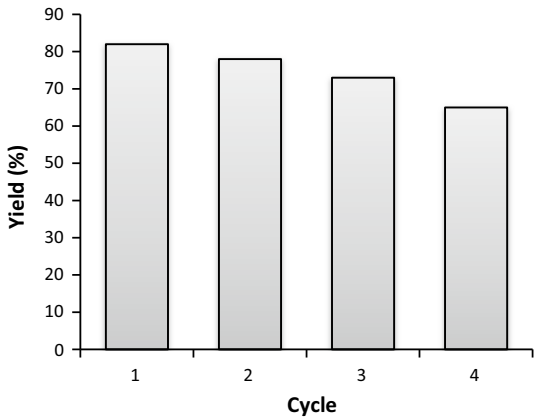
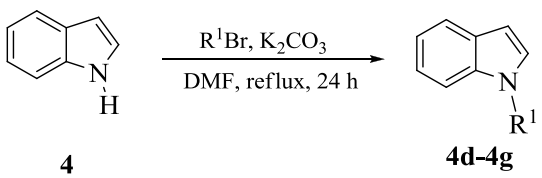


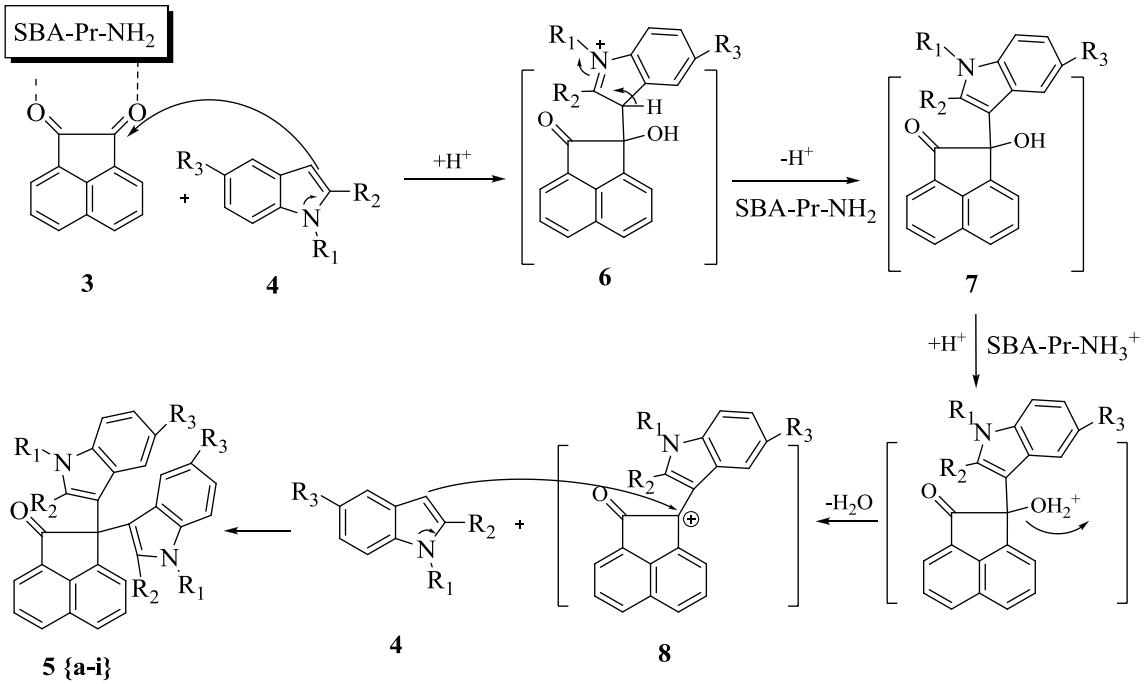
Fig. 3 Reusability of catalyst in the synthesis of compound **5a**



4 **4d-4g**

R^1=*n*-Hexyl, *n*-Heptyl, *n*-Octyl, Methyl

Scheme 3 Synthesis of *N*-alkylated indoles



Scheme 2 Proposed mechanism for the formation of compound (**5a**-**5i**)

Catalyst

As a part of our current studies on the development of new routes in using nanoporous silica in the multi-component reactions [35, 36], here we reported an efficient synthetic route of 2,2-bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-ones in the presence of catalytic amount of SBA-Pr-NH_2. The catalyst surface was analyzed by different methods such as N_2 adsorption–desorption isotherms, textural properties of NH_2-SBA-15, XRD pattern, FT-IR spectra, TGA analysis and TEM image of SBA-Pr-NH_2 were discussed in our previous report and demonstrated that the organic groups (propyl amine) were immobilized into the pores [38].

Conclusion

In summary, we have developed an efficient and clean protocol for the synthesis of symmetrical 2,2-bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-one derivatives from acenaphthenequinone and indoles in the presence of amino-functionalized silica (SBA-Pr-NH_2) as a heterogeneous nanocatalyst. The use of solvent-free condition makes the process economical and environmentally friendly. The significant features of this protocol are good yields, short reaction time, mild reaction conditions, operational simplicity and an easy workup procedure, which makes it an attractive strategy.

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