Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 21 (2010) 1057–1061
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

An efficient synthesis of 2,2-bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-one catalyzed by recyclable solid superacid SO_4^{2-}/TiO_2 under grinding condition

Guo Liang Feng

School of Science, Hebei University of Science and Technology, Shijiazhuang 050018, China

Received 7 January 2010

Abstract

An efficient synthesis of symmetrical 2,2-bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-one is achieved via a reaction of acenaphthenequinone and indoles catalyzed by solid superacid SO_4^{2-}/TiO_2 under solvent-free conditions at room temperature by grinding, which provides an efficient route to the synthesis of symmetrical 2,2-bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-one. This procedure offers several advantages including solvent-free conditions, excellent yields of products, simple work-up as well as reuse of catalysts which makes it a useful and attractive protocol for the synthesis of these compounds.

Keywords: Acenaphthenequinone; Indole; Solid superacid SO_4^{2-}/TiO_2; 2,2-Bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-one

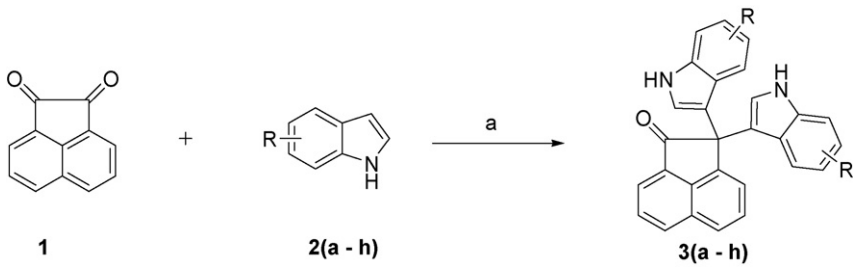
The indole fragment is a common and important feature of a variety of natural products [1], as well as in many compounds that show pharmacological and biological activities [2]. Among them, bisindolylalkanes (BIAs) are important class of bioactive metabolite [3]. With the continuing isolation of structurally more versatile bisindolylalkanes [4], the demand for efficient synthesis of bisindolylalkanes has become an increasing interest in organic synthesis [5]. The bis(indolyl)alkane moiety is also present in various natural products possessing important biological activity [6]. Therefore, a number of synthetic methods for preparation of bis(indolyl)alkane derivatives have been reported in the literature by reaction of indole with various aldehydes and ketones in the presence of catalyst [7].

In recent times, the progress in the field of solvent-free reactions is gaining significance because of their high efficiency, operational simplicity and environmentally benign processes. Solventless organic reactions based on grinding have been investigated for the intensive subject in recent years. The grinding mode for the solid-state reactions has earlier been reported for Grignard reaction, Reformatsky reaction, Aldol condensation, Dieckmann condensation, Knoevenagel condensation, reduction, *etc*. [8]. Most of these reactions are carried out at room temperature in absolutely solvent-free environment using only a mortar and pestle.

Solid superacids have received considerable attention as powerful reaction media for effecting various transformations [9]. In addition solid superacids are attractive because they are stable, reusable, green and cheap. As a part of ongoing work by grinding and solid superacid catalysis, we now describe a facile and solvent-free, simple and

E-mail address: fgl197012@163.com.

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2010.05.009

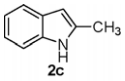
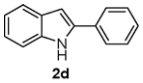
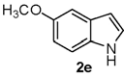
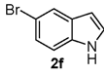
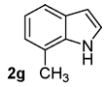
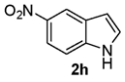


Scheme 1. Condition and regent: (a) SO_4^{2-}/TiO_2, grinding.

practical method for synthesizing 2,2-bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-one from acenaphthenequinone with indoles catalyzed by solid superacid SO_4^{2-}/TiO_2 at room temperature by grinding, which provides an efficient route to the synthesis of symmetrical 2,2-bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-one derivatives (Scheme 1). The synthesis of 2,2-bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-one under mild conditions has not been reported.

The optimized procedure for reaction was found to be as follows: the mixture of acenaphthenequinone (1 mmol), indole (2.1 mmol) and SO_4^{2-}/TiO_2 (20 mg) was grinded at room temperature. Representative results of this study are summarized in Table 1. As shown in Table 1, acenaphthenequinone in the presence of SO_4^{2-}/TiO_2 were grinded with

Table 1
The reaction of acenaphthenequinone with indoles catalyzed by SO_4^{2-}/TiO_2 under grinding condition.

Entry	Acenaphthenequinone	Indoles	Products	Time (min)	Yield (%)[a]	M. P. (°C)
1		 2a	**3a**	30	88	289–290
2		 2b	**3b**	30	86	>300
3		 2c	**3c**	30	87	292–293
4		 2d	**3d**	30	81	>300
5		 2e	**3e**	30	90	>300
6		 2f	**3f**	30	84	>300
7		 2g	**3g**	30	90	258–259
8		 2h	**3h**	60	70	211–212

[a] Isolation yields.

Table 2
The reaction of acenaphthenequinone with indole **2g** catalyzed by recycled SO_4^{2-}/TiO_2.

Entry	Time (min)	Yield (%)[a]
1	30	90
2	30	88
3	30	87
4	30	85
5	30	78

[a] Isolation yields.

indoles in free solvent, the corresponding 2,2-bis(1*H*-indol-3-yl)-2*H*-acenaphthen-1-one were obtained in good to excellent yield. The reaction proceeded cleanly and work-up was simple, involving only filtration of the catalyst to obtain the product. We were pleased to find that the conversion rate of the indoles bearing electron-withdrawing group (5-nitro-1*H*-indole **2h**) provided lower conversion rate than the indoles bearing donate group (5-methoxyl-1*H*-indole **2e**, 7-methyl-1*H*-indole **2g**), this indicated that electron-donating groups had increased reaction yields. On the other hand electron-withdrawing groups, which deactivated the indole ring, had decreased yields.

It should be noted that in the absence of catalyst lower yields of product were observed even with prolonged reaction time. For example, entry 1 without catalyst after 60 min 30% yield of product was obtained, whereas 88% yield was obtained with catalyst for 30 min. With the success of the above reactions, we continued our task by exploring the reusability and recycling of SO_4^{2-}/TiO_2. After the reaction completed, insoluble catalyst SO_4^{2-}/TiO_2 could be easily recovered by filtration. Further drying and activation in microwave oven for 2 min, the catalyst could be directly recycled in subsequent runs. The catalyst could be recycled in the reaction of indole **2g** with acenaphthenequinone up to 5 times without showing any significant decrease in activity (Table 2).

In conclusion, solid superacid SO_4^{2-}/TiO_2 was demonstrated to be an efficient, convenient and economical catalyst for electron-donating substitution of indole with acenaphthenequinone by grinding. Furthermore, it is remarkable that the solid superacid SO_4^{2-}/TiO_2 can be reused at least 5 times without significant loss of activity. The use of an easily accessible and recyclable solid superacid can make this procedure quite simple, more convenient and environmentally benign. The simplicity of the reaction procedure should make this method attractive for scale-up purposes.

1. Experimental

Melting points were uncorrected. ^{1}H NMR spectra were determined on a Varian VXP-500 s spectrometer using DMSO as solvent and tetramethylsilane (TMS) as internal reference. IR Spectra was obtained on a Nicolet FT-IR500 spectrophotometer using KBr pellets. Elementary analyses were performed by a Carlo-Erba EA1110 CNNO-S analyzer. The catalyst SO_4^{2-}/TiO_2 solid superacid was prepared as follows. $Ti(OH)_4$ was obtained by hydrolyzing $TiCl_4$ with aqueous ammonium hydroxide, washing the precipitates, drying them at 120 °C for 4 h, and powdering the precipitates below a 100 mesh. After hydroxide was treated with 2 mol/L H_2SO_4 for 4 h which filtrated, dried and calcined in furnace at 450 °C for 4 h, and finally stored in a desiccator until use.

The mixture of **1** (0.18 g, 1 mmol), **2** (2.1 mmol) and SO_4^{2-}/TiO_2 (20 mg) were ground by mortar and pestle at room temperature for proper time. After completion of the reaction as monitored by TLC, the mixture was washed with EtOAc and dried over $MgSO_4$; then the filtrate was concentrated in vacuum to yield the crude product **3**, which was purified by column chromatography to afford the pure product **3**.

3a 2,2-Bis(1*H*-indol-3-yl)-2*H*-acenaphthylen-1-one. IR (KBr) ν 3418, 3359, 3121, 3056, 1685, 1621, 1600, 1492, 1457, 1430, 1340, 1102, 781 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.99 (s, 2H, NH), 8.35 (d, 1H, J = 8.0 Hz), 8.01–7.98 (m, 2H), 7.91–7.88 (m, 1H), 7.71–7.67 (m, 1H), 7.55 (d, 1H, J = 7.0 Hz), 7.35 (d, 2H, J = 8.5 Hz), 7.03–6.97 (m, 4H), 6.85 (d, 2H, J = 2.5 Hz), 6.76–6.72 (m, 2H). Anal. Calcd. for $C_{28}H_{18}N_2O$: C, 84.40; H, 4.55; N, 7.03. Found: C, 84.34; H, 4.66; N, 6.94.

3b 2,2-Bis(1-methyl-1*H*-indol-3-yl)-2*H*-acenaphthylen-1-one. IR (KBr) ν 3418, 3055, 2932, 2881, 2821, 1718, 1621, 1601, 1545, 1533, 1466, 1208, 977 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.36 (d, 1H, J = 8.0 Hz), 8.01 (t, 2H, J = 7.5 Hz), 7.90 (d, 1H, J = 8.0 Hz), 7.70 (t, 1H, J = 8.0 Hz), 7.55 (d, 1H, J = 8.0 Hz), 7.37 (d, 2H, J = 8.0 Hz),

7.08–7.03 (m, 4H), 6.87 (s, 2H), 6.79 (t, 2H, J = 7.5 Hz), 3.68 (s, 6H). Anal. Calcd. for $C_{30}H_{22}N_2O$: C, 84.48; H, 5.20; N, 6.57. Found: C, 84.41; H, 5.22; N, 6.63.

3c 2,2-Bis(2-methyl-1*H*-indol-3-yl)-2*H*-acenaphthylen-1-one. IR (KBr) ν 3386, 3343, 3048, 1714, 1619, 1601, 1491, 1461, 1428, 1022 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 10.90 (s, 2H, NH). 8.34 (d, 1H, J = 8.0 Hz), 8.03–8.00 (m, 2H), 7.89–7.85 (m, 1H), 7.66–7.62 (m, 1H), 7.42 (d, 1H, J = 7.0 Hz), 7.21 (t, 2H, J = 7.0 Hz), 6.89–6.84 (m, 2H), 6.59 (t, 1H, J = 7.5 Hz), 6.55–6.50 (m, 2H), 6.32 (d, 1H, J = 8.5 Hz), 1.80 (s, 6H). Anal. Calcd. for $C_{30}H_{22}N_2O$: C, 84.48; H, 5.20; N, 6.57. Found: C, 84.40; H, 5.31; N, 6.66.

3d 2,2-Bis(2-phenyl-1*H*-indol-3-yl)-2*H*-acenaphthylen-1-one. IR (KBr) ν 3411, 3337, 3052, 1710, 1599, 1488, 1456, 1224, 993 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 11.02 (s, 1H), 10.85 (s, 1H), 8.30 (d, 1H, J = 8.0 Hz), 7.84 (t, 1H, J = 7.5 Hz), 7.77 (d, 1H, J = 8.0 Hz), 7.66 (d, 1H, J = 7.0 Hz), 7.25 (d, 1H, J = 7.0 Hz), 7.21 (t, 1H, J = 7.5 Hz), 7.15 (d, 1H, J = 8.5 Hz), 7.10 (t, 1H, J = 7.5 Hz), 7.07–7.05 (m, 2H), 7.03 (d, 1H, J = 8.0 Hz), 6.95–6.82 (m, 8H), 6.66 (t, 1H, J = 7.0 Hz), 6.62 (d, 2H, J = 7.5 Hz), 6.56 (t, 1H, J = 7.5 Hz), 6.43 (s, 1H). Anal. Calcd. for $C_{40}H_{26}N_2O$: C, 87.25; H, 4.76; N, 5.09. Found: C, 87.31; H, 4.82; N, 4.98.

3e 2,2-Bis(5-methoxy-1*H*-indol-3-yl)-2*H*-acenaphthylen-1-one. IR (KBr) ν 3399, 3371, 3138, 2933, 2825, 1701, 1622, 1583, 1484, 1456, 1437, 1259, 1217 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 10.82 (s, 2H), 8.3 (d, 1H, J = 8.0 Hz), 8.02 (t, 2H, J = 7.0 Hz), 7.93–7.89 (m, 1H), 7.72–7.68 (m, 1H), 7.54 (d, 1H, J = 7.0 Hz), 7.24 (d, 2H, J = 9.0 Hz), 6.85 (d, 2H, J = 3.0 Hz), 6.68–6.65 (m, 2H), 6.42 (d, 2H, J = 2.5 Hz), 3.40 (s, 6H). Anal. Calcd. for $C_{30}H_{22}N_2O_3$: C, 78.59; H, 4.84; N, 6.11. Found: C, 78.47; H, 4.82; N, 6.23.

3f 2,2-Bis(5-bromo-1*H*-indol-3-yl)-2*H*-acenaphthylen-1-one. IR (KBr) ν 3431, 3340, 3122, 3051, 1709, 1683, 1601, 1564, 1493, 1457, 1417, 1334, 1283, 1096 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 11.25 (s, 2H), 8.41 (d, 1H, J = 8.0 Hz), 8.06–8.03 (m, 2H), 7.94–7.90 (m, 1H), 7.76–7.72 (m, 1H), 7.53 (d, 1H, J = 7.0 Hz), 7.36 (d, 2H, J = 9.0 Hz), 7.16–7.13 (m, 4H), 6.93 (d, 2H, J = 2.5 Hz). Anal. Calcd. for $C_{28}H_{16}Br_2N_2O$: C, 60.46; H, 2.90; N, 5.04. Found: C, 60.37; H, 2.97; N, 5.13.

3g 2,2-Bis(7-methyl-1*H*-indol-3-yl)-2*H*-acenaphthylen-1-one. IR (KBr) ν 3425, 3126, 3049, 2967, 2851, 1711, 1598, 1493, 1458, 1430, 1101 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 10.93 (s, 2H, NH), 8.35 (d, 1H, J = 8.0 Hz), 7.99 (t, 2H, J = 6.5 Hz), 7.89 (t, 1H, J = 8.0 Hz), 7.67 (t, 1H, J = 8.0 Hz), 7.53 (d, 1H, J = 7.0 Hz), 6.85–6.79 (m, 6H), 6.65 (t, 2H, J = 7.5 Hz), 2.42 (s, 6H). Anal. Calcd. for $C_{30}H_{22}N_2O$: C, 84.48; H, 5.20; N, 6.57. Found: C, 84.56; H, 5.13; N, 6.64.

3h 2,2-Bis(5-nitro-1*H*-indol-3-yl)-2*H*-acenaphthylen-1-one. IR (KBr) ν 3365, 1706, 1623, 1518, 1470, 1429, 1333, 1256, 1110 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 11.83 (s, 2H), 8.46 (d, 1H, J = 8.0 Hz), 8.10 (t, 2H, J = 7.0 Hz), 7.98–7.93 (m, 5H), 7.78–7.76 (m, 1H), 7.61(d, 1H, J = 6.5 Hz), 7.55(d, 2H, J = 9.0 Hz), 7.24 (d, 2H, J = 2.5 Hz). Anal. Calcd. for $C_{28}H_{16}N_4O_5$: C, 68.85; H, 3.30; N, 11.47. Found: C, 68.92; H, 3.21; N, 11.39.

Acknowledgment

This work was financially supported by the research foundation of Hebei University of Science and Technology.

References

[1] (a) A.L. Smith, G.I. Stevenson, S. Lewis, et al. Bioorg. Med. Chem. Lett. 10 (2000) 2693;
(b) Y. Liu, G.W. Gribble, Tetrahedron Lett. 41 (2000) 8717.
[2] (a) R.A. Glennon, J. Med. Chem. 40 (1997) 1;
(b) M. Lounasmaa, A. Tolvanen, Nat. Prod. Rep. 17 (2000) 175;
(c) S. Hibino, T. Chozi, Nat. Prod. Rep. 18 (2001) 66;
(d) H.C. Zhang, H. Ye, A.F. Moretto, et al. Org. Lett. 2 (2000) 89.
[3] (a) T. Osawa, M. Namiki, Tetrahedron Lett. 24 (1983) 4719;
(b) G. Bifulco, I. Bruno, R. Riccio, J. Nat. Prod. 58 (1995) 1254.
[4] R. Veluri, I. Oka, I. Wagner-Dobler, et al. J. Nat. Prod. 66 (2003) 1520.
[5] (a) A. Mahadevan, H. Sard, M. Gonzalez, et al. Tetrahedron Lett. 44 (2003) 4589;
(b) J. Li, M. Zhou, B.G. Li, et al. Synth. Commun. 34 (2004) 275.
[6] (a) M.L. Bennasar, B. Vidal, J. Bosch, J. Org. Chem. 62 (1997) 3597;
(b) M. Amat, S. Hadida, G. Pshenichnyi, et al. J. Org. Chem. 62 (1997) 3158;
(c) J.D. Rainier, A.B. Smith, Tetrahedron Lett. 41 (2000) 9419.

[7] (a) K.N. Kim, K.C. Song, J.H. Noh, et al. Bull. Korean Chem. Soc. 30 (2009) 197;
(b) S.Y. Wang, S.J. Ji, Tetrahedron 62 (2006) 1527;
(c) P.Y. Paira, A.H. Hazra, Bioorg. Med. Chem. Lett. 19 (2009) 4786.
[8] (a) K. Tanaka, F. Toda, Chem. Rev. 100 (2000) 1025;
(b) Z.J. Ren, W.G. Cao, W.Y. Ding, W. Shi, Synth. Commun. 34 (2004) 4395.
[9] (a) M. Hino, K. Arata, J. Chem. Soc. Chem. Commun. 101 (1979) 1148;
(b) M. Hino, S. Kobayashi, K. Arata, J. Am. Chem. Soc. 101 (1979) 6439.