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A NEW CATALYTIC APPLICATION OF A KEGGIN ACID IN THE SYNTHESIS OF SYMMETRICAL BIS(INDOLYL)ALKANES

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Abstract- Silicotungstic acid, $H_4SiW_{12}O_{40}$, an important Keggin heteropoly acid, efficiently catalysed the reaction of indoles with aryl aldehydes in ethyl acetate solution at room temperature to furnish symmetrical bis(indolyl)alkanes expeditiously.

INTRODUCTION

The Keggin heteropoly acids (HPAs), $H_{8-n}XM_{12}O_{40}$ (where X is Si^{4+}, P^{5+}, etc., n is the oxidation state of X, and M is Mo^{6+} or W^{6+}), are exceptionally strong Brönsted acids,[1] which are mainly due to their possessing a pseudoliquid phase[2] which allows both the bulk protons and the surface protons to participate in catalytic activity. Moreover, these HPAs are environmentally benign. As a result, the major Keggin acids, viz. phosphotungstic, silicotungstic, phosphomolybdic and siliocomolybdic acids are being increasingly applied as catalysts in homogeneous, heterogeneous and biphasic reactions.[3]

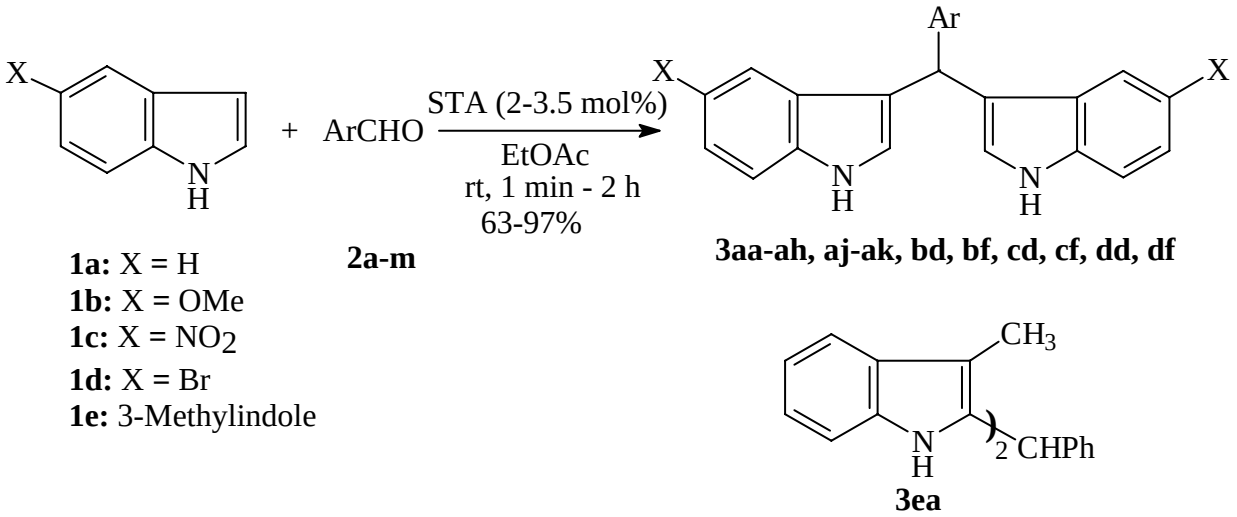
Indolic, bisindolic, and trisindolic substances as well as annulated indoles have been our major synthetic targets in recent years.[4] The well-documented anti-cancer property of bis(indol-3-yl)methane[5] and bis(5-methoxyindol-3-yl)methane[6] have brought to fore the importance of the symmetrical bis(indolyl)alkanes (BIAs). The BIAs, though of synthetic origin, have also been reported from fungi, bacteria, tunicates and sponges[7] and display significant biological activities. These are mainly prepared by the reaction of indoles or indolyl Grignard reagents with aldehydes or ketones or their masked forms using protic or Lewis acids and even solid acids, sometimes applying alternative sources of energy.[8]

Nevertheless, the increasing importance of green chemistry[9] and the various disadvantages (like the use of

stoichiometric or larger amounts of acids, creation of toxic wastes, very long reaction periods, very low or widely varying yields, etc.) of the extant synthetic routes warrant newer applications of particularly eco-friendly catalysts for the synthesis of the symmetrical BIAs. In response to this need and in continuation of our ongoing interest in this field,[10] we have now successfully employed the Keggin HPA, silicotungstic acid (STA), $H_4SiW_{12}O_{40}$, as an efficient homogeneous catalyst for the solution phase synthesis of the symmetrical BIAs from indoles and aryl aldehydes at room temperature. Our findings, since important, are presented herein.

RESULTS AND DISCUSSION

Five assorted indoles (**1a-e**) were treated separately at room temperature with several aryl aldehydes (**2a-m**; 0.75-2.0 equiv[11]) in ethyl acetate solution using 2.0-3.5 mol% of STA (i.e. 50% w/w with respect to the indoles). Indole (**1a**) failed completely to react with **2i**, **2l** and **2m**. In all other cases, the corresponding symmetrical BIAs (**3aa-ah**, **aj**, **ak**, **bd**, **bf**, **cd**, **cf**, **dd**, **df**, **ea**) were obtained as the sole products, isolated in 63-97% yields (Scheme 1, Table 1). The known BIAs were identified either from their ^{1}H NMR spectroscopic data or by direct comparisons (mp, mixed mp, co-TLC) and the new BIAs by IR, ^{1}H and ^{13}C NMR spectra, including DEPT 135, LR and HR EI/FAB-MS spectral and micro-analytical data.



Scheme 1

The results unveiled the influence of the electronic nature of the substituents of both indoles and aryl aldehydes on the time of the reactions. Thus, except for the 2/3-formyl heteroarenes (**2j-m**), the reaction of indole (**1a**), 5-methoxyindole (**1b**) and 5-bromoindole (**1d**) with benzaldehyde (**2a**) and its 2/3/4-nitro, 4-trifluoromethoxy and 4-methoxy derivatives (**2b-f**) were quite expeditious (1-5 min), except for the reaction of **1b** with **2f**, which inexplicably required 45 min for the completion of the reaction. In contrast,

Table 1. Application of STA as catalyst in the synthesis of symmetrical BIAs

Entry	Indoles (**1**) X=	ArCHO (**2**)	Equiv of (**2**)	Time	BIA (**3**)	Yield (%)[a]
1	**a**: H	**a**: Ph	0.75	5 min	**aa**	95
2	**a**	**b**: 2-$NO_2C_6H_4$	1.5	5 min	**ab**	95
3	**a**	**c**: 3-$NO_2C_6H_4$	0.75	5 min	**ac**	82
4	**a**	**d**: 4-$NO_2C_6H_4$	0.75	5 min	**ad**	74
5	**a**	**e**: 4-$CF_3OC_6H_4$	0.75	1 min	**ae**	88
6	**a**	**f**: 4-$MeOC_6H_4$	1.5	5 min	**af**	90
7	**a**	**g**: 2-HOC_6H_4	1.0	2 h	**ag**	63
8	**a**	**h**: 4-HOC_6H_4	0.75	1.5 h	**ah**	93
9	**a**	**i**: 4-$Me_2NC_6H_4$	1.0	6 h[b]	–	–
10	**a**	**j**: 2-Thienyl[c]	2.0	7 min	**aj**	90
11	**a**	**k**: 2-Furyl[c]	2.0	30 min	**ak**	73
12	**a**	**l**: 2-Pyrrolyl	2.0	6 h[b]	–	–
13	**a**	**m**: 3-Indolyl	1.0	6 h[b]	–	–
14	**b**: OMe	**d**	0.75	1 min	**bd**	73
15	**b**	**f**	1.0	45 min	**bf**	78
16	**c**: NO_2	**d**	0.75	2 h	**cd**	97
17	**c**	**f**	1.0	1 h	**cf**	82
18	**d**: Br	**d**	0.75	5 min	**dd**	89
19	**d**	**f**	1.0	5 min	**df**	89
20	**e**: 3-Me	**a**	0.75	2 h	**ea**	94

[a]Refer to isolated pure products; [b]Carried out under reflux; [c]For **2j** and **2k** (Entries 10 and 11), a solution of STA in EtOAc added dropwise.

the reaction of **1a** with 2/4-hydroxybenzaldehydes (**2g**/**h**) required considerably longer periods (2/1.5 h), while that with 4-dimethylaminobenzaldehyde (**2i**) led to a complete failure of the reaction. Among the four 2/3-formylheteroarenes (**2j**-**m**) reacting with **1a**, the aldehydes (**2j)** and (**2k)** required 7 min and 30 min, respectively for the completion of their reactions, whereas **2l** and **2m** did not react at all. These observations are compatible with the decreasing electrophilic character of the formyl carbon in these substrates. As anticipated, 5-nitroindole (**1c**), with its reduced nucleophilicity, took longer periods (2/1 h) in its reactions with two aryl aldehydes (**2d**/**f**). In the case of the reaction of 3-methylindole (**1e**) with **2a**, the expected symmetrical BIA, bis(3-methylindol-2-yl)phenylmethane (**3ea**) was formed in a comparable yield but

requiring a much longer period, which is due to the well known nucleophilicity at C-2, as compared to that at C-3, of the indole nucleus.

When applied to the reaction of indole (**1a**) with acetaldehyde, propionaldehyde and (±)-glyceraldehyde as well as with acetone, 2-butanone and acetophenone separately but under similar conditions, STA (2 mol%) proved to be less effective for the first two alkanals (furnishing the respective BIAs in 30% and 35% yields, respectively) but failed for glyceraldehyde and the ketones. Pertinently, the recyclability of STA could not be checked because of its high solubility in both ethyl acetate and water.

To conclude, the eco-friendly Keggin HPA, silicotungstic acid, has been demonstrated to be highly efficacious even at low catalytic concentrations (2-3.5 mol%) for the solution-phase synthesis of symmetrical BIAs and remarkably rapid for those BIAs (e.g. entry 14), which stem from both indoles bearing electron-donating substituents (e.g. 5-MeO-indole, **1b**) and benzaldehydes bearing electron-withdrawing groups (e.g. 4-$NO_2C_6H_4CHO$, **2d**).

EXPERIMENTAL

Mps were determined on a Toshniwal apparatus and are uncorrected. IR spectra were recorded on a Nicolet Impact 410 or a Perkin-Elmer RX 1FT-IR spectrophotometer, LR EI/FAB-MS in JEOL JMS-AX505HA and HR EI/FAB-MS in JEOL JMS-700 MStation mass spectrometers, ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra, both 1D and 2D, including DEPT 135, HMQC and HMBC spectra, in a Bruker DRX 500 NMR spectrometer. In FAB-MS spectrum, *m*-nitrobenzyl alcohol was used as the liquid matrix. Individual ^{1}H and ^{13}C NMR spectral assignments of **3bf**, **3cf** and **3df** were based on HMQC and HMBC spectral analyses. TLCs were carried out on silica gel G (Merck, India) plates. PE refers to petroleum ether, bp 60-80 °C.

General Experimental Procedure. STA, procured commercially (from Speer Laboratories, Kolkata, India) as a polyhydrate, was heated at *ca.* 110 °C for 1 h and then cooled to rt in a desiccator before use. To a solution of the indole (0.25 mmol) and aldehyde (0.75-2.0 equiv.) in EtOAc (4 mL) was added with stirring a solution of STA (2.0-3.5 mol%) in EtOAc (3 mL) at rt. The stirring was continued until the indole was consumed (TLC). The mixture was diluted a little with EtOAc, filtered through a bed of celite to free it from a small amount of precipitate and washed with EtOAc (2 × 5 mL). The pooled filtrates were washed with water (2 × 15 mL), the organic phase separated and dried (Na_2SO_4) and the solvent removed. The resulting residue was purified either by crystallisation or by preparative TLC using PE-EtOAc, followed by recrystallisation, to afford pure BIAs. Unless stated otherwise, the BIAs were crystallised from PE-EtOAc. The following BIAs were identified by direct comparison (for samples available in the laboratory) or by comparing their mps with the reported mps along with ^{1}H NMR spectroscopic data. **3aa**: mp 148 ºC (PE-

CCl_4) (lit.,[12] 150-152 ºC); **3ab**: mp 140 ºC (lit.,[13] 141-143 ºC); **3ac**: mp 218-220 ºC (lit.,[14] 218-220 ºC); **3ad**: mp 240 ºC (lit.,[13] 220-222 ºC); **3af**: mp 194-195 ºC (PE-CH_2Cl_2) (lit.,[15] 191-193 ºC); **3ag**: mp 198 ºC (PE-CH_2Cl_2) (lit.,[16] 199-200 ºC); **3ah**: mp 134-136 ºC (lit.,[15] 130-132 ºC); **3aj**: mp 160 ºC (lit.,[17] 163-165 ºC); **3ak**: mp >325 ºC (lit.,[18] 325 ºC); **3ea**: mp 162 ºC (lit.,[18] 160 ºC).

Bis(indol-3-yl)(4′-trifluoromethoxyphenyl)methane (**3ae**): mp 272-274 °C (decomp); IR (KBr): 3424, 1605, 1508, 1455, 1245, 1174, 1097, 1028, 794 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.88 (1H, s), 6.62 (2H, s), 7.0 (2H, t, *J*=7.5 Hz), 7.10 (2H, d, *J*=8 Hz), 7.17 (2H, t, *J*=7.5 Hz), 7.34 (4H, m), 7.35 (2H, d, *J*=7.5 Hz), 7.92 (2H, br s); ^{13}C NMR: δ 30.1 (OCF_3), 39.9 (Ar_3CH), 111.5, 119.7, 120.1, 121.0, 122.5, 124.0, 130.3 (all Ar-CH), 119.6, 127.3, 137.1, 143.1, 148.0 (all Ar-C); EI-MS: *m*/*z* (%) 406 (M^+, 100), 405 (41), 305 (20), 290 (14), 289 (19), 288 (12), 245 (52), 243 (13); HRMS (EI): calcd for $C_{24}H_{17}N_2OF_3$, 406.1293; found 406.1290; Anal. Calcd for $C_{24}H_{17}N_2OF_3$: C, 70.93; H, 4.19; N, 6.89. Found: C, 70.92; H, 4.18; N, 6.87.

Bis(5-methoxyindol-3-yl)(4′-nitrophenyl)methane (**3bd**): mp 142 ºC; IR (KBr): 3410, 1590, 1515, 1481, 1343, 1209, 1171, 1032, 1036, 797, 720 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.69 (6H, s), 5.86 (1H, s), 6.65 (2H, s), 6.74 (2H, d, *J*=2 Hz), 6.85 (2H, dd, J_1=8.5 Hz, J_2=2 Hz), 7.26 and 7.48 (2H, d each, *J*=8.5 Hz), 7.95 (2H, br s), 8.12 (2H, d, *J*=8.5 Hz); ^{13}C NMR: δ 40.6 (Ar_3CH), 56.3 (OCH_3), 102.1, 112.3, 112.5, 124.0, 124.9, 129.9 (all Ar-CH), 118.0, 127.5, 132.2, 146.9, 152.2, 154.3 (all Ar-C); EI-MS: *m*/*z* (%) 427 (M^+, 100), 426 (26), 396 (13), 305 (56), 281 (5), 280 (5), 234 (8), 147 (7); HRMS (EI): calcd for $C_{25}H_{21}N_3O_4$, 427.1532; found 427.1535; Anal. Calcd for $C_{25}H_{21}N_3O_4$: C, 70.25; H, 4.92; N, 9.83. Found: C, 70.32; H, 4.94; N, 9.81.

Bis(5-methoxyindol-3-yl)(4′-methoxyphenyl)methane (**3bf**): mp 198-200 °C; IR (nujol): 3316, 1626, 1580, 1245, 1205, 1170, 1037, 800 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.52 (6H, s, 2×5-OCH_3), 3.63 (3H, s, 4′-OCH_3), 5.61 (1H, s, Ar_3CH), 6.63 (2H, dd, J_1=9 Hz, J_2=2 Hz, 2×H-6), 6.66 (2H, d, *J*=2 Hz, 2×H-4), 6.72 (2H, d, *J*=1.5 Hz, 2×H-2), 6.77 (2H, d, *J*=8.5 Hz, H-3′,5′), 7.17 (2H, d, *J*=9 Hz, 2×H-7), 7.19 (2H, d, *J*=9 Hz, H-2′,6′), 10.54 (2H, br s, 2×NH); ^{13}C NMR: δ 39.6 (Ar_3CH), 55.8 (4′-OCH_3), 56.1 (2×5-OCH_3), 102.4 (2×CH-4), 111.3 (2×CH-6), 112.8 (2×CH-7), 114.2 (CH-3′, 5′), 118.9 (2×C-3), 125.0 (2×CH-2), 127.8 (2×C-3a), 130.0 (CH-2′, 6′), 132.7 (2×C-7a), 137.8 (C-1′), 153.4 (2×C-5), 158.1 (C-4′); EI-MS: *m*/*z* (%) 412 (M^+, 100), 397 (7), 381 (10), 305 (36), 265 (20), 250 (8); HRMS (EI): calcd for $C_{26}H_{24}N_2O_3$, 412.1787; found 412.1782; Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.73; H, 5.82; N, 6.79. Found: C, 75.78; H, 5.83; N, 6.77.

Bis(5-nitroindol-3-yl)(4′-nitrophenyl)methane (**3cd**): mp 293 °C (PE-C_6H_6); IR (nujol): 3384, 1622, 1596, 1507, 1465, 1324, 1086, 811, 739, 678 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.41 (1H, s), 7.15 (2H, d, *J*=1.5 Hz), 7.49 and 7.59 (2H, d each, *J*=9 Hz), 7.92 (2H, dd, J_1=9 Hz, J_2=2 Hz), 8.13 (2H, d, *J*=8.5 Hz), 8.32 (2H, d, *J*=2 Hz), 11.70 (2H, br s); ^{13}C NMR: δ 38.8 (Ar_3CH), 113.1, 116.9, 117.6, 124.6, 128.8, 130.2 (all

Ar-CH), 120.1, 126.4, 140.6, 141.2, 147.0, 152.6 (all Ar-C); FAB-MS: *m/z* (%) 480 (M+Na), 458 (M+H), 457 (M^+, 100), 441 (37), 412 (16), 335 (16), 296 (35); HRMS (FAB+): calcd for $C_{23}H_{16}N_5O_6$ (M+H), 458.1101; found 458.1105; Anal. Calcd for $C_{23}H_{15}N_5O_6$: C, 60.39; H, 3.28; N, 15.32. Found: C, 60.46; H, 3.27; N, 15.35.

Bis(5-nitroindol-3-yl)(4′-methoxyphenyl)methane (**3cf**): mp 294-295 °C (decomp); IR (KBr): 3291, 1620, 1511, 1465, 1324, 1242, 1088, 1029, 801, 736, 669 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.70 (3H, s, 4′-OCH_3), 6.11 (1H, s, Ar_3CH), 6.87 (2H, d, *J*=8.5 Hz, H-3′,5′), 7.09 (2H, d, *J*=1 Hz, 2×H-2), 7.28 (2H, d, *J*=8.5 Hz, H-2′,6′), 7.53 (2H, d, J=9 Hz, 2×H-7), 7.96 (2H, dd, J_1=9 Hz, J_2=2 Hz, 2×H-6), 8.29 (2H, d, *J*=2 Hz, 2×H-4), 11.62 (2H, s, 2×NH); ^{13}C NMR: δ 38.5 (Ar_3CH), 55.8 (4′-OCH_3), 112.9 (2×CH-7), 114.6 (CH-3′, 5′), 117.0 (2×CH-4), 117.4 (2×CH-6), 121.7 (2×C-3), 126.6 (2×C-3a), 128.3 (2×CH-2), 130.0 (CH-2′, 6′), 136.5 (C-1′), 140.6 (2×C-7a), 141.0 (2×C-5), 158.5 (C-4′); EI-MS: *m/z* (%) 442 (M^+, 100), 441 (22), 425 (15), 411 (10), 395 (11), 335 (18), 280 (19); HRMS (EI): calcd for $C_{24}H_{18}N_4O_5$, 442.1278; found 442.1276; Anal. Calcd for $C_{24}H_{18}N_4O_5$: C, 65.16; H, 4.07; N, 12.67. Found: C, 65.22; H, 4.06; N, 12.69.

Bis(5-bromoindol-3-yl)(4′-nitrophenyl)methane (**3dd**): mp 189-190 ℃ (decomp); IR (KBr): 3417, 1595, 1510, 1454, 1343, 1213, 1100, 860, 789 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.58 (1H, s), 6.65 (2H, d, *J*=2 Hz), 7.26-7.27 (4H, m), 7.42 (2H, d, *J*=1.5 Hz), 7.44 (2H, d, *J*=8.5 Hz), 8.10 (2H, br s), 8.15 (2H, d, *J*=8.5 Hz); ^{13}C NMR: δ 40.2 (Ar_3CH), 113.2, 122.3, 124.2, 125.2, 125.8, 129.8 (all Ar-CH), 113.4, 117.8, 128.6, 135.7, 147.2, 151.2 (all Ar-C); EI-MS: *m/z* (%) 527 (M+4, 74), 525 (M+2, 100), 523 (M^+, 79), 446 (16), 444 (18), 405 (28), 403 (57), 401 (34); HRMS (EI): calcd for $C_{23}H_{15}N_3O_2{}^{79}Br_2$, 522.9531; found 522.9533; Anal. Calcd for $C_{23}H_{15}N_3O_2{}^{79+81}Br_2$: C, 52.57; H, 2.85; N, 8.00. Found: C, 52.61; H, 2.84; N, 7.98.

Bis(5-bromoindol-3yl)(4′-methoxyphenyl)methane (**3df**): mp 250 °C (decomp) (PE-CH_2Cl_2); IR (KBr): 3411, 1611, 1506, 1458, 1419, 1262, 1217, 1164, 1014, 743 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.51 (3H, s, 4′-OCH_3), 5.58 (1H, s, Ar_3CH), 6.65 (2H, d, *J*=8.5 Hz, H-3′,5′), 6.65 (2H, d, *J*=2.5 Hz, 2×H-2), 6.94 (2H, dd, J_1=8.5 Hz, J_2=1.5 Hz, 2×H-6), 7.02 (2H, d, *J*=8.5 Hz, H-2′,6′), 7.13 (2H, d, *J*=8.5 Hz, 2×H-7), 7.20 (2H, d, *J*=1.5 Hz, 2×H-4), 10.83 (2H, br s, 2×NH); ^{13}C NMR: δ 38.9 (Ar_3CH), 55.8 (4′-OCH_3), 111.7 (2×C-5), 114.4 (2×CH-7; CH-3′,5′), 118.8 (2×C-3), 122.0 (2×CH-4), 124.2 (2×CH-6), 125.9 (2×CH-2), 129.2 (2×C-3a), 129.9 (CH-2′, 6′), 136.1 (2×C-7a), 137.1 (C-1′), 158.3 (C-4′); EI-MS: *m/z* (%) 512 (M+4, 49), 510 (M+2, 100), 508 (M^+, 55), 431 (7), 429 (11), 405 (12), 403 (26), 401 (18), 315 (20), 313 (22); HRMS (EI): calcd for $C_{24}H_{18}N_2O^{79}Br_2$, 507.9786; found 507.9801; Anal. Calcd for $C_{24}H_{18}N_2O^{79+81}Br_2$: C, 56.47; H, 3.53; N, 5.49. Found: 56.52; H, 3.54; N, 5.47.

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