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Copper Dipyridine Dichloride: An Efficient and Convenient Catalyst for the Synthesis of Bis (Indolyl) Methanes

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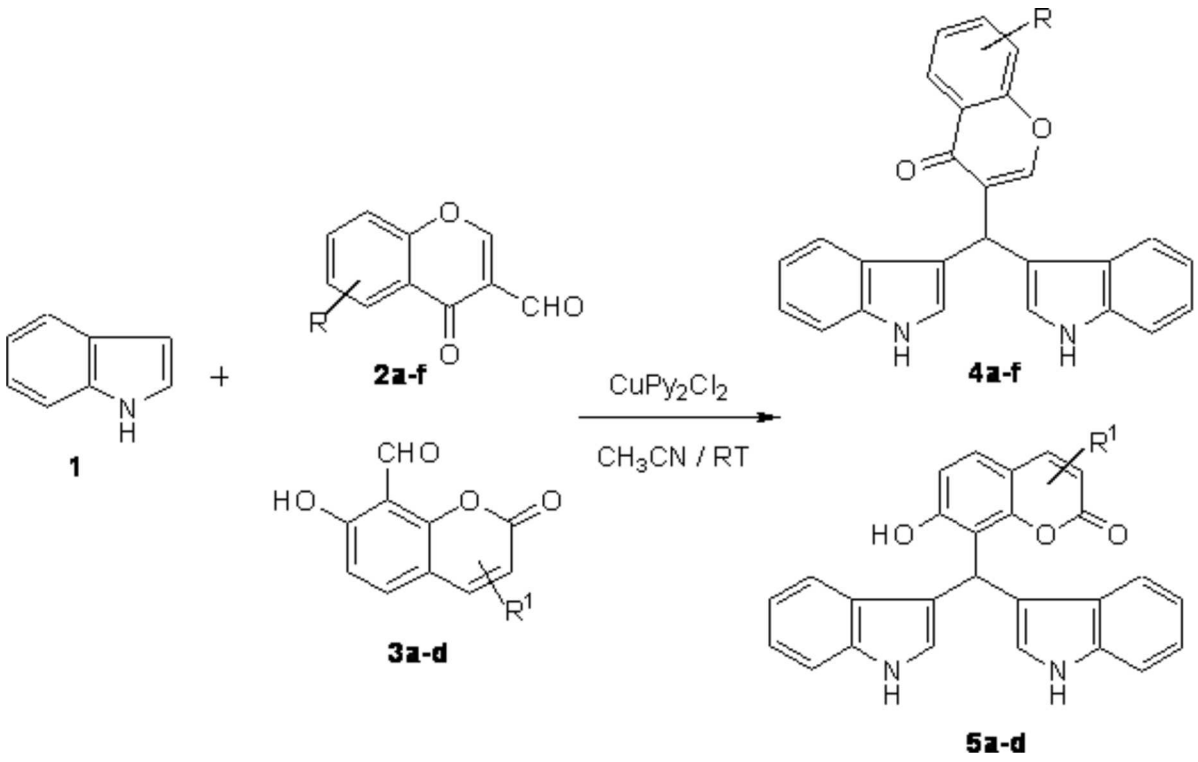
Abstract: Copper dipyridine dichloride is used as an efficient catalyst for the electrophilic substitution reaction of indoles with aromatic aldehydes in acetonitrile to afford the corresponding bis (indolyl)methanes in excellent yields at room temperature.

Introduction

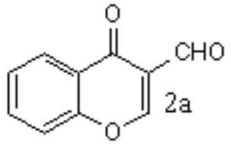
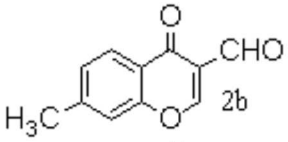
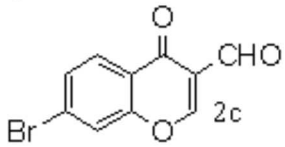
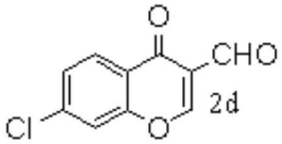
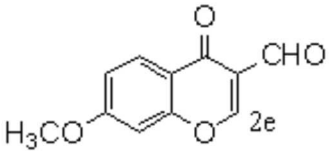
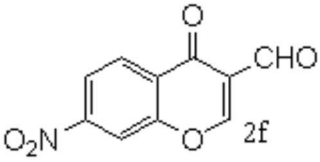
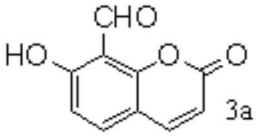
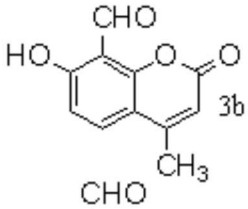
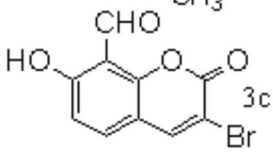
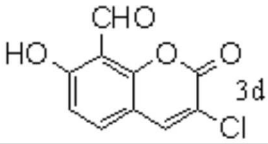
Indoles and their derivatives are used as antibiotics in the field of pharmaceuticals [1]. For example, Bisindolylalkanes and their derivatives are found in bioactive metabolites of terrestrial and marine origin [2]. Therefore, there is a great deal of interest in the synthesis of this class of compounds. Among the many methods, the reaction of indoles with aromatic or aliphatic aldehydes and ketones in the presence of Lewis acids, Bronsted acids or montmorillonite clay K-10, Phosphoric Acid on Silica Gel have been widely studied [3-9]. More recently, the use of other catalysts such as $InCl_3$, PPh_3, $HClO_4$, $LiClO_4$, $In(OTf)_3$, Zeolite-HY, $KHSO_4$ and so on [10] in acetonitrile was found to form bis(indolyl) methanes. However, many Lewis acids are deactivated or sometimes decomposed by nitrogen containing reactants. These problems can be somewhat circumvented by using expensive lithium perchlorate. However it requires longer reaction times for nitro-substituted aromatic aldehydes, giving the corresponding bis (indolyl) methanes in modereate yields. We now report here the synthesis of bis(indolyl)methanes by condensation of indoles with various aldehyde compounds using dipyridine copper chloride [11] in acetonitrile as an efficient catalyst due to the presence of two pyridine rings increases the electron deficiency on the nitrogen so it is efficiently act as a Lewis acid [12].

When indole (1) (10.0 mmol) was treated with various aldehydes (2 and 3) (5 mmol) in the presence of a catalytic amount of $CuPy_2Cl_2$ (10 mol%) in acetonitrile, the electrophilic substitution reactions of indoles with aldehydes proceeded smoothly at room temperature to form Bis(indolyl)methanes in almost quantitative yields. The results are summarized in Table 1.



Scheme 1

Table 1 $CuPy_2Cl_2$ catalyzed synthesis of Bis(Indolyl)methanes[a]

Entry	Aldehyde	t (min)	m.p	Yield(%)[b]
1		35	150-152	4a 90
2		35	171-173	4b 88
3		45	210-212	4c 82
4		45	230-232	4d 85
5		45	220-222	4e 88
6		45	280-282	4f 83
7		30	198-200	5a 89
8		35	190-193	5b 85
9		40	230-232	5c 82
10		45	228-230	5d 84

[a]All products were characterized by 1HNMR and mass spectral data
[b]Yield of isolated pure products.

General Procedure

A mixture of indole (10 mmol), aldehyde (5 mmol) and copper dipyridine dichloride (10% w/w of aldehydes) in CH_3CN (30 mL) was stirred at room temperature for the appropriate time. After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (20 mL), and extracted with ethyl acetate (2x20 mL). The combined organic layer was dried over Na_2SO_4. Concentrated under reduced pressure and purified by column chromatography (ethyl acetate: hexane=1:4) to afford the pure

product.

4a: ^{1}H NMR (DMSO-d_6): δ 9.31 (br s, 2H, NH), 8.01 (s, 1H, CH), 7.65 (d, 1H,Ar-H), 7.18-7.33 (m, 10H, Ar-H), 7.01 (d 1H,Ar-H), 6.60 (d, 2H, CH), 5.25 (s, 1H), Mass: m/z (%): 390 (M^+), Calcd. C, 79.98, H, 4.65, N, 7.17%. Found. C, 79.95, H, 4.63, N, 7.19%.

4b: ^{1}H NMR (DMSO-d_6): δ 9.50 (br s, 2H, NH), 8.05 (s, 1H, CH), 7.20-7.33 (m, 8H, Ar-H), 7.10 (d, 1H), 6.95 (d, 1H), 6.75 (s, 1H,), 6.45 (d, 2H,CH), 5.01(s, 1H) 2.35 (s, 3H, CH_3), Mass: m/z (%): 404 (M^+), Calcd. C, 80.18, H, 4.98, N, 6.93%. Found. C, 80.20, H, 4.95, N, 6.98%.

4c: ^{1}H NMR (DMSO-d_6): δ10.50 (br s, 2H, NH), 8.10 (s, 1H, CH), 7.23-7.33 (m, 8H, Ar-H), 7.01 (d, 1H), 6.90 (d, 1H), 6.75 (s, 1H,), 6.35 (d, 2H,CH), 5.25 (s, 1H), Mass: m/z (%): 463 (M^+) Calcd. C, 66.54, H, 3.65, N, 5.97%. Found. C, 66.50, H, 3.69, N, 5.95%.

4d: ^{1}H NMR (DMSO-d_6): δ 10.35 (br s, 2H, NH), 7.95 (s, 1H, CH), 7.01-7.23 (m, 8H, Ar-H), 7.30 (d, 1H), 6.90 (d, 1H), 6.75 (s, 1H,), 6.40 (d, 2H,CH), 5.85 (s, 1H) Mass: m/z (%): 424 (M^+), Calcd. C, 73.50, H, 4.03, N, 6.59%. Found. C, 73.54, H, 4.09, N, 6.62%.

4e: ^{1}H NMR (DMSO-d_6): δ 10.95 (br s, 2H, NH), 7.90 (s, 1H, CH), 7.22-7.31 (m, 8H, Ar-H), 7.20 (d, 1H), 6.95 (d, 1H), 6.45 (s, 1H,), 6.30 (d, 2H,CH), 5.90 (s, 1H), 3.70 (s, 3H, CH_3), Mass: m/z (%): 420 (M^+), Calcd. C, 77.13, H, 4.79, N, 6. 66%. Found. C, 77.10, H, 4.82, N, 6.69%.

4f: ^{1}H NMR (DMSO-d_6): δ 11.25 (br s, 2H, NH), 8.15 (s, 1H, CH), 7.32-7.45 (m, 8H, Ar-H), 7.25 (d, 1H), 6.95 (d, 1H), 6.50 (s, 1H,), 6.30 (d, 2H,CH), 5.45 (s, 1H), Mass: m/z (%): 435 (M^+), Calcd C, 71.72, H, 3.94, N, 9.65%. Found. C, 71.70, H, 3.96, N, 9.67%.

5a: ^{1}H NMR (DMSO-d_6): δ 11.05 (br s, 2H, NH), 10.50 (s, 1H, OH), 8.10 (d, 1H), 7.10-7.23(m, 8H, Ar-H), 6.90 (d, 1H), 6.45 (d, 2H), 6.30 (d, 1H), 6.12 (d, 1H), 5.30 (s, 1H, CH), Mass: m/z (%): 406 (M^+), Calcd. C, 76.83, H, 4.46, N, 6.89%. Found. C, 76.80, H, 4.40, N, 6.82%.

5b: ^{1}H NMR (DMSO-d_6): δ 11.20 (br s, 2H, NH), 10.45 (s, 1H, OH), 7.20-7.40 (m, 8H, Ar-H), 6.90 (d, 1H), 6.75 (d, 2H), 6.35 (d, 1H), 6.03 (s, 1H), 5.20 (s, 1H, CH), 2.60 (s, 3H, CH_3), Mass: m/z (%): 420 (M^+), Calcd. C, 77.13, H, 4.79, N, 6.66%. Found. C, 77.10, H, 4.73, N, 6.69%.

5c: ^{1}H NMR (DMSO-d_6): δ 11.20 (br s, 2H, NH), 10.10 (s, 1H, OH), 8.40 (s, 1H), 7.26-7.43(m, 8H, Ar-H), 6.93 (d, 1H), 6.50 (d, 2H), 6.29 (d, 1H), 5.45 (s, 1H, CH), Mass: m/z (%): 485 (M^+), Calcd. C, 64.34, H, 3.53, N, 5. 77%. Found. C, 64.30, H, 3.59, N, 5.2%.

5d: ^{1}H NMR (DMSO-d_6): δ 11.50 (br s, 2H, NH), 10.45(s, 1H. OH), 8.15(s, 1H), 7.19-7.41 (m, 8H, Ar-H), 6.95 (d, 1H), 6.40 (d, 2H), 6.37 (d, 1H), 5.20 (s, 1H, CH), Mass: m/z (%): 440 (M^+), Calcd. C, 70.83, H, 3.89, N, 6.35%. Found. C, 70.80, H, 3.83, N, 6.40%.

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