Global Journal of Science Frontier Research: B
Chemistry
Volume 14 Issue 6 Version 1.0 Year 2014
Type : Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4626 & Print ISSN: 0975-5896

Novel Aspects of Domino Reaction of Indoles with Homo-Phthalaldehyde and Tere-Phthalaldehyde

By Mardia T. El Sayed, Khadiga M. Ahmed, Kazem Mahmoud & Andreas Hilgeroth

National Research Centre, Egypt

Abstract- In the present work domino reaction of indole with homophthaladehyde (1) have been investigated for the first time. The reaction have been done in presence of glacial acetic acid as catalyst and solvent afford the novel un probable mixture of two isomers A and B of benzo[7]anulene (2) that couldn't be divided accompany with the formation of the predictable tetraindole (3) in a yield of 46 to 38 % respectively. Terephthaladehyde (4) condensed with indoles in glacial acetic acid in a molar ratio (1:4) affording compounds $5_{a,b}$ in a high yield of 93 - 95 % after a short time of stirring at room temperature. Compounds $5_{a,b}$ can act as nucleophile due to the unoccupied two positions of the four indole rings. Accordingly we now present for the first time a expedient method for the synthesis of the novel extensive ring systems 6 and (7_{a-f}) via condensation reaction of compound 5_a with aryl or heteroaryl substituted aldehydes in a molar ratio (1:2).

GJSFR-B Classification : FOR Code: 030601p

Strictly as per the compliance and regulations of :

Novel Aspects of Domino Reaction of Indoles with Homo-Phthalaldehyde and Tere-Phthalaldehyde

Mardia T. El Sayed [α], Khadiga M. Ahmed [σ], Kazem Mahmoud [ρ] & Andreas Hilgeroth[ω]

Abstract- In the present work domino reaction of indole with homophthaladehyde (1) have been investigated for the first time. The reaction have been done in presence of glacial acetic acid as catalyst and solvent afford the novel un probable mixture of two isomers A and B of benzo[7]anulene (2) that couldn't be divided accompany with the formation of the predictable tetraindole (3) in a yield of 46 to 38 % respectively. Terephthaladehyde (4) condensed with indoles in glacial acetic acid in a molar ratio (1:4) affording compounds $5_{a,b}$ in a high yield of 93 - 95 % after a short time of stirring at room temperature. Compounds $5_{a,b}$ can act as nucleophile due to the unoccupied two positions of the four indole rings. Accordingly we now present for the first time a expedient method for the synthesis of the novel extensive ring systems 6 and (7_{a-f}) via condensation reaction of compound 5_a with aryl or heteroaryl substituted aldehydes in a molar ratio (1:2).

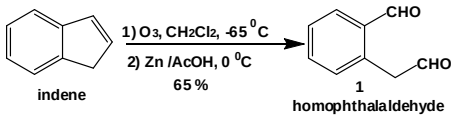
I. Introduction

A straightforward and direct method for the electrophilic substitution reaction of indole involves the condensation reaction with aliphatic or aromatic aldehydes. Typically these reactions arise in presence of several types of catalysts for instance protic[1-4] or Lewis acids[5-9] or ionic liquids.[10] The electron rich indole nucleus shows an superior reactivity in the direction of carbon electrophiles that commonly results in the formation of three substituted indole derivatives.[11] The 3-position of the indole ring is the favourite site for the electrophilic substitution reactions. 3-Alkyl or 3-acyl indoles are versatile intermediates for the synthesis of a extensive series of indole derivatives possessed pharmaceutical significance.[12]

II. Result and Discussion

a) Synthesis of Homophthalaldehyde

Homophthalaldehyde is of significant concern as a precursor of isoquinoline and its derivatives.[13-17] Homophthalaldehyde (1) is not commercially accessible so that we were synthesized it via an ozonolysis of indene in dry dichloromethane at - 65 ^{0}C followed by reduction with zinc in acetic acid at 0 ^{0}C affording the homophthalaldehyde after an azeotropic distillation to remove the water, [18] (Scheme 1).

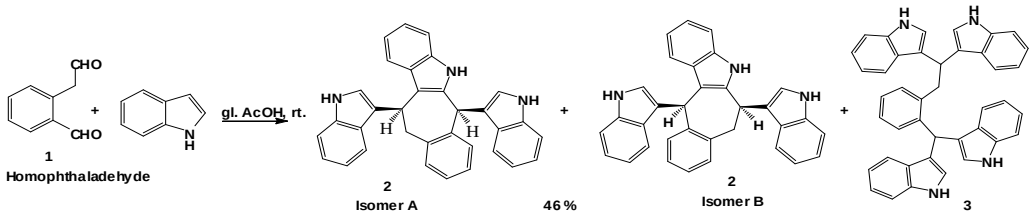


Scheme 1: Synthesis of homophthalaldehyde.

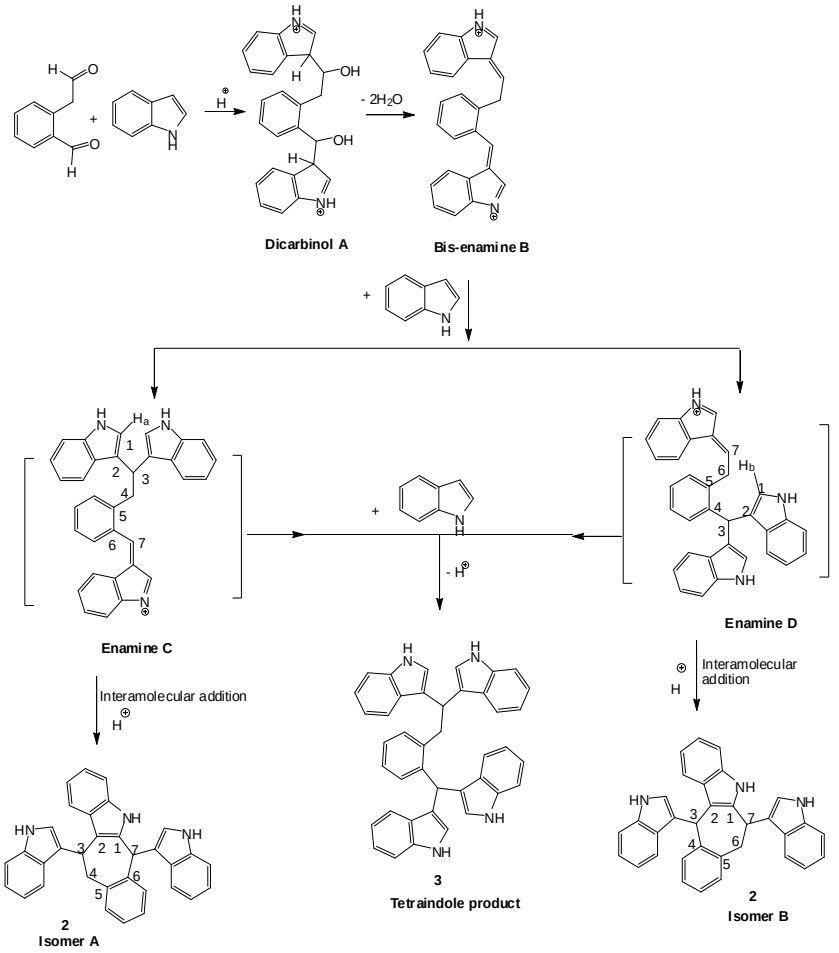
After an azeotropic distillation the formed dialdehyde was used straightforwardly in the condensation reaction with indole in acetic acid at room temperature acquiescent a novel benzo[7]annulene derivatives of type 2 in a average yield of 46 % and the tetraindole product 3 in 38 % yield. Both products 2 and 3 are novel compounds which have not reported in the literature.

Compound 2 was set up to be a mixture consists of two isomers A and B, where its ^{1}H-NMR spectrum showed two signals multiplets for the two protons at C_3 of both isomer A and B at δ = 4.98 ppm and 5.71 ppm values, and two signal multiplets for the two protons at C_7 of both isomers A and B at δ = 5.86 and 6.03 ppm. Also the CH_2 group at position 4 in isomer A and at position 6 in isomer B gives each one multiple signal at 2.85 - 2.89 ppm and 3.94 - 4.03 ppm values. These ^{1}H-NMR data give strong suggestion that we have a mixture of both isomers A and B. From the ^{1}H-NMR spectra and referring to the successful single crystal X-ray crystallography of the triindole product that has synthesized and established in our previous work.[19] In which confirmed that the presence of two different signals for the two protons of C_3 and C_7 in every isomer of compound 2, pointed to that we have cis-forms for both isomers A and B, (Scheme 1).

Author α ρ ω: Institute of Pharmacy, Martin-Luther University, Research Group of Drug Development and Analysis, Wolfgang-Langenbeck-Straße Halle, Saale, Germany. e-mail: mardia_elsayed2009@yahoo.co
Author α: Applied Organic Chemistry Department, National Research Centre, Cairo, Egypt.
Author σ: Natural Compounds Laboratory, National Research Centre, Cairo Egypt.



Scheme 2: Domino reaction of indole with homophthaladehyde.



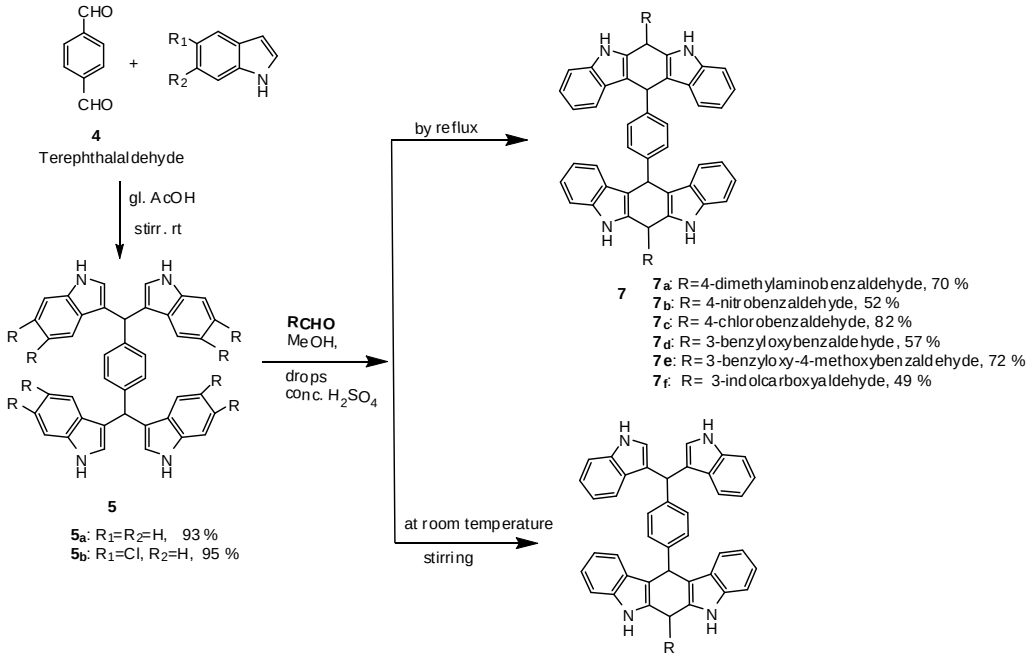
Scheme 3: Expected reaction mechanism for the condensation of indole with homophthaladehyde.

The mechanism of formation of both isomers A and B of triindole (2) accompanied with tetraindole (3) can be explained by the mechanism showed in (Scheme 3). Indole condensed with homophthalaldehyde in acid medium formed the dicarbinol A which underwent dehydration via an elimination of two molecules of water to give the bisenamine B. This bisenamine B reacted with the third indole to give the mono enamine C or D. If the intramolecular addition takes place via α-indole C-Ha in enamine C, the formed triindole (2) was isomer A. And if The intramolecular addition with α-indole C-H_b in enamine D yielded the triindole *isomer* B. A successful addition of the fourth indole to either enamine C or enamine D tends to the formation of the tetraindole product 3. The α-electrophilic attacks in the indole units leading to cyclization have been reported in several indole reactions yielding indole alkaloids.[20,21]

b) Reaction with Terephthalaldehyde

Indolo-carbazoles s have been reported as a primary compound for the synthesis of various drugs and possess important biological, pharmacological, and medicinal activities.[22-24] Indolo-carbazoles are associated with anticancer, antimicrobial and antifungal activities. In most of these belongings biological activity is simultaneous with indolo-carbazoles contain heteroatom. The biological activity depends on the interaction potential with DNA.[25, 26] The electrophilic substitution reactions of indoles with terephthaladehyde

have been reported in the literature as a possible way for the synthesis of supramolecular compounds containing bis-indolylmethane (BIMs), namely 3,3′,3″,3‴-tetraindolyl(terphthalayl)dime-thane (5_a).[27] This reaction has been done in presence of several catalysts such as iodine and N-bromosuccinimide (NBS)28,29 affording the tetra substituted product in good yields[28-32]. In view of the present work, terephthaladehyde (4) condensed with indoles in glacial acetic acid in a molar ratio (1:4) afford compounds $5_{a,b}$ in a high yield of 93-95 % respectively after a short time of stirring at room temperature 2 to 4 hours, (Scheme 4).



Scheme 4: Condensation reaction of **5_a** with aldehydes.

Compounds $5_{a,b}$ can acts as nucleophile due to the vacant two positions of the four indole rings, hence we now present a convenient method for the synthesis of the novel extended ring systems (7_{a-f}) via the condensation reaction of compound 5a with aryl or heteroaryl substituted aldehydes in a molar ratio (1:2), (Scheme 4). The reaction was proficient by let the compounds reacting in methanol solution containing drops of conc. H_2SO_4 under reflux. The product was detected by TLC and isolated easily by column chromatography using dichloromethane as an eluent. However, when the reaction has carried out at room temperature under stirring for long time, the main product which was separated and identified was compound 6 by using p-dimethylaminobenzaldehyde.

Compound 6 can be considered as an intermediate product for the formation of the compound 7_a. A modified synthesis for the novel extended ring system indolo-biscarbazoles (7_{a-f}) has been done by one step procedure by an acid-catalyzed intermolecular reaction as in the reported belongings of condensation of BIMs and aldehydes to afford the analogous substituted indolo[3,2-b]-bis-carbazoles.[33-37] The proposed mechanism expected that the successful condensation of the tetraindole 5_a with the first mole of aldehyde afforded the bisindole monocarbazole as an intermediate 6 which can be isolated from the reaction.

This intermediate gave the novel extended ring system indolocarbazoles (7) as a final product as a result of the condensation with the second mole of an aldehyde. This suggested mechanism is supported by an isolation of the intermediate 6, so we can say that the second condensation step with the second mole of aldehyde may need heat energy with the acid catalyst for promotion of the reaction to take place. The ^{1}H-NMR spectrum of compounds 7_{a-f} detected the aliphatic hydrogenated protons of dihydroindolo [3,2-*b*]carbazoles as a single signal at δ value of about 4.5 to 5.5 ppm with an integral for four protons and one with an integral for three protons in the case of the compound 6.

III. Conclusion

First domino reaction of indole with homophthaladehyde and terephthalaldehyde have been investigated. The reaction have been done in presence of glacial acetic acid as catalyst and solvent affording in case of homophthalaldehyde novel and un expected mixture of two isomers of benzo[7]anulene (2) that couldn't be separated accompanied with the formation of the expected tetraindole (3) in a yield of 46 to 38 % respectively. Terephthaladehyde (4) condensed with indoles in glacial acetic acid in a molar ratio (1:4)

affording compounds $5_{a,b}$ in a high yield of 93-95 % followed by condensation with series of aryl aldehydes to synthesis of the novel extended ring systems 6 and 7_{a-f} in a molar ratio (1:2).

IV. Expremental

The melting points were measured on a Boetius-Mikroheiztisch the company "VEB weighing. Rapido Radebeul / VEB NAGEMA "measured and are uncorrected. TLC for the analyzes were with aluminium foil fluorescent indicator from Merck KGaA (silica gel 60 F254, layer thickness 0.2 mm). R_f -values (run level relative to the solvent front). The separations were with column chromatography at atmospheric pressure on silica gel 60 (Grain size from 0.063 to 0.200 mm) from Merck KGaA. NMR spectra were recorded on a "Gemini 2000" (400/100 MHz). The ATR spectra were recorded on a FT-IR spectrometer "IFS 28" by "Bruker. The ESI mass spectra were recorded on a "Finnigan LCQ Classic". The EI mass spectra were recorded on an "Intel 402".

a) Procedure for the preparation of Homophthalaldehyde (1)

Ozonolysis of indene: freshly distilled indene (10 ml, 9.8 mg, 85 mmol) was added to dry dichloromethane (200 ml, distilled from P_2O_5). The solution was cooled dawn to -65 ^{0}C, and ozone (about 3 % in oxygen, flow rate 11/min.) was bubbled through the solution for 10 mines. The resulting blue solution was flushed with nitrogen until the blue colour disappeared for about 10 mines, and then zinc (4.0 mg) and acetic acid (20 ml) were added. The solution was allowed to warm to 0 ^{0}C under stirring. Four similar portions of zinc in acetic acid were added over the next 2 and 1/2 h. The resulting mixture was then filtered, the filtrate washed with aqueous 2 N sodium carbonate solution (50 ml), water (3 x 50 ml), and dried over sodium sulphate. Evaporation of the solvent under reduced pressure gave pale yellow oil. Dry benzene (100 ml) was added and the mixture was heated to distil off the benzene. This isotropic distillation was repeated, and the residue was then distilled under reduced pressure with a yield of 65 % b.p. 90 / 0.1 mm. The distillation temperature must be kept below 100 ^{0}C otherwise extensive decomposition occurs. Colourless liquid, $C_9H_8O_2$, 148.16 g/mol, EI-MS: (m/z) = 148 [M^+] 6 %, 147 [M^+-H] 4 %, 134 [M^+-CH_2] 6 %, 120 [M^+-CO] 97 %, 119 [M^+-CHO] 100 %, ^{1}H-NMR: (400 MHz, DMSO-d_6) δ (ppm) = 4.75 (d, 2H, J=6.5 Hz, CH_2), 7.01 - 7.22 (m, 2H), 7.30 - 7.52 (m, 2H), 9.72 (t, 1H, J=4.7 Hz, CH_2CHO), 10.00 (s, 1H, CHO)

b) Procedure for the preparation of compounds 2 and 3

2 Mmol of the aromatic dialdehyde homophthalaldehyde were added in a round bottom flask containing 5 mL of glacial acetic acid at room temperature. Then 5 mmol of indole were added to the reaction mixture. The clear light yellow solution was left to stirring overnight, when the solution became dark brown. The product was detected by TLC (100 % CH_2Cl_2). The TLC showed the formation of the two products, compound 2 at high R_f value and compound 3 at low R_f value where the indole was not finished from the reaction mixture. At this point the reaction was worked up by neutralization with a cold solution of 10 % NaOH affording a brown precipitate. Then the mixture was extracted with CH_2Cl_2 three times 200 mL, washed with water for two times 150 mL and brine for two times 150 mL then dried over anhydrous sodium sulphate, filtered and finally concentrated in vacuum. The crude reaction mixture was purified *via* column chromatography on silica gel eluting with dichloromethane, to remove at first the un reacted indole, and then compound 2 was collected, followed by compound 3.

c) Cis-distereomer: 6,10-Di(1H-indol-3yl)-5,10,11,12-tetra- hydrodibenzo[a,g]azulene[b]ind- -ole (2)

Puff powder, $C_{33}H_{25}N_3$, 463.57 g/mol, mp: 255 – 257 ^{0}C, ESI-MS: (m/z) = 462.14 [M^+-H], EI-MS: (m/z) = 463 [M^+] 4 %, 347 [M^+-indolyl] 100 %, 333.9 [M^+-indolyl-CH_2] 13 %, 256.6 [M^+-indolyl-CH_2-Ph] 3 %, 245 [indolyl.CH.indolyl] 9 %, 230 [indolyl.indolyl] 15 %, 217 [indolyl.CH_2.CH.Ph] 12 %, 130 [indolyl.CH_2] 10 %, 117 [indolyl] 20 %, 90 [Ph.CH_2] 8 % , IR-Spectrum: (ATR,cm^{-1}) = 2922 (CH_2), 3401 (NH), ^{1}H-NMR: (400 MHz, acetone-d_6) δ (ppm) = 2.85 - 2.89 (m, 2H, CH_2), 3.94 - 4.03 (m, 2H, CH_2), 4.98 (s,br., 1H, CH), 5.71 (s,br., 1H, CH), 5.85 - 5.89 (m, 1H, CH), 6.03 (s, br., 1H, CH), 6.25 - 6.32 (m, 2H,), 6.22 (s, 1H), 6.68 (s, 1H), 6.85 (t, 2H, J=9.1 Hz), 6.88 - 7.02 (m, 4H), 7.09 - 7.34 (m, 5H), 7.44 - 7.51 (m, 1H), 7.67 (d, 1H, J=7.1 Hz), 7.78 (s, 1H), 10.33 (s, 1H, NH), 10.57 (d, 1H, NH), 10.92 (s, 1H, NH), ^{13}C-NMR: (100 MHz, acetone-d_6) δ (ppm) = 26.32 (CH), 26.34 (CH), 31.47 (CH_2), 32.06 (CH_2), 110.43, 111.17, 111.31, 111.46, 112.73, 116.37, 116.59, 117.34, 117.72, 117.89, 117.97, 118.03, 118.26, 118.49, 119.02, 119.32, 120.23, 120.32, 120.48, 120.69, 123.02, 123.34, 124.77, 125.39, 125.64, 125.90, 126.00, 126.28, 126.33, 126.44, 126.89, 127.73, 128.31, 128.42, 128.89, 131.44, 131.64, 131.89, 134.71, 134.87, 135.13, 135.98, 136.57, 136.73, 138.10, 138.84, 141.51, Elemental analysis: calcd. C, 85.50; H, 5.44; N, 9.06, found C, 85,53, H, 5.42, N.8.99, R_f -Value: 0.72 (CH_2Cl_2), yield: 427 mg, 46 %.

d) 3,3'-((2-(2,2-di(1H-indol-3-yl)ethyl)phenyl)methylene) bis (1H-indole) (3)

Light brown powder, $C_{41}H_{32}N_4$, 580.72 g/mol, 168 – 172 ^{0}C, ESI-MS: (m/z) = 579.08 [M^+-H], IR (ATR, cm^{-1}): 2922 (CH_2), 3407 (NH), ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 3.59 (d, 2H, J=6.9 Hz, CH_2), 4.80 - 4.83 (m, 1H, CH-CH_2), 5.71 (s, 1H, CH), 6.13 (s, 2H), 6.47 (s, 2H), 6.72 - 6.77 (m, 4H), 6.89 - 7.19 (m, 8H), 7.22 (d, 4H, J=7.9 Hz), 7.32 (t, 4H, J=7.7 Hz), 10.63 (s,

2H, 2NH), 10.71 (s, 2H, 2NH), ^{13}C-NMR: (100 MHz, DMSO-d_6) δ (ppm) = 41.52 (CH_2), 46.00 (CH), 59.01 (CH), 102.00, 105.22, 111.33, 115.02, 116.55, 117.80, 118.03, 118.23, 118.93, 120.44, 122.00, 124.00, 125.50, 126.02, 129.00, 130.00, 132.23, 134.61, 135.02, 138.52, 139.00, 142.00, EA: calcd. C, 84.80; H, 5.55; N, 9.65, found C, 84.87, H, 5.56, N, 9.56, R_f : 0.54 (CH_2Cl_2), yield: 441 mg, 38 %.

e) General procedure for the preparation of compound $5_{a,b}$

In a flask containing 20 ml glacial acetic acid, (1 mmol, 0.134 gm) of terphthalaldehyde was added under stirring at room temperature. And after all the amounts of the dialdehyde were dissolved, indole (4 mmol, 0.47 gm) or 5-chloroindole (4 mmol, 0.61 gm) was added. Then the reaction mixture was allowed to stirring overnight at room temperature. The reaction solution curved from light yellow to dark pink colour. The product was detected by TLC (100 % CH_2Cl_2) until the reaction was finished. In the case of indole the product was precipitated from the reaction mixture, filtered off, washed with AcOH, and washed with water until AcOH is removed, dried over P_2O5 to give a pure light pink powder of compound 5_a,[28,29] in 98 % yield. The case of 5-chloroindole the product precipitated by the addition of 10 ml water and filtered off, washed with water under suction and dried to afford compound 5_b

f) 1,4-Bis(bis(5-chloro-1H-indol-3-yl)meth-yl)benzene (5_b)

Pink powder, $C_{40}H_{26}C_{l4}N_4$ (704.47) g/mol, mp 160 - 163^{0}C, ESI-MS: (m/z) = 705.35 [M^++H], IR (ATR, cm^{-1}) = 1458 (CCl), 3424 (NH), ^{1}H-NMR: (400 MHz, $CDCl_3$) δ (ppm) = 5.63 (s, 2H, 2CH), 6.49 - 6.50 (m, 4H), 7.05 (dd, 4H, J=1.9, 8.6 Hz), 7.11 (s, 4H), 7.17 (d, 4H, J=7.4 Hz), 7.20 - 7.29 (m, 4H), 7.79 (s, 4H, 4NH), ^{13}C-NMR: (100 MHz, $CDCl_3$) δ (ppm) = 39.67 (2CH), 112.21, 119.15, 119.26, 122.31, 124.97, 125.09, 128.06, 128.71, 135.06, 141.35, EA. calcd. C, 68.20; H, 3.72; Cl, 20.13; N, 7.95, found C, 68.24, H, 3.75, Cl, 20.7, N, 8.00, R_f - Value 0.55 (CH_2Cl_2), yield (669 mg), 95 %.

g) General procedure for the preparation of compounds 6 and 7_{a-f}

To a flask containing 50 ml MeOH 1mmol, 0.567 mg of compound 1_a was added under stirring and heating until it completely dissolved. Then 2 mmol of the appropriate aromatic or heterocyclic aldehyde was added to the reaction mixture, and after the aldehyde was dissolved, a few drops of conc. H_2SO_4 were added drop wisely, where the reaction solution became pink colour. Then the reaction mixture was left stirring for about 1h under reflux. The reaction afforded a precipitate and when the reaction was finished, the precipitate was filtered off while the solution was still hot, dried to afford compound 7_{a-f}, which was purified by passing over a column and eluted with 30 % Et.Ac/hexane. Whereas the monocondensed product 6 was formed by leaving the same reactants in a ratio of 1 mmol, 0.567 mg of compound 5_a and 2 mmol, 0.3 gm of 4-*N*,*N*-dimethylaminobenzaldehyde under stirring at room temperature for a long time.

h) 4-(8-(4-(Di(1H-indol-3-yl)methyl)phenyl)-1,2,3,8-tetra -hydroindolo[2,3-b]carbazol-2-yl)-N,N dimethylaniline (6)

Light brown powder, $C_{49}H_{39}N_5$, 697.87 g/mol, mp 218 - 220 ^{0}C, ESI-MS (m/z): 699.12 [M^++H], 697.09 [M^+-H], IR (ATR, cm^{-1}): 1590 ($N(Me)_2$), 2850, 2922 (CH), 3407 (NH), ^{1}H-NMR: (400 MHz, acetone-d_6) δ (ppm) = 2.80 (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 5.93 (s, 2H, 2CH), 6.18 (s, 1H, CH), 6.85 (s, 4H), 6.91 (t, 4H, J=7.3 Hz), 7.10 (t, 6H, J=7.6 Hz), 7.12 - 7.34 (m, 4H), 7.39 (t, 8H, J=8.6 Hz), 9.96 (s, 2H, 2NH), ^{3}C-NMR: (100 MHz, acetone-d_6) δ (ppm): 29.95 (CH_3), 30.05 (CH_3), 30.26 (CH), 40.86 (CH), 40.93 (CH), 111.90, 112.08, 112.24, 114.01, 118.32, 119.24, 120.10, 120.35, 121.96, 123.15, 123.92, 124.48, 125.18, 128.17, 129.21, 131.82, 133.07, 134.17, 137.33, 143.48, EA calcd. C, 84.33; H, 5.63; N, 10.04, found C, 84.24, H, 5.70, N, 10.00, R_f 0.6 (CH_2Cl_2), yield (426 mg), 61 %.

i) 4,4'-(8,8'-(1,4-Phenylene)bis(1,2,3,8-tetrahydroindolo [2,3-b]carbazole-8,2-diyl))bis-(N,N-dimethylaniline (7_a)

Pink powder, $C_{58}H_{48}N_6$, 829.04 g/mol, mp 140 - 144 ^{0}C, ESI-MS: (m/z) = 828.26 [M^+-H], IR(ATR, cm^{-1}): 1540 ($N(Me)_2$), 3377 (NH), ^{1}H-NMR: (400 MHz, acetone-d_6) δ (ppm) = 2.79 (s, 6H, $2CH_3$), 2.98 (s, 6H, $2CH_3$), 5.79 (s, 4H, 4CH), 6.69 (d, 8H, J=8.8 Hz), 6.78 (t, 4H, J=7 Hz), 6.95 (t, 4H, J=6.7 Hz), 7.26 (t, 8H, J=7.3 Hz), 7.62 (d, 4H, J=9 Hz), 9.84 (s, br., 4H, 4NH), ^{13}C-NMR (100 MHz, acetone-d_6) δ (ppm): 26.64 (Me), 39.23 (CH), 40.01 (CH), 111.07, 111.24, 118.39, 118.64, 119.25, 119.50, 121.11, 121.38, 123.48, 123.63, 125.47, 127.31, 128.36,129.36, 129.41, 131.38, 137.06, 137.21, 142.59, R_f 0.44 (100 % CH_2Cl_2), yield (580 mg), 70 %.

j) 1,4-Bis(2-(4-Nitrophenyl)-1,2,3,8-tetrahydroindolo [2,3-b]carbazol-8-yl)benzene (7_b)

Yellow powder, $C_{54}H_{36}N_6O_4$, 832.90 g/mol, mp 260 – 262 ^{0}C, ESI-MS (m/z): 832.43 [M^+-H], IR (ATR, cm^{-1}): 1310, 1516 (NO_2), 2852, 2921 (CH), 3406 (NH), ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 6.02 (s, 4H, 4CH), 6.86 -6.97 (m, 8H), 7.04 (t, 4H, J=7.5 Hz), 7.27 (d, 4H, J=8 Hz), 7.35 (d, 4H, J=8.3 Hz), 7.59 (d, 4H, J=8.6 Hz, 8.15 (d, 4H, J=8.7 Hz), 10.91 (s, br., 4H, 4NH), ^{13}C-NMR: (100 MHz, DMSO-d_6) δ (ppm) = 29.46 (CH), 30.87 (CH), 108.32, 110.33, 111.05, 111.92, 112.06, 112.50, 115.20, 116.14, 117.15, 117.82, 118.34, 118.89, 119.38, 121.02, 121.57, 122.00, 123.89, 124.33, 126.84, 128.50, 129.93, 137.06, 144.22, 146.00, 147.90, EA calcd. C, 77.87; H, 4.36; N, 10.09, found C, 78.00, H, 4.39, N, 10.12, R_f 0.77 (CH_2Cl_2), yield (433 mg), 52 %.

k) 1,4-Bis(2-(4-Chlorophenyl)-1,2,3,8-tetrahydroindolo [2,3-b]carbazol-8-yl)benzene (7_c)

Yellow powder, $C_{54}H_{36}Cl_2N_4$, 811.80 g/mol, mp >350 ^{0}C, ESI-MS: (m/z) = 811.06 [M^+-H], IR (ATR, cm^{-1}): 2863, 2922 (CH), 3410 (NH), ^{1}H-NMR: (100 MHz, acetone-d_6) δ (ppm): 5.68 (s, 4H, 4CH), 6.77 (s, 4H), 6.82 (t, 4H, J= 4.1 Hz), 6.86 - 6.91 (m, 4H), 6.95 - 7.11 (m, 4H), 7.14 - 7.25 (m, 2H), 7.27 - 7.30 (m, 4H), 7.39 - 7.46 (m, 2H), 7.62 - 7.73 (m, 4H), 9.92 (s, br., 4H, 4NH), ^{13}C-NMR: (100 MHz, acetone-d_6) δ (ppm) = 29.71 (CH), 31.77 (CH), 111.24, 111.99, 114.50, 115.40, 117.34, 118.62, 119.37, 121.11, 121.87, 122.40, 124.39, 125.33, 126.14, 127.55, 128.37, 129.12, 129.92, 130.01, 131.13, 132.50, 134.00, 136.62, 137.21, 137.97, 144.15, EA calcd. C, 79.89, H, 4.47, Cl, 8.73, N, 6.90, found C, 80.02, H, 4.51, Cl, 8.75, N, 6.93, R_f 0.74 (CH_2Cl_2), yield (666 mg), 82 %.

l) 1,4-Bis(2-(3-(benzyloxy)phenyl)-1,2,3,8-tetrahydro - indolo[2,3-b]carbazol-8-yl)benzene (7_d)

Yellow powder, $C_{68}H_{50}N_4O_2$, 955.15 g/mol, mp >350 ^{0}C, ESI-MS (m/z): 954.23 [M^+-H], IR (ATR, cm^{-1}): 1456 (C-O), 2922 (CH_2), 3414 (NH), ^{1}H-NMR: (400 MHz, DMSO-d_6) δ (ppm) = 5.05 (s, 4H, $2CH_2$), 5.77 (s, 4H, 4CH), 5.95 - 6.08 (m, 4H), 6.43 - 6.77 (m, 8H), 6.82 - 6.85 (m, 4H), 6.92 - 6.95 (m, 6H), 7.03 - 7.09 (m, 4H), 7.11 - 7.24 (m, 8H), 7.34 - 7.41 (m, 4H), 7.51 (s, 1H), 10.68 (s, br., 4H, 4NH), R_f 0.75 (CH_2Cl_2), yield (544 mg), 57 %.

m) 1,4-Bis(2-(3-(benzyloxy)-4-methoxyphenyl)-1,2,3,8-tetrahydroindolo[2,3-b]carbazol-8-yl)benz- ene (7_e)

Yellow powder, $C_{70}H_{54}N_4O_4$, 1015.20 g/mol, mp 152 - 158 ^{0}C, ESI-MS: 1014.25 [M^+-H], IR(ATR, cm^{-1}): 1453 (C-O), 2922 (CH_2), 3391 (NH), ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 3.69 (s, 3H, OMe), 3.94 (s, 3H, OMe), 5.01 (s, 4H, $2CH_2$), 5.58 (s, 4H, 4CH), 6.66 (d, 4H, J=8.51 Hz), 6.76 - 6.71 (m, 6H), 6.86 - 6.93 (m, 6H), 6.97 - 7.18 (m, 4H), 7.21 (t, 6H, J=7.2 Hz), 7.26 - 7.38 (m, 4H), 7.41 (d, 4H, J=7.9 Hz), 7.52 (s, 2H), 10.55 (s, 4H, 4NH), ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 48.40 (CH), 55.38 (OMe), 55.53 (OMe), 69.83 (CH_2-O), 109.32, 109.58, 110.79, 111.17, 112.04, 112.57, 114.55, 117.92, 118.38, 119.16, 120.26, 120.64, 122.13, 123.23, 123.89, 124.76, 125.66, 126.44, 127.53, 127.75, 128.07, 128.18, 129.12, 136.42, 136.87, 137.02, 141.81, 147.19, 147.61, 148.14, 148.52, R_f 0.69 (CH_2Cl_2), yield (731 mg), 72 %.

n) 1,4-Bis(2-(1H-indol-3-yl)-1,2,3,8-tetrahydroindolo [2,3-b]carbazol-8-yl)-benzene (7_f)

Light brown powder, $C_{58}H_{40}N_6$, 820.98 g/mol, mp 115 - 118 ^{0}C, ESI-MS: (m/z) = 820.25 [M^+-H], IR (ATR, cm^{-1}): 2853, 2923 (CH), 3391 (NH), ^{1}H-NMR (400 MHz, acetone-d_6) δ (ppm): 4.21 (s, 4H, 4CH), 6.94 (t, 8H, J=7.4 Hz), 6.99 (s, 2H), 7.05 (d, 4H, J=7.7 Hz), 7.08 (d, 6H, J=6.9 Hz), 7.35 (d, 4H, J=8.1 Hz), 7.55 (d, 6H, J=8.1 Hz), 9.86 (s,br., 4H, 4NH), 9.96 (s,br., 2H, 2NH), ^{13}C-NMR (100 MHz, acetone-d_6) δ (ppm): 30.26 (CH), 111.27, 111.97, 112.02 (3C), 115.83 (2C), 119.16 (3C), 119.36, 119,67 (3C), 121.89 (3C), 123.28, 123.44 (3C), 128.64, 137.87, EA calcd: C, 84.85; H, 4.91; N, 10.24, found C, 84.88, H, 5.01, N, 10.22, R_f 0.76 (CH_2Cl_2), yield (402 mg), 49 %.

References Références Referencias

1. Yu, L.; Chen, D.; Li, J.; Wang, P. G. *J. Org. Chem.* 1997, 62, 3575.
2. Karthik, M.; Tripathi, A. K.; Gupta, N. M.; Palanichamy, M.; Murugesan, V. *Catal. Commun.* 2004, 5, 371.
3. Penieres-Carrillo, G.; Garcı´a-Estrada, J. G.; Gutie´rrez-Ramı´reza, J. L.; Alvarez-Toledanob, C. *Green Chem.* 2003, 5, 337.
4. Maiti, A. K.; Bhattacharyya, P. *J. Chem.* Res. 1997, 424.
5. Amoroso, A.; Radice, M.; Segall, A.; Rodero, L.; Hochenfellner, F.; Pizzorno, M. T.; Moretton, J.; Garrido, D.; Gutkind, G. *Pharmazie* 2000, 55, 151 - 152.
6. Segall, A.; Pizzorno, M. T. *Pharmazie* 2000, 55, 766 - 767.
7. Golob, T.; Biberger, C.; Walter, G.; Angerer, E. *Arch. Pharm.* 2000, 333, 305 - 311.
8. Frederich, M.; Jacquier, M.-J.; Thepenier, P.; Mol, P. D.; Tits, M.; Philippe, G.; Delaude, C.; Angenot, L.; Zeches-Hanrot, M. *J. Nat. Prod.* 2002, 65, 1381 - 1386.
9. Fertuck, K. C.; Kumar, S.; Sikka, H. C.; Matthews, J. B. ;Zacharewski, T. R., Toxicol. Lett. 2001, 121, 167 - 178.
10. (a): Ji, S.-J.; Zhou, M.-F.; Wang, S.-Y.; Loh, T.-P. Synlett 2003, 2077 – 2079. (b): Gu, D.-G.; Ji, S.-J.; Jiang, Z.-Q.; Zhou, M.-F.; Loh, T.-P. *Synlett,* 2005, 959 – 962.
11. Raju, B. C.; Rao, *J. M., Indian J. Chem.* 2008, 47B, 623.
12. Sujatha, K.; Perumal, P. T.; Muralidharan, D.; Rajendran, M. *Indian J. Chem.* 2009, 48B, 267.
13. B. K. Blount, *J. Chem. Soc.* 1933, 553.
14. B. K. Blount, R. Robinson, *J. Chem.* Soc. 1933, 555.
15. P. Baumgarten, J. Olshausen, *Chem. Ber.* 1931, 64, 925.
16. L. F. Fieser, M. M. Pechet, *J. Amer. Chem.* Soc.1946, 68, 2577.
17. J. L. Warnell, R. L. Shriner, *J. Amer. Chem.* Soc., 1957, 79, 3165.
18. P. J. Garratt and K. Peter C. Vollhardt, *Communications,* 1971, 423 - 424.
19. Mardia T. E., Kazem A. M., Frank. W, Heinemann, N, Sibel S., Nurten A. and Andreas H., *Journal of Heterocyclic Chemistry,* 2013. (accepted)
20. (a): M. Lluı¨sa Bennasar, Toma`s Roca, Rosa Griera, Marjan Bassa, and Joan Bosch. Generation

and Intermolecular Reactions of 3-Indolylacyl Radicals, *J. Org. Chem.* 2002, 67, 62686271. (b): Josep Bonjoch, Juan10 Catena, Dolors Terricabras, Joan-Carles Fem&ndez, Meritxell L6pez-Canet and Nativitat Valls. Synthesis of enantiopure (2R&3aS, 7aS)-2-ethyloctahydroindol-6-one and its Fischer indolization, *Tetrahedron Asymmetry,* Vol. 8, No. 18. pp. 3143 - 3151. (c): M. Lluisa Bennasar, Bernat Vidal and Joan Bosch, A synthetic route to the alkaloids of the ervatamine group. First total synthesis of (+)-6-oxo-16-episilicine, Chem. Commun., 1996, 2755. (d): Catalina Ferrer and Antonio M. Echavarren, Gold-Catalyzed Intramolecular Reaction of Indoles with Alkynes: Facile Formation of Eight-Membered Rings and an Unexpected Allenylation, Angew. Chem. Int. Ed. 2006, 45, 1105 – 1109.

21. Catalina F., Catelijne H. M. Amijs, and Antonio M. Echavarren, Intra- and Intermolecular Reactions of Indoles with Alkynes Catalyzed by Gold, *Chem. Eur. J.* 2007, 13, 1358 – 1373.
22. Biberger, C.; Walter, G.; Angerer, E., *Arch. Pharm.* 2000, 333, 305 -311.
23. Frederich, M.; Jacquier, M.-J.; Thepenier, P.; Mol, P. D.; Delaude, C.; Angenot, L.; Zeches-Hanrot, M. *J. Nat. Prod.* 2002, 65, 1381 - 1386.
24. Butera, J. A.; Antane, S. A.; Hirth, B.;Lennox, J. R.; Sheldon, J. H.; Norton, N. W.; Warga, D.; Argentieri, T. M.; *Bioorg. Med. Chem. Lett.* 2001, 11, 2093 - 2098.
25. Joseph, B.; Chapellier, V.; Merour, J.-Y.; Leonce, S. *Heterocycles,* 1998, 48, 1423 -1430.
26. Mo, L. P.; Ma, Z. C.; Zhang, Z. H. *Synth. Commun.* 2005, 35, 1997.
27. Shun-Jun Ji, Shun-Yi Wang, Yong Zhang and Teck-Peng Loh, *Tetrahedron,* 2004, 60, 2051 - 2055.
28. Hideko Koshima and Wataru Matsusaka, *J. Heterocyclic Chem.,* 2002, 39, 1089.
29. Gu, R.; Hameurlaine, A.; Dehaen, W. *Synlett,* 2006, 1535.
30. Remi and al, Synthetic Communication, 2012,42, 2048.
31. Gorbani-Vaghei et al. Molecular diversity, 2010, 14, 87.
32. Khaksar S. et al. Journal of Fluorine Chemistry 2012, 135, 87; Veisi H. et al. Journal of Heterocyclic Chemistry, 2010, 47, 1398 etc
33. Gu, R.; Hameurlaine, A.; Dehaen, W. *J. Org. Chem.* 2007, 72, 7207.
34. Gu, R.; Van Snick, S.; Robeyns, K.; Van Meervelt, L.; Dehaen, W. *Org. Biomol. Chem* 2009, 7, 380.
35. Black, D. S.; Ivory, A. J.; Kumar, N. *Tetrahedron* 1995, 51, 11801.
36. Janosik, T.; Wahlstrom, N.; Bergman, J. *Tetrahedron* 2008, 64, 9159.
37. Bergman, J.; Janosik, T.; Wahlstrom, N. *In Advances in Heterocyclic Chemistry;* Katritzky, A., Ed. Academic Press New York, 2001; Vol. 80, pp 1 - 71.

This page is intentionally left blank