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SYNTHESIS OF NOVEL METHYLENE BRIDGE FUNCTIONALIZED BIS(INDOLYL)METHANES THOROUGH A DOUBLE MICHAEL ADDITION

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Abstract – A simple synthesis of a series of novel diethyl bis(indol-3-yl)-methylmalonate is described. This involves domino Michael addition/ elimination/Michael addition of indoles to diethyl ethoxymethylenemalonate as double Michael acceptor.

INTRODUCTION

Diethyl ethoxymethylenemalonate (DEEM) and similar so-called "*β*-alkoxyacrylates" are utilized extensively as Michael acceptors and usually form Michael monoadducts with retention of the double bond. A broad range of their applications in the synthesis of chain, cyclic, heterocyclic and fused heterocyclic structures have been reported and reviewed.[1] Michael addition of amine nucleophiles to "alkoxyacrylates" are most common. Syntheses of "floxacine" type anti-bacterials start with addition of anilines or 2-aminopyridines to DEEM.[2] However, there are not many reports on the reactions of carbon nucleophiles with DEEM.[1]

The chemistry of indole is also one of the most active areas of research in heterocyclic chemistry.[3] Medicinal chemists frequently turn to indole based compounds as target pharmacophores for the development of therapeutic agents.[4] More recently simple 1,1-bis(3-indolyl)-1-(substituted phenyl)methanes have been introduced as anti-cancer drugs as they are cancer cell proliferation inhibitors and apoptosis inducers.[5]

Numerous methods have been reported for the synthesis of bis(indolyl)methanes. Among them, the acid catalyzed reaction of indoles with alkyl or arylaldehydes is a simple and straightforward approach.[6] However, most bis(indolyl)methanes produced by these methods lack non-hydrocarbon functional groups on the methylene bridge of the products.

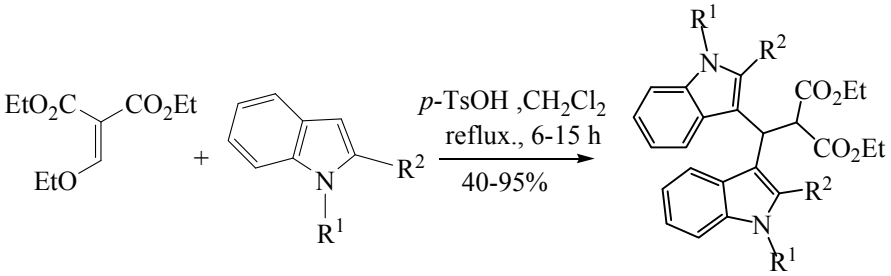
Exceptions are those prepared using oxazines,[7] unsaturated α-ketoesters,[8] glyoxylic acid,[9] acetylene-carboxylates,[10] α-oxoketenedithioacetals,[12] 2-hydroxy-(2-indolyl)acetamides[13] and 1,3-dicarbonyls[14] as starting materials. Most of the above protocols require rather expensive catalysts such as silylated *N*-triflylphosphoramides,[8] (*S*)-BINOL/Ti(O-*i*Pr)$_4$,[9a] Sc(OTf)$_3$,[9b] $AuCl_3$,[10a] $PtCl_2$,[10b] Pd(OAc)$_2$,[10c] Dy(OTf)$_3$,[11] and TFA.[12]

We are pleased to report for the first time, a *p*-TsOH-catalyzed double Michael addition of 1- or 2-substituted indoles to DEEM. This simple protocol leads to the synthesis of novel bis(indolyl)methanes **3a-e** (**Scheme 1**), having a malonate group on the methylene bridge. The protocol also presents novel examples of double Michael addition of carbon nucleophiles to *"β*-alkoxyacrylate" type push-pull olefins such as DEEM. It is noteworthy that unlike most previous reports, here both the reagents and the catalyst are easily available and of low cost.

RESULTS AND DISCUSSION

In our model experiment, *p*-TsOH catalyzed reaction of DEEM **1** with 2-methylindole **2a** in a polar aprotic solvent such as CH_2Cl_2 at reflux within 6 hours, afforded diethyl bis(2-methylindolyl-3-yl)methylmalonate **3a**, at 95% yield (**Table 1 entry 1**).

This interesting result, exhibiting a tandem Michael addition/elimination/Michael addition reaction sequence by DEEM is unprecedented. Extensive survey of literature showed no reports, either of the compounds presented in this paper, or of this new application of DEEM as a double Michael acceptor synthon.



1 **2a-e** **3a-e**

R^1= H, Me
R^2= H, 4-ClC_6H_4 -, Me, 4-MeC_6H_4 -, C_6H_5 -

Scheme 1. Double Michael addition of some indole derivatives to DEEM

In order to evaluate the scope of the process, 2-phenylindole **2d** and some 2-(substituted phenyl)indoles **2b**,**c** were synthesized and used in this protocol. These indoles afforded moderate yields of the corresponding bridge substituted bis(indolyl)methanes **3b-d**. The higher yield and faster reaction rate of

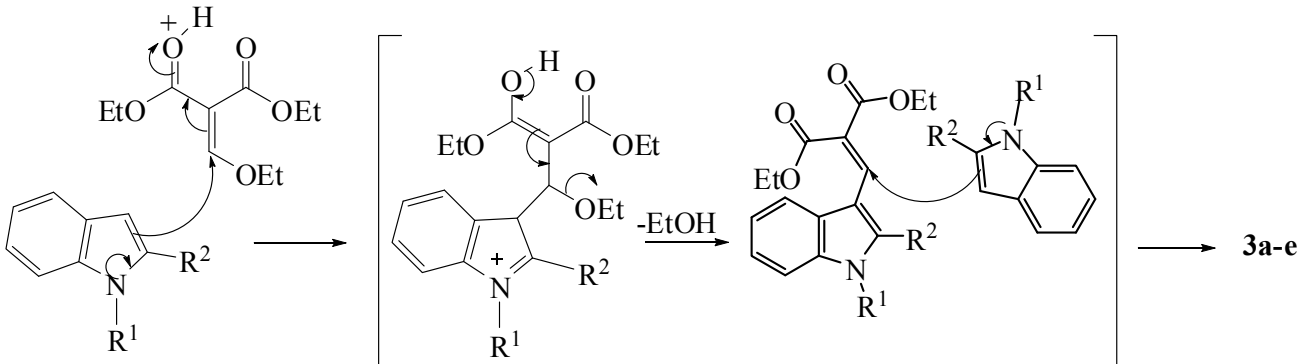
2-methylindole **2a** as compared to 2-phenylindole **2d** and its derivatives **2b**,**c** demonstrate the great influence of the steric effect of bulky 2-aryl groups in this reaction. Results of the experiments are summarized in **Table 1**.

Table 1. Synthesis of diethyl bis(indolyl-3-yl)methylmalonates

Entry	Indole derivatives			Product	Time (h)	Yield[a] (%)
	R^1	R^2				
1	H	Me	**2a**	**3a**	6	95
2	H	4-Me-C_6H_4	**2b**	**3b**	14	72
3	H	4-Cl-C_6H_4	**2c**	**3c**	15	70
4	H	C_6H_5	**2d**	**3d**	14	71
5	Me	H	**2e**	**3e**	12	40[b]

a. Yields refer to isolated products.
b. Major product was tris(1-methylindolyl)methane **4** in 50% yield.

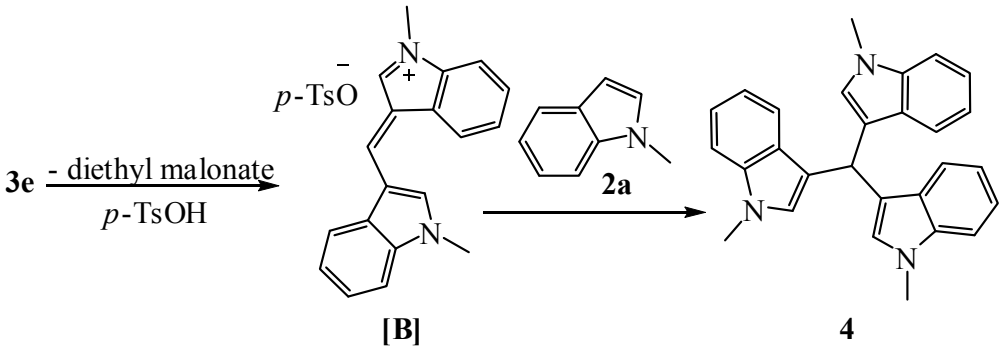
A plausible mechanism for the synthesis of bis(indolyl)methanes **3a-e**, has been shown in **Scheme 2**. The first step is the production of monoadducts [**A**] through a Michael addition of indole to DEEM followed by ethanol elimination. A second molecule of indole is then added to the monoadduct [**A**] to produce **3a-e**.



2a-e
R^1= H, Me
R^2= H, 4-ClC_6H_4 -, Me,
4-MeC_6H_4 -, C_6H_5 -

Scheme 2. Plausible mechanism for the formation of **3a-e**

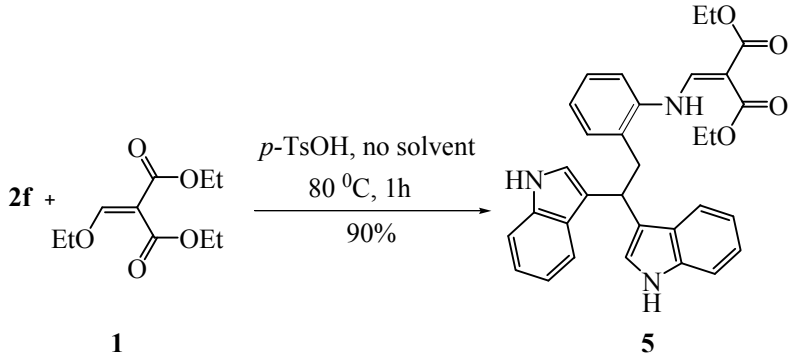
In the case of 1-methylindole **2e** (entry 5), in addition to the expected product **3e**, we also isolated tris(1-methylindolyl)methane **4**[15] in 50% yield. Apparently, **3e** undergoes a facile elimination reaction, losing a diethyl malonate molecule, to produce the unisolated intermediate [**B**]. **4** is the product of the Michael addition of a third 1-methylindole to [**B**] (**Scheme 3**).



Scheme 3. Formation of tris(1-methylindolyl)methane **4**

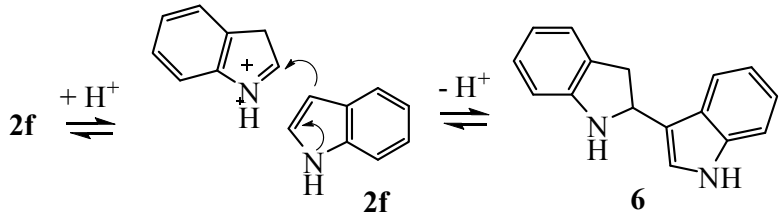
Structures assigned to **3a-e** are fully consistent with spectral data. In the mass spectra of **3a-e**, main peaks were assigned to corresponding fragments produced by loss of malonate moiety. The OCH_2 protons of the ethyl groups in compounds **3a-e** are not isochronous, and give rise to an ABX_3. The IR spectra of **3b-d**, show two ester C=O bands but the IR spectra of **3a** and **3e** show only one ester C=O band.

Curiously enough, contrary to the findings of previous reports of acid catalyzed reactions with aldehydes, 1*H*-indole **2f** itself did not produce the corresponding bis(indolyl)methane, but instead furnished diethyl-2-[({2-[2,2-bis(1*H*-indol-3yl)ethyl]phenyl}amino)methylidene]propane-1,3-dioate **5** in moderate yield. Production of **5** was optimized for higher yield and purity, by performing the reaction under solvent free conditions at 80 ºC for 1 h (**Scheme 4**).



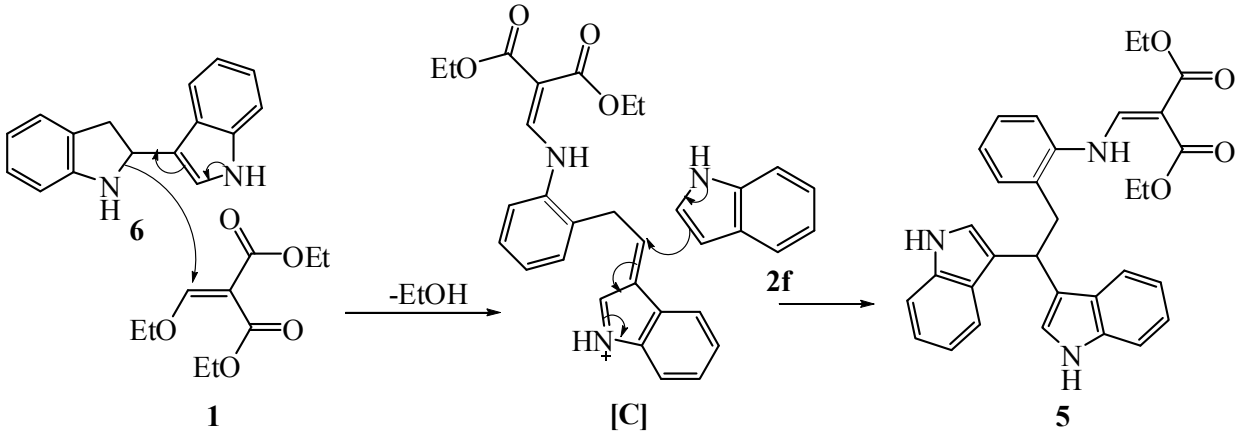
Scheme 4. Reaction of 1*H*-indole with DEEM

A plausible mechanism for this transformation is proposed in **Schemes 5** and **6**. Under acidic conditions, 1*H*-indole is in equilibrium with 3-(indolin-2-yl)indole (indole dimer) **6** (**Scheme 5**).[16]



Scheme 5. 1*H*-indole/indole dimer equilibrium

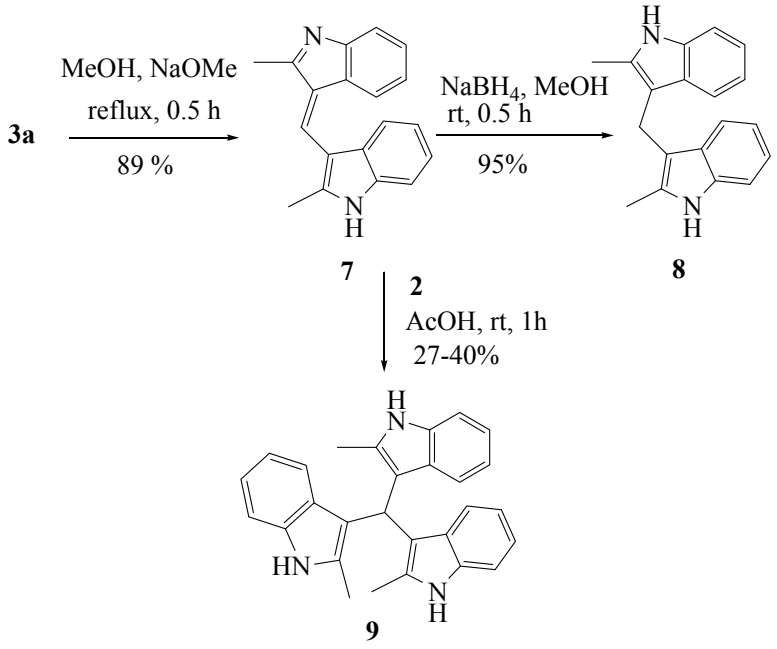
Reaction of indoline "NH" group of dimer **6** with electrophile such as DEEM, causes drain of reaction equilibrium towards production of intermediate [**C**]. Addition of a third molecule of indole to [**C**] leads to the formation of novel substituted trimer **5** in almost quantitative yield.



Scheme 6. Plausible mechanism for the formation of **5**

In the mass spectrum, compound **5** shows a base peak at *m/z* 245, assignable to the bis(indolyl)methyl moiety. The IR spectrum shows two NH bands at 3430 and 3320 cm^{-1} and four carbonyl bands at 1693, 1651, 1620 and 1593 cm^{-1}. The ^1H NMR spectrum (500 MHz, DMSO-d_6) shows a singlet ascribable to two indolic NH groups at δ 10.71, two doublets at 10.97 (J = 13.6 Hz, $NH_{aniline}$) and 8.14 (J = 13.6 Hz, =C<u>H</u>-NH) and fourteen aromatic protons [set a (δ 6.78, 6.93 and 6.99), set b (7.14, 7.20 and 7.39)], together with a triplet at 4.79 (J = 7.8 Hz, CH_2-C<u>H</u>) and a doublet at 3.55 (J = 7.8 Hz, C<u>H_2</u>-CH). Methyl signals (CO_2CH_2<u>CH_3</u>) of compound **5** in $CDCl_3$ appeared at δ 1.27 and 1.31 and in DMSO-d_6 as solvent; these signals were observed at δ 1.19 and 1.21. This indicates that these methyl groups are subject to different field anisotropic effects of the aromatic rings at different solvents.

3a was chosen as a model compound to further investigate the chemistry and reactivity of this type of bis(indolyl)methanes. Bis(indolyl)methane **3a**, having a malonate leaving group, was found to be labile in basic conditions. Thus, treating **3a** with NaOMe in refluxing MeOH afforded (2-methyl-3-indolyl)(2-methyl-3-indolinylidene)methane **7** (Urorosein type base)[17] in very good yield (**Scheme 7**). ^1H NMR spectrum of compound **7** shows an olefinic proton (Bridge CH) at δ 8.2 but no N-H signals were observed, which is probably due to the fast exchange of N-H single proton between two nitrogen atoms. The absence of an N-H signal of the similar type of structure has been previously reported.[18]

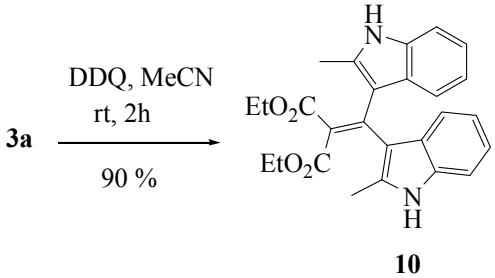


Scheme 7. Synthesis of **8** and **9** from **3a**

The structure of **7** was further confirmed by $NaBH_4$ reduction producing the previously reported bis(2-methyl-indol-3-yl)methane **8**.[19]

Attempts to add indole and various 2-substituted indoles to compound **7** in glacial acetic acid, with the aim of obtaining unsymmetrical tris-indoles, failed and spontaneous decomposition of the unstable compound **7**, led to the production of tris(2-methylindolyl)methane **9** as the main product.

Oxidation of **3a**, with DDQ in acetonitrile led to a novel alkenyl substituted bisindole **10**, retaining the malonate moiety on the methane bridge (**Scheme 8**). This type of bisindole has been reported via the reaction of indoles with α-oxoketenedithioacetal.[12]



Scheme 8 Oxidation of **3a** to **10**

In conclusion, the present paper reports for the first time, the simple synthesis of the novel bis(indolyl)methylmalonates based on Michael addition-elimination-addition of the indole derivatives to

double Michael acceptor DEEM. A particularly significant feature of this work is the introduction of diethylmalonate on the methylene bridge of bis(3-indolyl)methanes. These novel compounds and their derivatives may be directly used for screening as potential drugs or may further be built up and used as scaffolds in the synthesis of more complex molecules. Commercial availability and low cost of the DEEM and the catalyst used in this protocol, is an advantage that justifies pursuing further studies in this direction.

EXPERIMENTAL

General information

2-Phenylindole derivatives were synthesized according to reported procedures.[20] All other chemicals were purchased from Kimia Exir Co. Tehran, Iran. Barnstead Electrothermal 9200 melting point apparatus was used for melting point determinations. GC/Mass analyses were performed using Agilent 6890 GC system Hp-5 capillary 30 m × 530 μm × 1.5 μm nominal. IR spectra were recorded as KBr disc on the FT-IR Bruker Tensor 27 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500-AVANCE spectrometer at 500 (^{1}H) and 125 MHz (^{13}C). Elemental analyses were carried out by a CHN-Rapid Heraeus elemental analyzer (Wellesley, MA).

Typical procedure for the synthesis of 3a-d

A 100 mL round bottom flask was charged with DEEM (25 mmol, 5.4 g) and a solution of indole derivative **2** (50 mmol) in CH_2Cl_2 (20 mL) was added. *p*-TsOH (5 mol%, 0.23 g) was added to the stirring solution. The mixture was refluxed for the appropriate time (**Table1**). The progress of the reaction was monitored by TLC using petroleum ether: EtOAc (4:1) as eluent. When the starting materials were no longer consumed, the solvent was removed by short path distillation. The resulting residue was dissolved in EtOAc and petroleum ether was added to precipitate the product. The produced solid was filtered, and dried under reduced pressure to yield the target bis(indolyl)methanes **3a-d**. Further purification of the product was normally not needed.

***Diethyl bis(2-methyl1H-indol-3-yl)methylmalonate* 3a**

Compound **3a** was obtained as white powder, Mp 194-196 ºC; yield: (10.3g, 95%); IR (KBr) 3410, 3357, 3050, 2978, 1743, 1459, 1392, 1372, 1300, 1266, 1146, 1017, 742 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.89 (6H, t, J = 7.0 Hz, 2OCH$_2$Me), 2.32 (6H, s, 2Me$_{indole}$), 3.86-3.88 (2H, m, OCH$_2$Me), 3.91-3.95 (2H, m, OCH$_2$Me), 4.99 (1H, d, J = 12.5 Hz, CH-CH(CO$_2$Et)$_2$), 5.25 (1H, d, J = 12.5 Hz, CH(CO$_2$Et)$_2$), 6.94-7.00 (4H, m, Ar*H*), 7.13 (2H, d, J = 7.7 Hz, Ar*H*), 7.70 (2H, d, J = 7.7 Hz, Ar*H*), 8.35 (2H, s, 2NH); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 12.9, 14.0, 35.1, 55.8, 61.5, 110.6, 111.7, 119.2, 119.5, 120.6, 128.1, 132.3 135.6, 168.9; MS *m*/*z* 432 (M^{+}, 10), 273 (100), 257 (21), 216 (6), 158 (15), 130 (13), 81 (30), 69 (51), 55 (36), 43 (52%); Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.22; H, 6.53; N, 6.48%. Found: C, 72.26; H,

6.55; N, 6.43%.

***Diethyl bis[2-(4-methylphenyl)-1H-indol-3-yl]methylmalonate* 3b**

Compound **3b** was obtained as pinkish powder, Mp 199-200 ºC; yield: (10.5 g, 72%); IR (KBr) 3409, 3383, 977, 1731, 1710, 1457, 1271, 1184, 1153, 1033, 847, 737, 519 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 0.71 (6H, t, J = 7.0 Hz, 2OCH$_2$Me), 2.38 (6H, s, 2CH$_3$-Ar), 3.74-3.79 (2H, m, OCH$_2$Me), 3.81-3.84 (2H, m, OCH$_2$Me), 5.03 (1H, d, J = 12.0 Hz, CH-CH(CO$_2$Et)$_2$), 5.80 (1H, d, J = 12.1 Hz, CH-CH(CO$_2$Et)$_2$), 6.82 (2H, t, J = 7.4 Hz, Ar*H*), 6.96 (2H, t, J = 7.5 Hz, Ar*H*), 7.09 (4H, d, J = 7.8 Hz, Ar*H*), 7.20 (6H, m, Ar*H*), 7.55 (2H, d, J = 8.0 Hz, Ar*H*), 10.88 (2H, s, 2NH); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 14.0, 35.1, 55.3, 61.7, 111.7, 112.6, 119.1, 120.9, 121.4, 128.0, 129.5, 129.9, 131.3, 136.2, 136.5, 137.7, 168.9; MS *m*/*z* 584 (M^+, 87), 425 (100), 377 (21), 333 (27), 304 (22), 258 (73), 231 (53.9), 207 (34), 133 (40), 115 (53), 88 (38), 60 (16), 43 (62%); Anal. Calcd for $C_{38}H_{36}N_2O_4$: C, 78.06; H, 6.21; N, 4.79 %. Found: C, 78.04; H, 6.20; N, 4.82%.

***Diethyl bis[2-(4-chlorophenyl)-1H-indol-3-yl]methylmalonate* 3c**

Compound **3c** was obtained as yellow powder, Mp 137-139 ºC; yield: (10.9 g, 70%); IR (KBr) 3410, 3357, 3055, 2978, 1735, 1704, 1485, 1372, 1331, 1186, 1093, 1014, 833, 739, 518 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ = 0.73 (6H, t, J = 7.0 Hz, 2OCH$_2$Me), 3.82-3.85 (2H, m, OCH$_2$Me), 3.89-3.91 (2H, m, OCH$_2$Me), 5.28 (1H, d, J = 12.2 Hz, CH-CH(CO$_2$Et)$_2$), 5.81 (1H, d, J = 12.2 Hz, CH-CH(CO$_2$Et)$_2$), 6.92 (2H, t, J = 7.6 Hz, Ar*H*), 7.00 (2H, t, J = 7.6 Hz, Ar*H*), 7.22 (2H, d, J = 7.9 Hz, Ar*H*), 7.28 (8H, m, Ar*H*), 7.82 (2H, d, J = 8.0 Hz, Ar*H*), 11.03 (2H, s, 2NH); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 14.1, 34.6, 55.3, 61.7, 112.0, 113.0, 119.5, 121.1, 121.8, 127.4, 129.0, 131.3, 132.6, 133.6, 135.1, 136.8, 168.9; MS *m*/*z* 624 (M^+-1, 3), 577 (51), 551 (71), 465 (100), 77 (6), 42 (3%); Anal. Calcd for $C_{36}H_{30}N_2O_4Cl_2$: C, 69.12; H, 4.83; N, 4.48%, Found: C, 69.15; H, 4.85; N, 4.44%.

***Diethyl bis[2-(phenyl)-1H-indol-3-yl]methylmalonate* 3d**

Compound **3d** was obtained as pinkish powder, Mp 184-185 ºC; yield: (9.8 g, 71%); IR (KBr) 3396, 3346, 2983, 1742, 1697, 1453, 1288, 1224, 1026, 769, 734, 502 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 0.69 (6H, t, J = 7.0 Hz, 2OCH$_2$Me), 3.70-3.75 (2H, m, OCH$_2$Me), 3.79-3.81 (2H, m, OCH$_2$Me), 4.91 (1H, d, J = 12.1 Hz, CH-CH(CO$_2$Et)$_2$), 5.75 (1H, d, J = 12.1 Hz, CH-CH(CO$_2$Et)$_2$), 6.78 (2H, t, J = 7.2 Hz, Ar*H*), 6.96 (2H, t, J = 7.9 Hz, Ar*H*), 7.19 (2H, d, J = 8.0 Hz, Ar*H*), 7.31-7.39 (10H, m, Ar*H*), 7.44 (2H, d, J = 8.0 Hz, Ar*H*), 11.5 (2H, s, 2NH); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 14.0, 35.1, 55.3, 61.7, 111.7, 113, 119.2, 121, 121.7, 128.0, 129.5, 129.9, 131.3, 136.5, 137.7, 168.9; MS *m*/z 556 (M^+, 8), 397 (16), 193 (100), 165 (27), 133 (38), 115 (51), 88 (18), 60 (11), 43 (35%); Anal. Calcd for $C_{36}H_{32}N_2O_4$: C, 77.68; H, 5.79; N, 5.03 %. Found: C, 77.60; H, 5.72; N, 5.07%.

Procedure for the synthesis of 3e and 4

In the case of 1-methylindole **2e**, following the same procedure as the ones for **3a-d**, after 12 h, product **4**

precipitated from the reaction mixture, from which was separated by simple vac. filtration. The filtrate was evaporated and the residue was crystallized from light petroleum ether: toluene (7:3), to afford **3e**.

***Diethyl bis(1-methyl-1H-indol-3-yl)methylmalonate* 3e**

Compound **3e** was obtained as yellow powder, Mp 140-142 ºC; yield: (4.3 g, 40%); IR (KBr) 3112, 2977, 2933, 1755, 1470, 1369, 1325, 1240, 1132, 1072, 1024, 859, 740 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 0.84 (6 H, t, J = 7.0 Hz , $2OCH_2\underline{Me}$), 3.69 (6H, s, N-$\underline{Me}$), 3.84-3.91 (4H, m, $OC\underline{H}_2Me$), 4.52 (1H, d, J = 11.9 Hz, $C\underline{H}$-$CH(CO_2Et)_2$), 5.14 (1H, d, J = 11.9 Hz, $C\underline{H}(CO_2Et)_2$, 6.92 (2H, t, J = 7.4 Hz, Ar*H*), 7.04 (2H, t, J = 7.2 Hz, Ar*H*), 7.28 (2H, d, J = 8.1 Hz, Ar*H*), 7.38 (2H, s, Ar*H*), 7.60 (2H, d, J = 7.9 Hz, Ar*H*); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 14.3, 33.2, 34.3, 58.0, 61.5, 110.3, 115.6, 119.2, 119.8 121.8, 127.5, 127.6, 137.3, 168.4; MS m/z 432 (M^+, 8.5), 313 (4.7), 286 (5.5), 273 (100), 257 (12.6), 217 (3.9), 158 (10), 69 (8), 43 (9%); Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48%. Found: C, 72.27; H, 6.55; N, 6.43%.

***Tris(1-methylindol-3-yl)methane* 4**

This compound is previously reported; Mp 263-265 ºC (lit.,[15a] Mp 264-266 ºC).

Procedure for the production of Compound 5

A 50 mL round bottom flask was charged with indole (purity 97%) (60 mmol, 7.2 g), DEEM (20 mmol, 4.4 g) and *p*-TsOH (1 mmol, 0.2 g). The reaction mixture was heated at 80 ºC for 1 h. The reaction mixture was then cooled to room temperature and 30 mL CH_2Cl_2 was added and the mixture stirred for 15 min. The undissolved solid was filtered and dried to yield the product. Beautiful large crystals were obtained by recrystallization from $MeNO_2$-MeOH (7:3).

***Diethyl-2-[({2-[2,2-bis(1H-indol-3-yl)ethyl]phenyl}amino)methylidene]propane-1,3-dioate* 5**

Compound **5** was obtained as white powder, Mp 188 ºC; yield: (9.4 g, 90%); IR (KBr) 3414, 3324, 2977, 1693, 1650, 1619, 1592, 1184, 1494, 1263, 1220, 744, 672 cm^{-1}; H NMR (500 MHz, DMSO-d_6) δ 1.19 (3H, t, J = 7.0 Hz, $OCH_2\underline{Me}$), 1.22 (3H, t, J = 7.0 Hz , $OCH_2\underline{Me}$), 3.54 (2H, d, J = 7.8, CH-$C\underline{H}_2$), 4.09-4.16 (4H, m, $2OC\underline{H}_2Me$), 4.78 (1H, t, J = 7.8 Hz, $C\underline{H}$-CH_2), 6.78 (2H, t, J = 7.6 Hz, Ar*H*), 6.94 (2 H, t, J = 7.9 Hz, Ar*H*), 6.99 (1H, t, J = 7.2 Hz, Ar*H*), 7.14-7.25 (7H, m, Ar*H*), 7.39 (2H, d, J = 7.9 Hz, Ar*H*), 8.14 (1H, d, J = 13.6 Hz, NH-C$\underline{H}$), 10.71 (2 H, s, 2N$\underline{H}$), 10.97 (1H, d, J = 13.6 Hz, N$\underline{H}$-CH); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 15.0, 15.1, 34.7, 37.4, 60.1, 60.4, 93.5, 112.1, 118.5, 118.7, 119.6, 121.4, 123.1, 125.7, 127.3, 128.2, 131.8, 132.2, 137.1, 138.8, 153.8, 165.5, 168.8; MS m/z 521 (M^+, 4), 313 (3), 245 (100), 217 (23), 189 (6), 158 (7), 130 (13), 91 (6), 45 (14%); Anal. Calcd for $C_{32}H_{31}N_3O_4$: C, 73.68; H, 5.99; N, 8.06 %. Found: C, 73.66; H, 5.96; N, 8.10 %.

Procedure for the synthesis of 7

In a 50 ml, round bottom flask, compound **3a** (10 mmol, 4.3 g) was dissolved in MeOH (20 mL) and heated to a temperature of 40-45 ºC. A 30% solution of NaOMe in MeOH (1 mL) was added. The resulting solution was heated to reflux. After about 30 min TLC showed the **3a** to have been consumed.

The mixture was then cooled to 10 ºC and the red precipitate was filtered, washed with cold MeOH and dried to give **7** as an orange powder of low solubility in most organic solvents. This compound which is readily soluble in acids, has previously been reported only in various salt forms.[17]

***(2-methyl-3-indolyl)(2-methyl-3-indolinylidene)methane* 7**

Compound **7** was obtained as orange powder. Mp 272 ºC (decomp.) (lit.,[17b] Mp 236 °C as hydrobromide); yield: (2.4 g, 89 %); IR (KBr) 2768, 1681, 1600, 1577, 1456, 1426, 1382, 1327, 1246, 1201, 1161 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.49 (6H, s, 2Me), 6.94 (2H, d, J = 7.5 Hz, Ar*H*), 6.98 (2H, t, J = 7.3 Hz, Ar*H*), 7.15 (2H, t, J = 7.1 Hz, Ar*H*), 7.40 (2H, d, J = 7.8 Hz, Ar*H*), 8.02 (1H, s, =C<u>H</u>-).

Procedure for the reduction of 7; synthesis of bis(2-methylindol-3-yl)methane 8

Reduction of **7** (2.7 g, 10 mmol) as dispersed in MeOH (16 mL), was performed by adding powdered $NaBH_4$ (0.2 g, 6 mmol) portion-wise. Within 30 min the suspension changed to a clear and colorless solution. To neutralize excess $NaBH_4$, a few drop of AcOH were added. H_2O (10 mL) was added. The mixture cooled to 15 ºC and the precipitate was filtered, washed with 20 mL MeOH-H_2O (5:5) and dried to give 95% yield of a white powder which was identical in all respects with the reported compound.[21]

***Bis(2-methyl-indol-3-yl)methane* 8**

Compound **8** was obtained as a white powder. Mp 234-236 ºC (lit.,[21] Mp 235-238 ºC).

Procedure for the synthesis of 9

In a 50 ml, round bottom flask, compounds **7** (10 mmol, 2.72 g) was dissolved in AcOH (30 mL) and compound **2** (5 mmol) was added. The resulting solution was stirred at room temperature about 1 h. The product **9** precipitated from the reaction mixture, from which it was separated by simple vac. filtrations. The filtrate was a complex mixture and was not pursued further.

***Tris(2-methyl-1H-indol-3-yl)methane* 9**

Compound **9** was obtained as pink powder, Mp 320-323 ºC (lit.,[15] Mp 333-335 ºC); yield from **2a** (40%), **2b** (30%), **2c** (28%), **2d** (31%), **2e** (27%). IR (KBr) 3399, 1458, 1340, 1218, 1009, 747 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 1.90 (9H, s, 3Me), 6.09 (1H, s, CH), 6.60 (3H, t, J = 7.6, Ar*H*), 6.78 (3H, d, J = 7.9, Ar*H*), 6.84 (3H, t, J = 7.6, Ar*H*), 7.18 (3H, d, J = 8.0, Ar*H*), 10.60 (3H, s, $3NH_{indole}$); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 11,7, 30.5, 110.1, 112.2, 117.8, 118.2, 119.3, 128.8, 131.6, 134.8.

Procedure for DDQ oxidation of compound 3a to produce 10

Compound **3a** (5 mmol) was dispersed in MeCN (8 mL). Upon gradual addition of a solution of DDQ (0.7 g, 3 mmol) in MeCN (10 mL) suspended powder started to dissolve. The reaction mixture was stirred for 2 h, when a dark red precipitate formed. The solid was filtered, washed with MeCN and dried to give **10** as a dark red powder.

***Ethyl bis(2-methyl-1H-indol-3-yl)methylmalonate* 10**

Compound **10** was obtained as pale yellow powder, Mp 295-296 ºC; yield (1.9 g, 90%); IR (KBr) 3328,

1686, 1546, 1455, 1242, 1025, 750 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 0.80 (6H, t, J = 7.0 Hz, 2OCH$_2$Me), 2.02 (6H, s, 2Me $_{indoles}$), 3.85-3.89 (4H, m, 2OCH$_2$Me), 6.82 (2H, t, J = 7.6 Hz, Ar*H*), 6.89 (4 H, m, Ar*H*), 7.26 (2H, d, J = 7.9 Hz, Ar*H*), 11.32 (2H, s, 2N*H*); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 13.0, 14.4, 60.7, 111.6, 119.0, 120.2, 121.6, 122.2, 128.4, 136.2, 137.5, 146.1, 167.6; MS m/z 429 (M^+-1, 3), 347 (12), 235 (5), 176 (100), 142 (64), 100 (32), 57 (20), 41 (31%); Anal. Calcd for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51%. Found: C, 72.51; H, 6.04; N, 6.50 %.

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