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Synthesis of Some New Heterocyclic Nitrogen Compounds Starting from Pyromellitic Dianhydride

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ABSTRACT

Pyromellitic dianhydride 1 was used as starting compound for the synthesis of some new derivatives of condensed dipyrrole, dibenzoxazine, and dipyridazine. Thus, the diimide 2 was formed on fusion of 1 with urea, thiourea and/or thiosemicarbazide. Also, 1 reacted with benzylamine to give terephthalic acid derivative 3 which on fusion afforded the cyclic diimide 4. The reaction of 1 with o-aminothiophenol under different reaction conditions was investigated to give 5 in acetic acid or 6 in toluene and the later could be decarboxylated to 7. On the other hand, the action of $AlCl_3$ on 1 in presence of reactive aromatic substrates afforded the corresponding isomers 8a-d and 9a-d. which could be cyclized using hydroxylamine hydrochloride to give the dioxazine isomers 10a-d and 11a-d. The dioxazine isomers 10b and 11b were also obtained when 14 was allowed to react with $AlCl_3$ in anisol. Cyclization of 8a-d and/or 9a-d using hydrazine or phenylhydrazine gives the dipyridazine isomers 13a-h and/or 14a-f respectively.

Key words: Pyromellitic dianhydride; Pyromellitimide; Dipyridazines; Dibenzoxazines; Dipyrroles.

INTRODUCTION

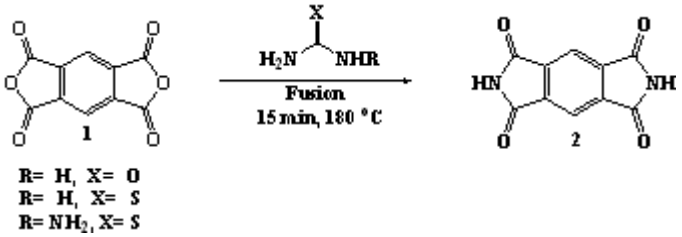
Owing to the wide spread applications of pyromellitic dianhydride (PMDA) in several fields, such as synthesis of polyimides[1-3], epoxy resins[4] and Metal Carboxylate[5,6] Complexes. In addition, pyrrole, benzoxazine and phthalazine derivatives exhibit wide range of pharmacological and biological applications, such as analgesic[7-9], antifungal[10-12], antitoxic[13], anticancer [14-17], alkaloids, agro-chemicals[18,19] and dyes applications[20], this encourage us to synthesize new derivatives of condensed dipyrrole, dibenzoxazine and dipyridazine starting with pyromellitic dianhydride which may posses a greater certain pharmacological activity.

RESULTS AND DISCUSSION

During the last few years our research group has been interested in the chemistry of anhydrides with the objective of finding new routes

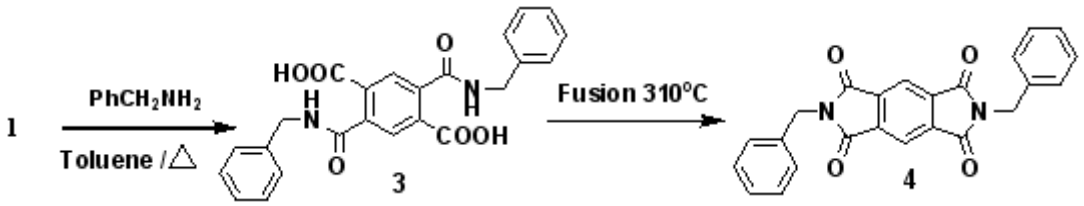
for the synthesis of new heterocyclic derivatives with expected biological activities[21-24].

E.V.Ganin *et al.,*[25], were able to fined a synthetic procedure for the preparation of pyromellitic diimide 2 by the reaction of PMDA 1 with formamide. In our work, we have investigated the action of other amides such as urea, thiourea, and thiosemicarbazide on the anhydride 1 in order to synthesize new diimide derivatives which may undergo cyclization or further polymerization, the only product isolated from these reactions was pyromellitic diimide 2 in good yield (cf. Scheme 1).



Scheme 1

When compound 1 was allowed to react with benzylamine in dry toluene, 2,5-di[(benzylamino) carbonyl]terephthalic acid 3 was formed through cross linked nucleophilic attack. The presence of electron withdrawing carbonyl group in *para* position to the anhydride carbonyl carbones facilitates the cross nucleophilic attack[26]. Fusion of compound 3 gave the corresponding cyclic diimide assigned as 2,6-dibenzylpyrroloisoindole-1,3,5,7-tetrone 4 (cf.Scheme 2).



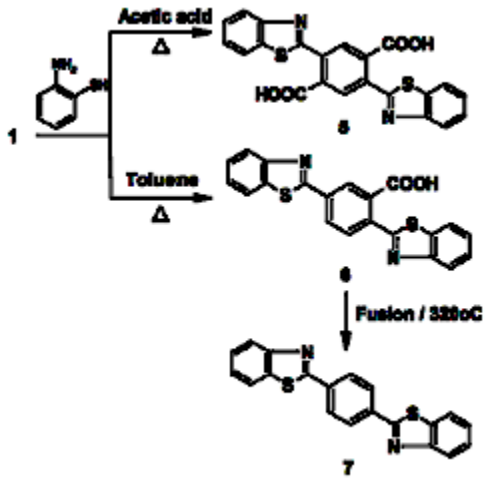
Scheme 2

PMDA was reacted with 2-aminothiophenol in glacial acetic acid as a proteic solvent to give 2,5-di(benz-1,3-thiazol-2-yl)terephthalic acid 5 through cross nucleophilic ring opening of PMDA followed by intramolecular nucleophilic cyclization to give benzothiazole moiety. Repeating the reaction in non-polar solvent namely, toluene gave 2,5-di(benz-1,3-thiazol-2-yl)benzoic acid 6 which on thermal decarboxylation at 320°C gave 1,4-di(benz-1,3-thiazole)benzene 7 via losses of CO_2 (cf. Scheme3).

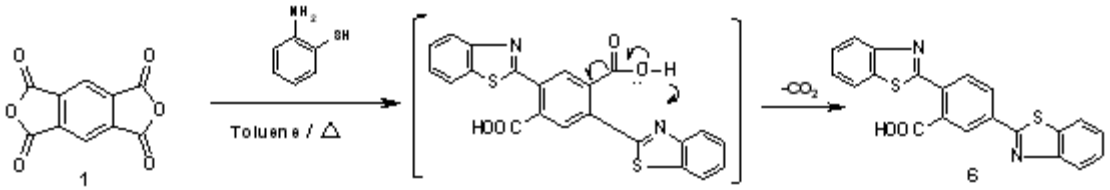
The reaction of 1 to give compound 6 may proceed via losses of CO_2 through the following intermediate shown in (Scheme 4):

The molecular ion peak of compound 6 indicated ($M^{+\cdot}$) at *m/z* = 388 (9.2%) corresponding to the formula $C_{21}H_{12}N_2O_2S_2$, and the following fragents observed in the mass spectrum of the compound 6 confirms its assigned structure (Scheme 5): The peaks at 387, 344, 343, 311, and 235 are characteristic peaks corresponding to the fragments. Thus the structure of compound 6 is in agreement with the observed spectral data.

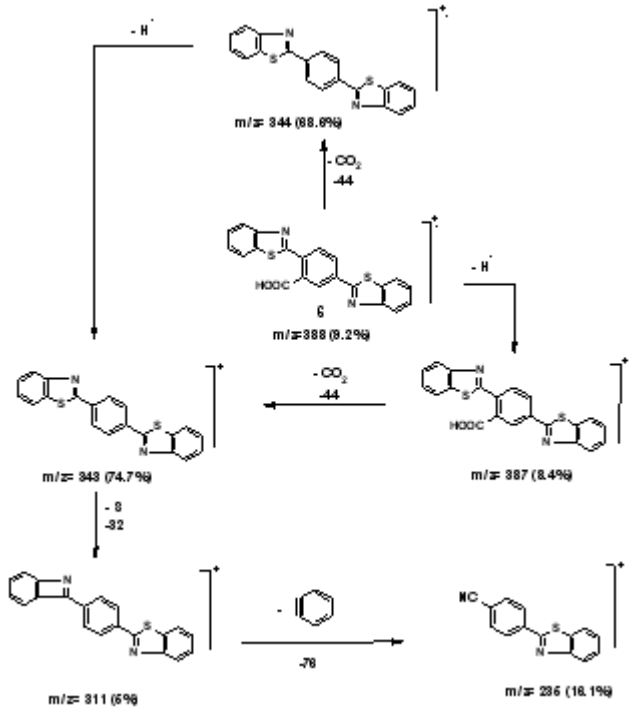
On the other hand, the Friedel-Crafts reaction of pyromellitic dianhydride with benzene to give 2,5-dibenzoylterephthalic acid 8a and its isomer 4,6-dibenzoyl- isophtalic acid 9a was previously described[27]. In our work, the same



Scheme 3



Scheme 4

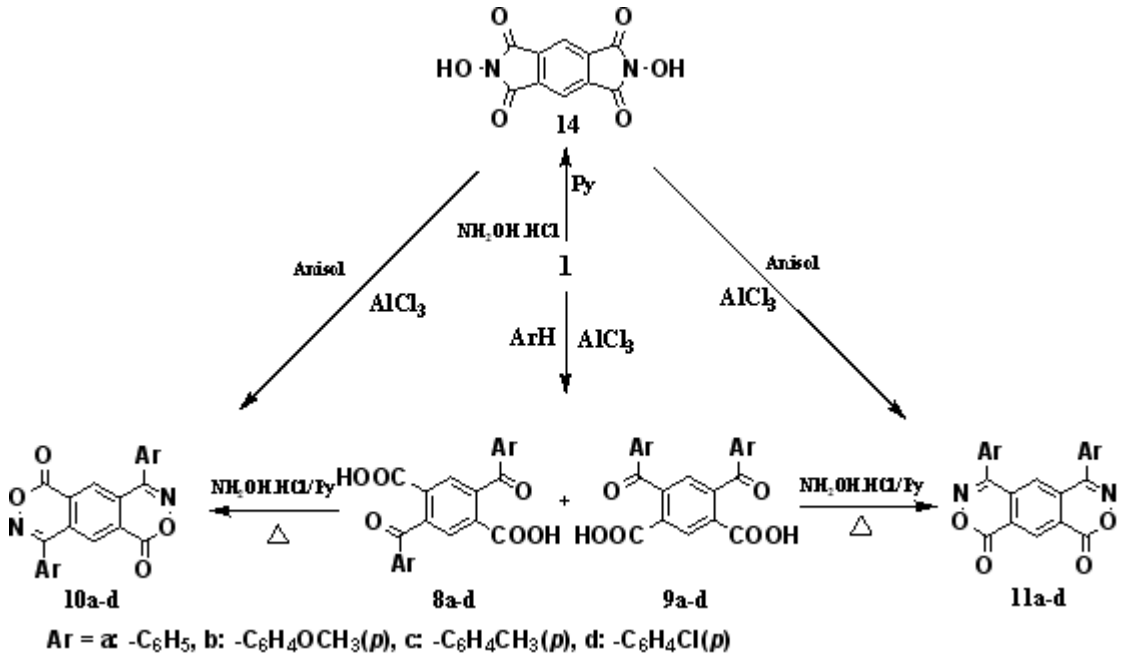


Scheme 5

reaction was intensively investigated using more reactive aromatic substrates namely anisol, toluene in addition to chlorobenzene.

The two isomeric structures formed in each reaction were separated by fractional crystallization to give 2,5-diaroylterephthalic acid 8a-d and 2,6-diaroylisophthalic acid 9a-d (Scheme 6). The configuration assigned to these proposed structures was based on the IR spectroscopic evidence. ^{1}H-NMR for terephthalic isomers 8a-d indicates the presence of a singlet for the two identical benzene protons at δ 7.88-7.92, while for isophthalic isomers 9a-d showed two different benzene protons at δ7.31-7.95 and at δ 8.55-8.77 respectively.

2,5-diaroylterephthalic acids 8a-d and/or 2,6-diaroylisophthalic acids 9a-d were reacted with hydroxylamine hydrochloride in pyridine under reflux, compounds 10a-d identified as 4,9-diaryl-1H,6H[1,2]oxazino[5,4-g][2,3]benzoxazine-1,6-diones and/or 11a-d identified as 4,6-diaryl-1H,9H[1,2]oxazino[4,5-g][2,3]benzoxazine-1,9-diones were obtained respectively (Scheme 6).



Scheme 6

The *H-C* COSY technique (Carbon-13 detection and proton decoupling) is attractive because it efficient and provides unequivocal results; it allows the shift of two nuclei (^{1}H and ^{13}C) to be measured in a single experiment. Figs (1) and (2) showed *H-C* COSY for the two isomers 8d and 9d in which the shifts of the ^{1}H and ^{13}C nuclei are bonded to one another are read as coordinates of the cross signal. In (Fig. 1), for example, the protons with shifts 7.6 and 7.96 are bonded to the carbon atoms at 128.91 and 128.82 respectively for compound 8d. On the other hand, compound 9d, the protons with shifts 7.58 and 7.95 are bonded to the carbon atoms C-2 and C-9 at 128.84, while the protons with shifts 7.74 and 8.54 are bonded to the carbon atoms C-3 and C-10 at 130.67 and 131.38 respectively (cf. Fig. 2).

13C-NMR data were also useful to differentiate between the two isomers 8d and 9d in which compound 8d showed nine different signals for nine non identical carbon atoms, while for 9d showed ten different carbon atoms.

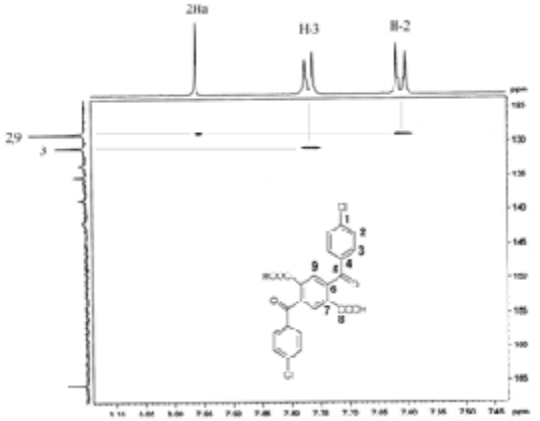


Fig. 1: 1H-13C correlation spectrum of 8d

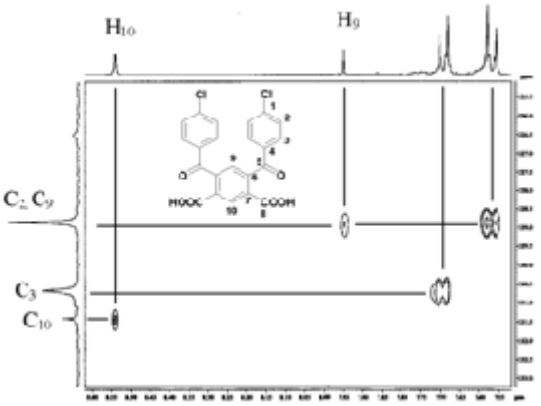
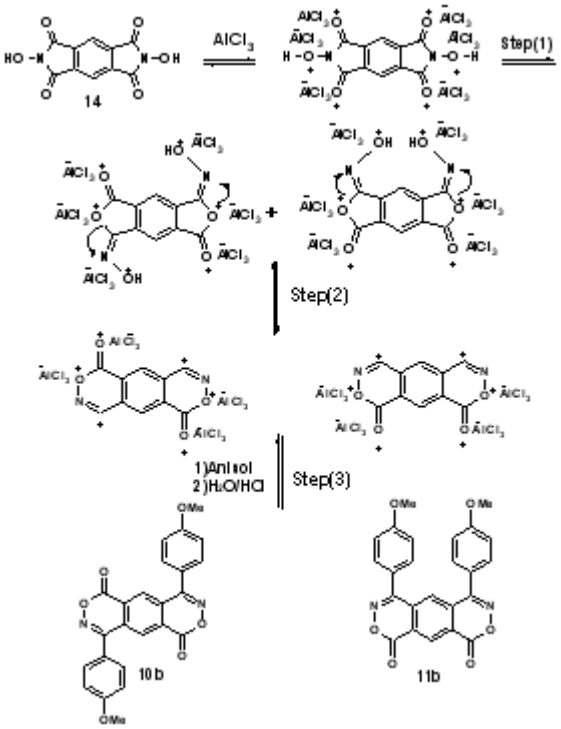


Fig. 2: 1H-13C correlation spectrum of 9d

Through another synthetic route, the two isomeric structures 10b and 11b were also obtained by the reaction of 2,6-dihydroxypyromellitimide [28] 14 with anisole in presence of anhydrous aluminum chloride (Scheme 6). The chemical structures of 10b and 11b were established on the basis of NMR spectrocopy, which were found to be completely fit with the proposed structures. ^{13}C-NMR data were found to be ideal technique for the differentiation between the two isomers 10b and 11b. Compound 10b revealed the presence of ten different carbon signals, while 11b showed eleven different carbon signals, which were in good agreement with the proposed structures.

The reaction of 14 to give the two isomers 10b and 11b may proceed according to the mechanism shown in (Scheme 7).

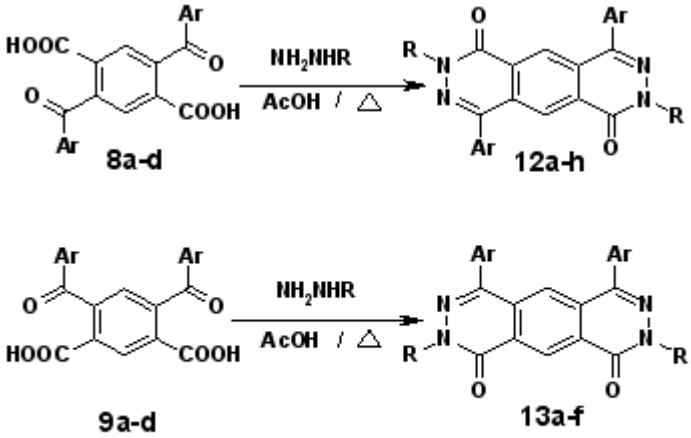


Scheme 7

Also, treatment of the acids 8a-d and/or 9a-d with hydrazine hydrate and/or phenylhydrazine gave the corresponding pyridazino[4,5-g]phthalazine-1,6-diones 12a-h and/or pyridazino [4,5-g]phthalazine-1,9-diones 13a-f respectively (Scheme 8).

The structure of compounds 12a-h and 13a-f were characterized by elemental analysis, IR and MS data.

^{1}H-NMR spectra were not available because of low solubility of these compounds in organic solvents.



Ar = a; C_6H_5, b; $C_6H_4OCH_3$ (p), c; $C_6H_4CH_3$ (p), d; C_6H_4Cl (p), R = H, P

Scheme 8

EXPERIMENTAL

Melting points were uncorrected determined on an electric melting point apparatus (Kofler). The IR spectra (KBr) were recorded on a Shimadzu 408 spectrometer. The ^{1}H-NMR spectra were recorded by 400 MHz Varian EM 390 spectrometer. The ^{13}C-NMR spectra and The ^{1}H-^{13}C-NMR (H-C COSY) were measured on Avance 600 spectrometer; chemical shifts are reported in ppm with TMS as an internal standard and are given in ä units. Electron impact mass spectra were obtained at 70 ev using a GCMS sp.1000 Shimadzu. Elemental analyses were carried out at Microanalysis Unit at Regensburg University.

Pyromellitic diimide 2

A mixture of pyromellitic dianhydride 1 (1.09 g, 5 mmol) and the appropriate amide, namely, urea, thiourea and/ or thiosemicarbazide (20 mmol) was fused in an oil bath at 180° until the odour of ammonia was stopped (15 min). The residue was washed with water and crystallized from ethanol/DMF (2:1), as greenish white crystals in 93% yield; mp >360°C; IR (KBr): ν 3250 cm^{-1} (NH) 1780 ; 1700 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 8.05 (s, 2H, two identical benzene protons) 11.82 (s, 2H, 2NH);; MS: *m/z* 216(M+). *Anal.* Calcd. For $C_{10}H_4N_2O_4$: C, 55.57; H, 1.87; N, 12.96; Found; C, 55.60; H, 1.77; N, 13.03%.

2,5-di[(benzylamino)carbonyl]terephthalic acid 3

A mixture of pyromellitic dianhydride 1 (2.18 g, 10 mmol) and benzylamine (2.14 ml, 20 mmol) in toluene (50 ml) was refluxed for 1 hrs. After cooling, the solid crystals was filtered off and crystallized from acetic acid, as white crystals in 88% yield; mp 298-300°C; IR (KBr): ν 3300 cm^{-1} (NH) 1710 ; 1660 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d6): δ 4.43 (s, 4H, 2CH_2), 7.22-7.43(m, 10H, arom.H), 7.77(s, 2H, two identical benzene protons), 9.17(s, 2H, 2COOH). *Anal.* Calcd. For $C_{24}H_{20}N_2O_6$: C, 66.66; H, 4.66; N, 6.48; Found; C, 66.71; H, 4.57; N, 6.52%.

2,6-dibenzylpyrrolo[3,4-f]isoindole-1,3,5,7(2H,6H)tetrone 4.

1.08 g (2.5 mmol) of 3 was fused at 310 ° for 15 min. The solid formed was washed with water then ethanol and crystallized from DMF, as white crystals in 81% yield; mp 308-9°C; IR (KBr): ν 1740 ; 1700 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 4.85 (s, 4H, $2CH_2$), 7.34 (m, 10H, arom.H), 8.22 (s, 2H, two identical benzene protons). *Anal.* Calcd. For $C_{24}H_{16}N_2O_4$: C, 72.72; H, 4.07; N, 7.07; Found; C, 72.69; H, 4.13; N, 7.04 %.

2,5-di(benz-1,3-thiazol-2-yl)terephthalic acid 5

A mixture of pyromellitic dianhydride 1 (2.18 g, 10 mmol) and 2-aminothiophenol (2.5 g, 20 mmol) in glacial acetic acid (50 ml) was refluxed for 5 hrs. After cooling, the solid precipitated was filtered off and crystallized from DMF/ acetic acid (4:1), as white crystals in 83% yield; mp 335-37°C; IR (KBr): ν 3600-3250 cm^{-1} (COOH), 1779, 1726 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 7.51-8.25 (m, 10H, arom.H), 13.8 (s, 2H, 2COOH); MS: *m/z* =432(M). *Anal.* Calcd. For $C_{22}H_{12}N_2O_4S_2$: C, 61.10; H, 2.80; N, 6.48; S, 14.82; Found; C, 61.21; H, 2.84; N, 6.42; S, 14.73 %.

2,5-di(benz-1,3-thiazol-2-yl)benzoic acid 6

Pyromellitic dianhydride 1 (2.18 g, 10 mmol) and 2-aminothiophenol (2.5 g, 20 mmol) in toluene (50 ml) were refluxed for 10 hrs. After cooling, the solid precipitated was filtered off and crystallized from ethanol, as green crystals in 77% yield; mp 323-25°C; IR (KBr): ν 3600-3250 cm^{-1} (COOH), 1707cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 7.36-8.25 (m, 11H, arom.H), 13.65 (s,1H, COOH); MS: *m/z* 388(M). *Anal.* Calcd. For $C_{21}H_{12}N_2O_2S_2$: C, 64.92; H, 3.11; N, 7.21; S, 16.51; Found; C, 64.96; H, 3.18; N, 7.14; S, 16.47 %.

1,4-di(benz-1,3-thiazol-2-yl)benzene 7

1 g (2.6 mmol) of 6 was fused at 320°C for 5 min. The solid formed was washed with water then sodium bicarbonate solution and crystallized from benzene, as brown crystals in 68% yield; mp 160-62°C; MS: *m/z* 344(M). *Anal.* Calcd. For $C_{20}H_{12}N_2S_2$: C, 69.74; H, 3.51; N, 8.13; S, 18.62; Found; C, 69.80; H, 3.47; N, 8.20; S, 18.53 %.

2,5-diaroylterephthalic acid 8a-d and 2,6-diaroylisophthalic acid 9a-d

General procedure

Anhydrous aluminium chloride (8 g, 60 mmol) was added gradually while stirring to pyromellitic dianhydride (2.18 g, 10 mmol) in dry aromatic substrate, namely, benzene, anisole, toluene and/or chlorobenzene (30 ml). The reaction mixture was refluxed for 2 hrs. and then left overnight. The complex formed was decomposed with ice-cold dilute hydrochloric acid (1:1). The solvent was steam distilled, and after cooling, the solid isomers precipitated (83-94% yield) and were separated by column chromatography (30 cm height, 3 cm diameter) using benzene/ethanol (4:1) as an eluent to give 8a-d and 9a-d as white crystals.

2,5-dibenzoylterephthalic acid 8a

Compound 8a was obtained in 56% yield, crystallized from ethanol/benzene (3:2); mp 320-22°C; IR (KBr) ν 3400-2550 cm^{-1} (COOH), 1750; 1680 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 7.52-7.75 (m, 10H, arom.H), 7.92 (s, 2H, two identical benzene protons) and disappearance of COOH protons. *Anal.* Calcd. For $C_{22}H_{14}O_6$: C, 70.59; H, 3.77. Found; C, 70.56; H, 3.80%.

2,5-di(4-methoxybenzoyl)terephthalic acid 8b

Compound 8b was obtained in 49% yield, crystallized from ethanol/benzene (2:1); mp 325-27°C; IR (KBr) ν 3200-2500cm^{-1} (COOH), 1700;1660 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ = 3.81 (s, 6H, 2 OCH_3), 7.04-7.72 (dd, A_2B_2 system, 8H arom.), 7.85 (s, 2H, two identical benzene protons) and disappearance of COOH protons; MS: *m/z* 434. *Anal.* Calcd. For $C_{24}H_{18}O_8$: C, 66.36; H, 4.18. Found; C, 66.40; H, 4.14 %.

2,5-di(4-methylbenzoyl)terephthalic acid 8c

Compound 8c was obtained in 52% yield, crystallized from ethanol/benzene (3:2); mp 310-12°C; IR (KBr) ν 3400-2800 cm^{-1} (COOH), 1720;1680 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d6): δ 2.37 (s, 6H, 2 CH_3), 7.32-7.65 (dd, A_2B_2 system, 8H arom.), 7.88 (s, 2H, two identical benzene protons) and disappearance of COOH protons. *Anal.* Calcd. For $C_{24}H_{18}O_6$: C, 71.64; H, 4.51. Found; C, 71.62; H, 4.52%.

2,5-di(4-chlorobenzoyl)terephthalic acid 8d

Compound 8d was obtained in 55% yield, crystallized from ethanol/benzene (3:1); mp 320-23°C; IR (KBr) ν 3400-2800cm^{-1} (COOH), 1720;1680cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 7.55-

7.79 (dd, A_2B_2 system, 8H arom.), 7.85 (s, 2H, two identical benzene protons) and disappearance of COOH protons; ^{13}C-NMR (DMSO-d_6): 128.82, d, C-2; 128.91, d, C-9; 130.90, d, C-3; 133.40 , s, C-4; 135.16, s, C-1; 138.40, s, C-6; 141.82, s, C-7; 165.63, s, C-5; 194.05, s, C-8. *Anal*. Calcd. For $C_{22}H_{12}Cl_2O_6$: C, 59.62; H, 2.73; Cl, 15.99. Found; C, 59.65; H, 2.74; Cl, 15.95 %.

4,6-dibenzoylisophthalic acid 9a

Compound 9a was obtained in 38% yield, crystallized from ethanol/benzene (1:3); mp 278-79°C; IR (KBr) ν 3300-2800 cm^{-1} (COOH), 1720;1670 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 7.78-7.76 (m, 11H, arom.H + H-5), δ 8.85 (s, 1H, H-2) and disappearance of COOH signal. *Anal*. Calcd. For $C_{22}H_{14}O_6$: C, 70.59; H, 3.77. Found; C, 70.61; H, 3.75 %.

4,6-di(4-methoxybenzoyl)isophthalic acid 9b

Compound 9b was obtained in a 34% yield, crystallized from ethanol/benzene (1:3); mp 215-17°C; IR (KBr) ν 3300-2500 cm^{-1} (COOH), 1730; 1680 cm^{-1} (C=O's); ^{1}H-NMR ($CDCl_3$): δ 33.85 (s, 6H, 2OCH_3), 7.10-7.65 (dd, A_2B_2 system, 8H arom.), 7.40 (s, 1H, H-5),) 8.55 (s, 1H, H-2), 13.85 (s, 2H, 2COOH); ^{13}C-NMR ($CDCl_3$): 55.59, q; 114.04, d; 126.41, d; 129.29, s; 130.50, s; 131.39, d; 131.44, d; 144.95, s; 163.36, s; 165.63, s; 193.56, s.; MS: *m/z* 434 (M). *Anal*. Calcd. For $C_{24}H_{18}O_8$: C, 66.36; H, 4.18. Found; C, 66.39; H, 4.15 %.

4,6-di(4-methylbenzoyl)isophthalic acid 9c

Compound 9c was obtained in 40% yield, crystallized from ethanol/benzene (2:3); mp 248-50°C; IR (KBr) ν 3250-2500 cm^{-1} (COOH), 1700,1670 cm^{-1} (C=O's); ^{1}H-NMR ($CDCl_3$): δ 2.40 (s, 6H, 2CH_3), 7.22-7.37 (dd, A_2B_2 system, 8H arom.), 7.31 (s, 1H, H-5), 8.77 (s, 1H, H-2), 9.49 (s, 2H, 2COOH); MS: *m/z* 402(M). *Anal*. Calcd. For $C_{24}H_{18}O_6$. C, 71.64; H, 4.51. Found; C, 71.61; H, 4.53%.

4,6-di(4-chlorobenzoyl)isophthalic acid 9d

Compound 9d was obtained in 33% yield, recrystallized from ethanol/benzene (1:2); mp 240-42°C; IR (KBr) ν 3400-2270 cm^{-1} (COOH), 1740,1700 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 7.56-7.72 (dd, A_2B_2 system, 8H arom.), 7.95 (s, 1H, H-5), 8.55 (s, 1H, H-2) and disappearance of COOH protons; ^{13}C-NMR (DMSO-d6): 128.84, d, C-2, C-9; 130.67, d, C-3; 131.38, d, C-10; 135.03, s, C-1; 138.30, s, C-4; 141.73, s, C-6; 144.41, s, C-7; 165.56, s, C-5; 193.91, s, C-8; MS: *m/z* 442(M). Anal. Calcd. For $C_{22}H_{12}C_{l2}O_6$: C, 59.62; H, 2.73; Cl, 15.99. Found; C, 59.66; H, 2.74; Cl, 15.94%.

Synthesis of diaryl-[1,2]oxazinobenzoxazines 10a-d and 11a-d

General procedure

To a solution of 2,5-diaroylterephthalic acid 8a-d and/or 4,6-diaroylisophthalic acid 9a-d (5 mmol) in dry pyridine (10 ml), hydroxylamine hydrochloride (1.38 g, 20 mmol) was added, then the reaction mixture was refluxed for 1 hr. After cooling, the reaction mixture was poured onto ice-dilute hydrochloric acid, the solid precipitated was filtered off and crystallized from appropriate solvent to give 10a-d and/or 11a-d white crystals.

4,9-diphenyl-1H,6H[1,2]oxazino[5,4-g][2,3]benzoxazine-1,6-dione 10a

Compound 10a was obtained in 60% yield, crystallized from Ethanol/DMF (6:1); mp >360°C; IR (KBr) ν 1740 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 7.69(m, 10H , arom. H), 8.15 (s, 2H, two identical benzene protons). *Anal*. Calcd. For $C_{22}H_{12}N_2O_4$: C, 71.74; H, 3.28; N, 7.61. Found; C, 71.71; H, 3.27; N, 7.65 %.

4,9-di(4-methoxyphenyl)-1H,6H[1,2]oxazino[5,4-g][2,3]benzoxazine-1,6-dione10b

Compound 10b was obtained in 57% yield, recrystallized from acetic acid; mp 355-58°C; IR (KBr) ν 1750 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 3.72 (s, 6H, 2OCH_3), 6.89-7.13 (dd, A_2B_2 system, 8 H arom.), 7.72 (s, 2H, two identical benzene protons); MS: *m/z* 428(M). *Anal*. Calcd. For $C_{24}H_{16}N_2O_6$: C, 67.29; H, 3.76; N, 6.54. Found; C, 67.32; H, 3.71; N, 6.56 %.

4,9-di(4-methylphenyl)-1H,6H[1,2]oxazino[5,4-g][2,3]benzoxazine-1,6-dione 10c

Compound 10c was obtained in 66% yield, crystallized from DMF; mp 350-52°C; IR (KBr) ν 1750 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 2.45 (s, 6H, 2CH_3), 7.48-7.57 (dd, A_2B_2 system, 8 H arom.), 8.17 (s, 2H, two identical benzene protons); MS: *m/z* 396(M). *Anal*. Calcd. For $C_{24}H_{16}N_2O_4$: C, 72.72; H, 4.07; N, 7.07. Found; C, 72.77; H, 4.05; N, 7.04%.

4,9-di(4-chlorophenyl)-1H,6H[1,2]oxazino[5,4-g][2,3]benzoxazine-1,6-dione 10d

Compound 10d was obtained in 70% yield, crystallized from methanol; mp 358-59°C; IR (KBr) ν 1750; 1740 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 7.71-7.79 (dd, A_2B_2 system, 8 H arom.), 8.13 (s, 2H, two identical benzene protons); MS: *m/z* 436(M). *Anal.* Calcd. For $C_{22}H_{10}Cl_2N_2O$: C, 60.43; H, 2.31; N, 6.41; Cl, 16.22. Found; C, 60.39; H, 2.35; N, 6.46; Cl, 16.16%.

4,6-diphenyl-1H,9H[1,2]oxazino[4,5-g][2,3]benzoxazine-1,9-dione 11a

Compound 11a was obtained in 56% yield, crystallized from DMF; mp 305-8°C; IR (KBr): ν 1760 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 7.52-7.69(m, 11H, arom. H + H-5), 8.96 (s, 1H, H-10). *Anal*. Calcd. For $C_{22}H_{12}N_2O_4$: C, 71.74; H, 3.28; N, 7.61. Found; C, 71.78; H, 3.30; N, 7.55%.

4,6-di(4-methoxyphenyl)-1H,9H[1,2]oxazino[4,5-g][2,3]benzoxazine-1,9-dione11b

Compound 11b was obtained in 69% yield, crystallized from chloroform, mp 278-79°C; IR (KBr) ν = 2932-2832 cm^{-1} (CH_3), 1703 cm^{-1} (C=O's); ^{1}H-NMR (DMSO): δ 3.72 (s, 6H, $2OCH_3$), 6.83-7.10 (dd, A_2B_2 system, 8 H arom.), 7.62 (s, 1H, H-5), 7.97 (s, 1H, H-10). *Anal*. Calcd. For $C_{24}H_{16}N_2O_6$: C, 67.29; H, 3.76; N, 6.54. Found; C, 67.30; H, 3.74; N, 6.55%.

4,6-di(4-methylphenyl)-1H,9H[1,2]oxazino[4,5-g][2,3]benzoxazine-1,9-dione 11c

Compound 11c was obtained in 72% yield, crystallized from DMF; mp 292-94°C; IR (KBr) ν 1755 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 2.39 (s, 6H, $2CH_3$), 7.39-7.48 (dd, A_2B_2 system, 9 H, arom. H+ H-5), 8.97 (s, 1H, H-10). *Anal*. Calcd. For $C_{24}H_{16}N_2O_4$: C, 72.72; H, 4.07; N, 7.07. Found; C, 72.75; H, 4.09; N, 7.02%.

4,6-di(4-chlorophenyl)-1H,9H[1,2]oxazino[4,5-g][2,3]benzoxazine-1,9-dione 11d

Compound 11d was obtained in 76% yield, crystallized from acetic acid; mp 310-12°C; IR (KBr) ν 1760, 1730 cm^{-1} (C=O's); ^{1}H-NMR ($CDCl_3$): δ 7.24-7.50 (dd, A_2B_2 system, 9 H arom. H+ H-5) , 7.62 (s, 1H, H-10). *Anal*. Calcd. For $C_{22}H_{10}Cl_2N_2O$: C, 60.43; H, 2.31; N, 6.41; Cl, 16.22. Found; C, 60.46; H, 2.33; N, 6.40; Cl, 16.17%.

4,9-di(4-methoxyphenyl)-1H,6H[1,2]oxazino[5,4-g][2,3]benzoxazine-1,6-dione 10b and 4,6-di(4-methoxyphenyl)-1H,9H[1,2]oxazino[4,5-g][2,3]benzoxazine-1,9-dione 11b

Anhydrous aluminum chloride (8 g, 60 mmol) was added gradually while stirring to 2,6-dihydroxypyrrolo[3,4-f]isoindolo-1,3,5,7 (2H,6H) tetrone 14 (2.48g, 10 mmol) in dry anisole (20 ml). The reaction mixture was stirred for 1.5 hrs. left overnight and the complex formed was decomposed with ice-cold dilute hydrochloric acid (1:1). The solvent was steam distilled, the crude solid formed was filtered off and the two isomers were separated using hot ethanol. The insoluble isomer was filtered off and crystallized from acetic acid to give 10b. The soluble isomer was isolated and crystallized from chloroform to give 11b.

4,9-di(4-methoxyphenyl)-1H,6H[1,2]oxazino[5,4-g][2,3]benzoxazine-1,6-dione10b

Compound 10b was obtained in 45% yield; mp 355-58°C; IR (KBr) ν 1690 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 3.75 (s, 6H, $2OCH_3$), 6.85-7.13 (dd, A_2B_2 system, 8H, arom. H), 7.72 (s, 2H, two identical benzene protons); ^{13}C-NMR (DMSO-d_6): 55.08, q, C-1; 158.95, s, C-2; 113.76, d, C-3; 129.27, d, C-4; 74.00, s, C-5; 146.98, s, C-6; 161.03, s, C-7; 132.29, s, C-8; 131.56, s, C-9; 118.43, d, C-10. *Anal*. Calcd. For $C_{24}H_{16}N_2O_6$: C, 67.29; H, 3.76; N, 6.54. Found; C, 67.33; H, 3.74; N, 6.52%.

4,6-di(4-methoxyphenyl)-1H,9H[1,2]oxazino[4,5-g][2,3]benzoxazine-1,9-dione11b

Compound 11b was obtained in 25% yield; mp 278-89°C; IR (KBr) ν 1680 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 3.73 (s, 6H, $2OCH_3$), 6.87-7.08 (dd, A_2B_2 System, 8H, arom. H) and two non identical protons at 7.59 (s, 1H, H-5) and at 7.95 (s, 1H, H-10); ^{13}C-NMR (DMSO-d_6): 55.12, q, C-1; 158.89, s, C-2; 113.60, d, C-3; 129.30, d, C-4; 74.02, s, C-5; 150.68, s, C-6; 161.01, s, C-7; 131.55, s, C-8, C-9 (Interfered); 117.06, d, C-10; 120.12, d, C-11. *Anal*. Calcd. For $C_{24}H_{16}N_2O_6$: C, 67.29; H, 3.76; N, 6.54. Found; C, 67.32; H, 3.75; N, 6.52%.

Synthesis of pyridazinophthalazines 12a-h and 13a-f

General procedure

Hydrazine hydrate (20 mmol) and/or

phenylhydrazine (10 mmol) was added to a solution of 2,5-diaroylterephthalic acid 8a-d and/or 4,6-diaroylisophthalic acid 9a-d in acetic acid (30 ml). The reaction mixture was refluxed for 2 hrs and after cooling the solid formed was filtered and washed with DMF to give 12a-h as white crystals and/or 13a-f as yellow crystals respectively.

4,9-diphenyl-pyridazino[4,5-g]phthalazine-1,6(2H,7H)dione 12a

Compound 12a was obtained in 78% yield; mp >360°C; IR (KBr) ν 3150 cm^{-1} (NH) 1660 cm^{-1} (C=O's); MS: *m/z* 366(M). *Anal*. Calcd. For $C_{22}H_{14}N_4O_2$: C, 72.12; H, 3.85; N, 15.29. Found; C, 72.18; H, 3.81; N, 15.28%.

4,9-di(4-methoxyphenyl)-pyridazino[4,5-g]phthalazine-1,6(2H,7H)dione 12b

Compound 12b was obtained in 81% yield; mp >360°C; IR (KBr) ν 3200 cm^{-1} (NH), 1665cm^{-1} (C=O's); MS: *m/z* 426(M). Anal. Calcd. For $C_{24}H_{18}N_4O_4$: C, 67.60; H, 4.25; N, 13.14. Found; C, 67.58; H, 2.29; N, 13.12%.

4,9-di(4-methylphenyl)-pyridazino[4,5-g]phthalazine-1,6(2H,7H)dione 12c

Compound 12c was obtained in 73% yield; mp >360°C; IR (KBr) ν 3200 cm^{-1} (NH), 1660cm^{-1} (C=O's); MS: *m/z* 394(M). *Anal*. Calcd. For $C_{24}H_{18}N_4O_2$: C, 73.08; H, 4.60; N, 14.20. Found; C, 73.11; H, 4.65; N, 14.13%.

4,9-di(4-chlorophenyl)-pyridazino[4,5-g]phthalazine-1,6(2H,7H)dione 12d

Compound 12d was obtained in 84% yield; mp >360°C; IR (KBr) ν 3200 cm^{-1} (NH), 1680cm^{-1} (C=O's); MS: *m/z* 434(M). *Anal*. Calcd. For $C_{22}H_{12}Cl_2N_4O_2$: C, 60.71; H, 2.78; N, 12.87; Cl, 16.29. Found; C, 60.69; H, 2.81; N, 12.85; Cl, 16.30%.

4,9-diphenyl-2,7-diphenylpyridazino[4,5-g]phthalazine-1,6-dione 12e

Compound 12e was obtained in 83% yield, crystallized from xylene; mp >360°C; IR (KBr) ν 1670 cm^{-1} (C=O's); MS: *m/z* 518(M). *Anal*. Calcd. For $C_{34}H_{22}N_4O_2$: C, 78.75; H, 4.28; N, 10.80. Found; C, 78.79; H, 4.30; N, 10.74%.

4,9-di(4-methoxyphenyl)-2,7-diphenylpyridazino[4,5-g]phthalazine-1,6-dione 12f

Compound 12f was obtained in 85% yield, crystallized from xylene; mp 357-59°C; IR (KBr) ν 1670 cm^{-1} (C=O's); MS: *m/z* 578(M). *Anal*. Calcd. For $C_{36}H_{26}N_4O_4$: C, 74.73; H, 4.53; N, 9.68. Found; C, 74.78; H, 4.57; N, 9.59%.

4,9-di(4-methylphenyl)-2,7-diphenylpyridazino[4,5-g]phthalazine-1,6-dione 12g

Compound 12g was obtained in 81% yield, crystallized from xylene; mp >360°C; IR (KBr) ν 1670 cm^{-1} (C=O's); MS: *m/z* 546(M). *Anal*. Calcd. For $C_{36}H_{26}N_4O_2$: C, 79.10; H, 4.79; N, 10.25. Found; C, 79.16; H, 4.81; N, 10.18%.

4,9-di(4-chlorophenyl)-2,7-diphenylpyridazino[4,5-g]phthalazine-1,6-dione 12h

Compound 12h was obtained in 88% yield, crystallized from DMF; mp >360°C; IR (KBr) ν 1680 cm^{-1} (C=O's); MS: *m/z* 586(M). *Anal*. Calcd. For $C_{34}H_{20}Cl_2N_4O_2$: C, 69.51; H, 3.43; N, 9.54; Cl, 12.07. Found; C, 69.50; H, 3.45; N, 9.56; Cl, 12.04%.

4,6-diphenyl-pyridazino[4,5-g]phthalazine-1,9(2H,8H)dione 13a

Compound 13a was obtained in 74% yield; mp >360°C; IR (KBr) ν 3300-3200 cm^{-1} (NH), 1700 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 7.47-7.63(m, 10H, arom. H), 8.02 (S, 1H, H-5), 9.07 (s, 1H, H-10), 13.10 (s, 2H, 2NH). *Anal*. Calcd. For $C_{22}H_{14}N_4O_2$: C, 72.12; H, 3.85; N, 15.29. Found; C, 72.15; H, 3.88; N, 15.24%.

4,6-di(4-methoxyphenyl)-pyridazino[4,5-g]phthalazine-1,9(2H,8H)dione 13b

Compound 13b was obtained in 75% yield; mp >360°C; IR (KBr) ν 3494; 3447 cm^{-1} (NH), 1688 cm^{-1} (C=O's); MS: *m/z* 426(M). *Anal*. Calcd. For $C_{24}H_{18}N_4O_4$: C, 67.60; H, 4.25; N, 13.14. Found; C, 67.62; H, 4.27; N, 13.10%.

4,6-di(4-methylphenyl)-pyridazino[4,5-g]phthalazine-1,9(2H,8H)dione 13c

Compound 13c was obtained in 82% yield; mp >360°C; IR (KBr) ν 3200 cm^{-1} (NH), 1660 cm^{-1} (C=O's); MS: *m/z* 394(M). *Anal*. Calcd. For $C_{24}H_{18}N_4O_2$: C, 73.08; H, 4.60; N, 14.20. Found; C, 73.06; H, 4.64; N, 14.18%.

4,6-di(4-chlorophenyl)-pyridazino[4,5-g]phthalazine-1,9(2H,8H)dione 13d

Compound 13d was obtained in 72% yield; mp >360°C; IR (KBr) ν 3200 cm^{-1} (NH), 1680cm^{-1} (C=O's); MS: *m/z* 434(M). *Anal*. Calcd. For $C_{22}H_{12}Cl_2N_4O_2$: C, 60.71; H, 2.78; N, 12.87; Cl, 16.29. Found; C, 60.76; H, 2.72; N, 12.82; Cl, 16.35%.

2,4,6,8-tetraphenyl-pyridazino[4,5-g]phthalazine-1,9-dione 13e

Compound 13e was obtained in 78% yield, crystallized from xylene; mp 324-26°C. IR (KBr) í 1680 cm^{-1} (C=O's); MS: *m/z* 518 (M). *Anal*. Calcd. For $C_{34}H_{22}N_4O_2$: C, 78.75; H, 4.28; N, 10.80. Found; C, 78.79; H, 4.25; N, 10.79%.

4,6-di(4-chlorophenyl)-2,8-diphenyl pyridazino [4,5-g]phthalazine-1,9-dione 13f

Compound 13f was obtained in 64% yield, crystallized from Xylene / DMF; mp= 360°C; IR (KBr) ν 1680 cm^{-1} (C=O's); ^{1}H-NMR (DMSO-d_6): δ 7.53-7.81 (m, 19H, 18 arom. H + H-5) 8.67 (s, 1H, H-10); MS: *m/z* 586 (M). *Anal*. Calcd. For $C_{34}H_{20}Cl_2N_4O_2$: C, 69.51; H, 3.43; N, 9.54; Cl, 12.07. Found; C, 69.53; H, 3.45; N, 9.56; Cl, 12.01%.

CONCLUSIONS

In summary, we have found that pyromellitic dianhydride is extremely useful for the synthesis of biologically relevant heterocyclic compounds such as dipyrroles, dibenzoxazines, dipyridazines and isophthalic and terephthalic derivatives in good yields after short reaction times.

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