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Polyfunctional Fused Heterocyclic Compounds via Indene-1,3-diones

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ABSTRACT: *2-Dimethylaminomethylene- and 2-ethoxymethylene-1,3-indendione* **1a,b** *react with 6-amino-2-thioxopyrimidin-4(3*H*)-one* **2** *in boiling acetic acid to give 2-thioxo-1,3-dihydroindeno[3,2-*d*]pyrimidino[4,5-*b*]pyridine-4,9-dione (***4***). The latter compound reacts with hydrazonoyl chlorides* **5a–c** *to afford products* **12a–c**. *Formamidine* **15** *reacts with indene-1,3-dione in boiling ethanol to give acyclic compound* **16**, *which cyclizes to* **12a** *in boiling glacial acetic acid. Also, enaminone* **1a** *reacts with heterocyclic amines* **17a–e** *in boiling ethanol, affording the corresponding substitution products* **18a–c**, *respectively. The latter products* **18a–c** *cyclize in glacial acetic acid to give* **19a–c**, *respectively. The structures of the newly synthesized compounds are established on the basis of chemical and spectroscopic evidence.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:491–497, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10166

INTRODUCTION

Even though 2-dimethylaminomethylene- and 2-ethoxymethylene-1,3-indendione **1a,b** were synthesized long ago, their utility in the synthesis of fused heterocyclic compounds has received little attention [1–3]. The objective of our program is to develop the synthesis of functionally fused heteroaromatic compounds from readily obtainable starting materials such as **1a** and **1b**. In the following work, we report a novel synthesis of 2-thioxo-1,3-dihydroindeno[3,2-*d*]pyrimidino[4,5-*b*]pyridine-4,9-dione (**4**) and its utility for the synthesis of fused heterocyclic compounds **12**. We also report the reaction of **1a** or **1b** with heterocyclic amines.

RESULTS

We have found that **1a** or **1b**, obtained via condensation of the indene-1,3(2*H*)-dione with dimethylformamide dimethylacetal (DMFDMA) or triethyl orthoformate (TEOF), respectively, as has been described earlier [1,3], readily condenses with 6-amino-2-thioxopyrimidin-4(3*H*)-one [4] in acetic acid to give 2-thioxo-1,3-dihydro-indeno[3,2-*d*]pyrimidino[4,5-*b*]pyridine-4,9-dione (**4**) (Scheme 1).

It may be assumed that initially formed **3** cyclized to give **4** (Scheme 1). The structure of compound **4** is based on its elemental analysis and spectroscopic data (IR, ^{1}H NMR, and MS). The mass spectrum showed an intense peak at *m/z* 281 corresponding to its molecular ion peak. The ^{1}H NMR spectrum of **4** displayed three singlets at δ 8.09 (s, 1H, pyridine-H), 12.89 (s, 1H, NH), and 13.62 (s, 1H, NH) in addition to the multiplet in the aromatic region at δ 7.60–7.81 (4H). Its IR spectrum showed four absorption bands at 1682, 1716, 3350, and 3421, corresponding to two carbonyl and two NH groups, respectively.

Treatment of **4** with hydrazonoyl chlorides **5a–c** [5–7] in chloroform in the presence of triethylamine

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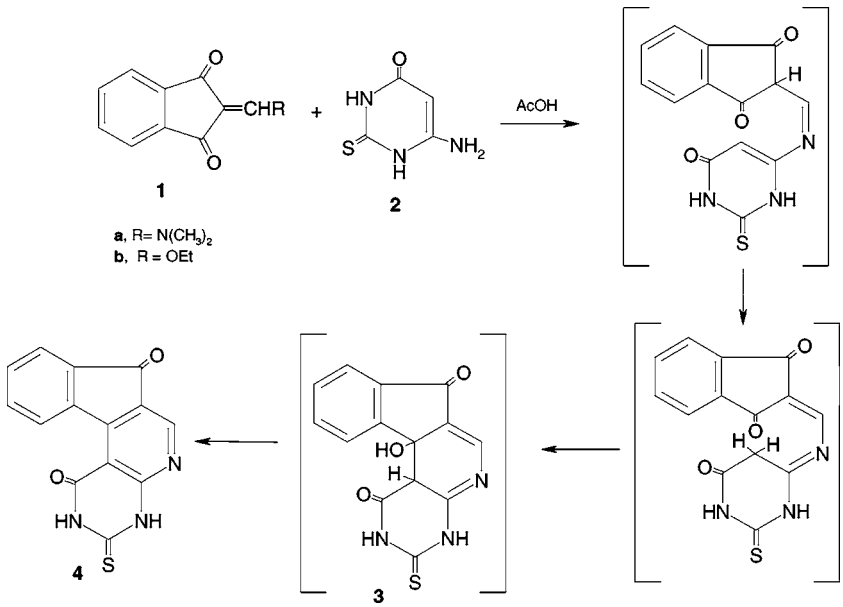


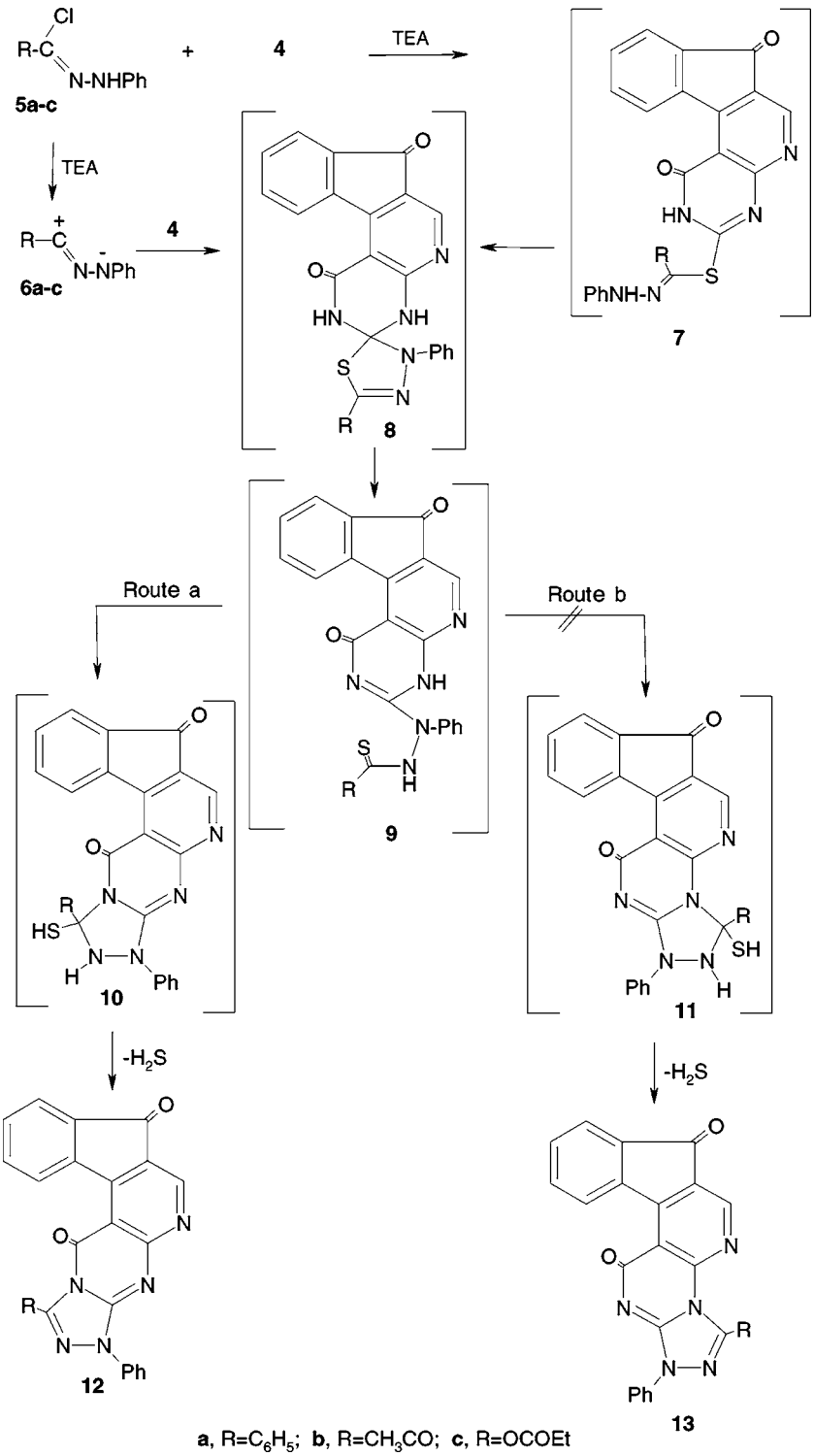
SCHEME 1

yields products that can be formulated as **12a–c** or their isomeric structures **13a–c** (Scheme 2). The reaction pathway that seems reasonable to account for the formation of **12** or **13** is outlined in Scheme 2. It is proposed that the reaction involves an initial nucleophilic substitution to give thiohydrazonate esters **7**, which undergo an S → N migration via the spiro intermediates **8** to give the thiohydrazides **9**. The spiro intermediates **8** may be also formed via 1,3-dipolar cycloaddition of nitrilimines **6a–c**, generated in situ from the reaction of hydrazonoyl chlorides **5a–c** with triethylamine, to the thione C=S group of compound **4**. The latter intermediates **9** undergo cyclization via elimination of hydrogen sulfide to give final products that may have structure **12** or **13** according to which cyclization step is followed (route a or b in Scheme 2). Isomers **12** and **13** will, of course, yield identical elemental analyses and mass spectra. These data thus cannot be used to determine the exact structure of the product; conclusive evidence for the structures were obtained by the synthesis of **12** by an alternative method.

Thus, treatment of 7-amino-1,3-diphenyl-1,2,4-triazolo[4,5-*a*]pyrimidin-5-one (**14**) [8], prepared via 1,3-dipolar cycloaddition reaction of **2** [4], with *N*-phenylbenzohydrazonoyl chloride (**5a**) [5] in boiling acetonitrile in the presence of triethylamine, with DMFDMA yields the corresponding formamidine compound **15** [9] (Scheme 3). Treatment of compound **15** with indene-1,3(2*H*)-dione in boiling ethanol leads to the formation of acyclic structure **16** (Scheme 3). Elemental analysis and spectroscopic data confirmed the structure **16**. Its ^{1}H NMR spectrum displayed two singlets at δ 6.19 (N=C<u>H</u>) and 11.18 (OH), which disappeared upon shaking with deuterium oxide, in addition to a multiplet of aromatic protons. Also, its mass spectrum gave an intense peak at *m/z* 459 corresponding to the molecular ion peak. Boiling of compound **16** in glacial acetic acid led to the formation of the cyclized product, via elimination of water, which was identical in all respects (mp, mmp, ^{1}H NMR, and MS) with compound **12a** that was prepared previously (Scheme 2).

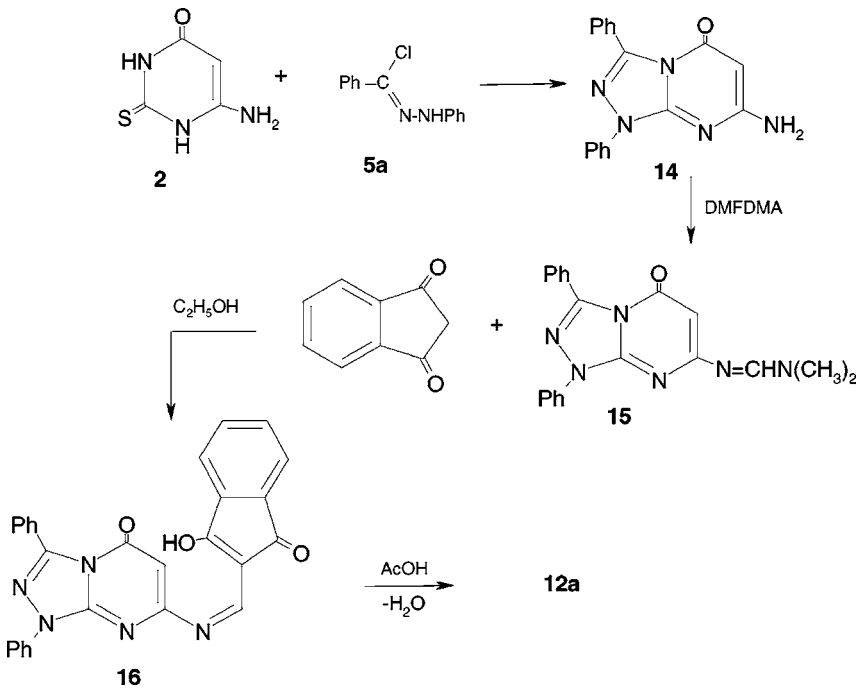
Treatment of **1a** or **1b** with 5-aminotriazole **17a** in boiling ethanol affords the substitution product **18a** or **21a** having a molecular formula $C_{12}H_8N_4O_2$ (Scheme 4). The resulting product gave an intense molecular ion peak at *m/z* 240 in its mass spectrum. Boiling of the resulting substitution product in glacial acetic acid results in formation of the cyclized product **19a** or its isomer **22a** via elimination of water (Scheme 4). The elemental analysis and spectral data (IR and MS) of the product agreed with either **19a** or **22a**. Conclusive evidence for the structure was obtained by an alternative synthesis. Thus, condensation of triazolylformamidine **20a** [10], prepared by reaction of 5-aminotriazole **17a** with DMFDMA, with indene-1,3-dione in boiling acetic acid leads to the formation of compound **19a** via elimination of dimethylamine and water molecules (Scheme 4).

Similarly, treatment of **1a** or **1b** with heterocyclic amines **17b–e** in boiling ethanol yields the substitution products **18b–e** or **21b–e**. The latter products are cyclized in boiling glacial acetic acid via



SCHEME 2

elimination of water to give **19b–e** or **22b–e**. The structures of **19b–e** are established for the products based on the identity reaction of formamidines **20b–e** [10], prepared by condensation of **17b–e** with DMFDMA, with 1,3-indenedione (Scheme 4). The structures were confirmed from spectral data and elemental analyses (see Experimental section).



SCHEME 3

EXPERIMENTAL

Melting points were determined on a Gallenkamp electrothermal apparatus and are uncorrected. Infrared spectra were recorded as KBr pellets with a Pye Unicam SP-3000 infrared spectrophotometer. ^{1}H NMR spectra were determined on a Varian Gemini 200 spectrometer (200 MHz) in DMSO-d_6 as solvent and TMS as internal standard. Chemical shifts δ are reported in ppm. Mass spectra were measured at 70 eV using a Shimadzu GCMS-QP 1000EX. Microanalyses were performed on a Perkin-Elmer 2400 CHN Elemental Analyzer at the microanalytical center, University of Cairo. Compounds **1a** [3], **1b** [1], **2** [4], **5a–c** [5–7], **14** [8], **15** [9], **20a** [10], **20b** [10], and **20e** [10] were prepared as previously described.

*Synthesis of 2-Thioxo-1,3-dihydroindeno[3,2-*d*]-pyrimidino[4,5-*b*]pyridine-4,9-dione (**4**)*

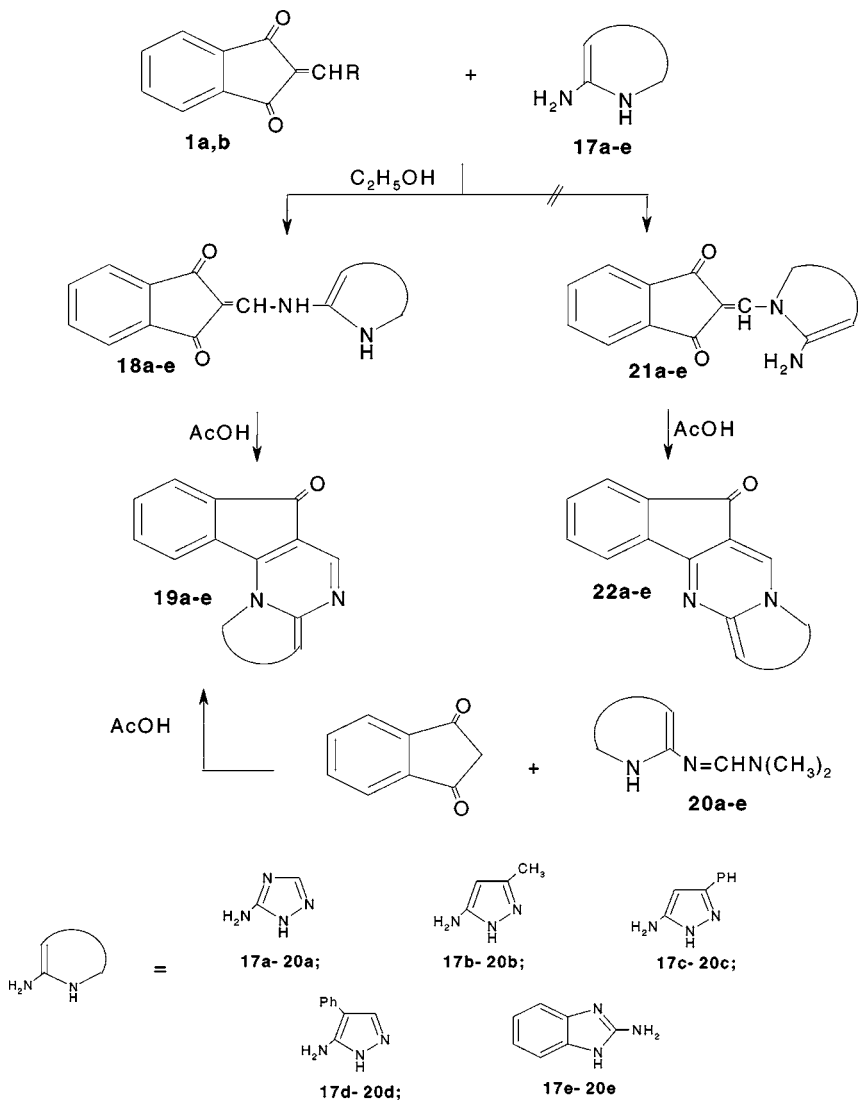
A solution of compound **1a** or **1b** (5 mmol) and **2** (0.72 g, 5 mmol) in acetic acid was refluxed for 2 h. The excess solvent was evaporated under reduced pressure and the residue was treated with methanol (10 ml). The solid that formed was collected and crystallized from dimethylformamide to give **4** in 90% yield; mp 311°C; IR (KBr) ν 3421 (NH), 3350 (NH), 1716 (C=O), 1682 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.60–7.81 (m, 4H), 8.09 (s, 1H), 12.89 (s, 1H), 13.62 (s, 1H); MS *m/z*: 281, 252, 237, 222, 138, 137, 110, 81, 59.

Anal. Calcd for $C_{14}H_7N_3O_2S$: C, 59.78; H, 2.51; N, 14.94; S, 11.40. Found: C, 59.48; H, 2.19; N, 14.65; S, 11.08%.

Synthesis of **12a–c**

Method A. To a stirred solution of the appropriate hydrazonoyl chlorides **5a–c** (5 mmol) and **4** (1.40 g, 5 mmol) in chloroform (40 ml) was added triethylamine (0.7 ml, 5 mmol). The reaction mixture was refluxed until the hydrogen sulfide gas ceased to evolve (8 h) as indicated by TLC analysis. The solvent was evaporated under reduced pressure and the residue was treated with methanol (10 ml). The solid formed was collected and crystallized from dimethylformamide to give the corresponding products **12a–c**, respectively.

Method B. A solution of compound **16** (2.29 g, 5 mmol) in acetic acid (30 ml) was refluxed for 2 h. The excess solvent was evaporated under reduced pressure and the residue was treated with methanol (10 ml). The solid that formed was collected and crystallized from dimethylformamide to give compound identical in all respects (mp, mmp and spectral data) with **12a** obtained by method A.



SCHEME 4

*1,3-Diphenyl-13-hydroindeno[3,2-*d*]1,2,4-triazolino[4′,5′-2,1]pyrimidino[4,5-*b*]pyridine-7,12-dione (***12a***)*

The compound was obtained in 89% yield; mp 303°C; IR (KBr) ν 1719 (C=O), 1675 (C=O) cm^{-1}; MS, *m/z*: 442, 441, 384, 339, 233, 204, 193, 103, 91, 77.

Anal. Calcd for $C_{27}H_{15}N_5O_2$: C, 73.46; H, 3.43; N, 15.87. Found: C, 73.16; H, 3.25; N, 15.53%.

*1-Acetyl-3-phenyl-13-hydroindeno[3,2-*d*]1,2,4-triazolino[4′,5′-2,1]pyrimidino[4,5-*b*]pyridine-7,12-dione (***12b***)*

The compound was obtained in 90% yield; mp 315°C; IR (KBr) ν 1708 (C=O), 1678 (C=O), 1652 (C=O) cm^{-1}; MS *m/z*: 408, 407, 406, 364, 310, 248, 193, 165, 138, 77.

Anal. Calcd for $C_{23}H_{13}N_5O_3$: C, 67.81; H, 3.22; N, 17.19. Found: C, 67.59; H, 3.11; N, 16.95%.

*1-Ethoxycarbonyl-3-phenyl-13-hydroindeno[3,2-*d*]1,2,4-triazolino[4′,5′-2,1]pyrimidino[4,5-*b*]pyridine-7,12-dione (***12c***)*

The compound was obtained in 91% yield; mp 265°C; IR (KBr) ν 1714 (C=O), 1669 (C=O), 1648 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.41 (t, J = 7 Hz, 3H) 4.59 (q, J = 7 Hz, 2H), 7.52–8.10 (m, 9H), 8.39 (s, 1H); MS *m/z*: 438, 437, 364, 324, 248, 205, 165, 138, 77.

Anal. Calcd for $C_{24}H_{15}N_5O_4$: C, 65.90; H, 3.46; N, 16.01. Found: C, 65.62; H, 3.13; N, 15.86%.

*Synthesis of 2-[(1,3-Diphenyl-7-amino-1,2,4-triazolo[4,3-a]pyrimidin-5-one)methylene]-1,3-indenedione (**16**)*

An equimolecular amount of **15** (1.79 g, 5 mmol) and 1,3-indene-dione (0.73 g, 5 mmol) was refluxed in boiling ethanol (30 ml) for 2 h. The excess solvent was evaporated under reduced pressure and the residue was treated with methanol (10 ml). The solid that formed was collected and crystallized from dimethylformamide to give **16** in 90% yield; mp 317°C; IR (KBr) ν 3440 (OH), 1717 (C=O), 1643 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.19 (s, 1H), 7.41–8.09 (m, 14H), 8.52 (s, 1H), 11.18 (s, 1H); MS *m/z*: 459, 383, 355, 303, 178, 163, 91, 76.

Anal. Calcd for $C_{27}H_{17}N_5O_3$: C, 70.58; H, 3.73; N, 15.24. Found: C, 70.45; H, 3.56; N, 14.98%.

*Synthesis of **18a–e**: General Method*

A mixture of compound **1a** or **1b** (5 mmol) and one of **17a–e** (5 mmol) in ethanol (30 ml) was refluxed for 2 h and left to cool. The solid product was collected by filtration and crystallized from dimethylformamide to give compounds **18a–e**, respectively.

*2-[(Triazol-5-ylamino)methylene]-1,3-indenedione (**18a**)*

The compound was obtained in 70% yield; mp 230°C; IR (KBr) ν 3325 (NH), 3201 (NH), 1665 (C=O), 1643 (C=O) cm^{-1}; MS *m/z*: 240, 201, 186, 159, 144, 101, 75, 53.

Anal. Calcd for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.32. Found: C, 59.70; H, 3.06; N, 23.10%.

*2-[(3-Methylpyrazol-5-ylamino)methylene]-1,3-indenedione (**18b**)*

The compound was obtained in 85% yield; mp 270°C; IR (KBr) ν 3202 (NH), 3140 (NH), 1697 (C=O), 1656 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.63 (s, 3H), 6.29 (s, 1H), 7.89 (s, 4H), 8.33 (s, 1H), 11.12 (s, 1H), 12.53 (s, 1H); MS *m/z*: 254, 253, 225, 196, 157, 129, 101, 76, 67; ^{13}C NMR (DMSO-d_6) δ 12.49, 77.22, 95.84, 123.13, 135.69, 141.33, 142.28, 144.96, 157.02, 177.36.

Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.39; H, 4.38; N, 16.59. Found: C, 66.23; H, 4.12; N, 16.42%.

*2-[(3-Phenylpyrazol-5-ylamino)methylene]-1,3-indenedione (**18c**)*

The compound was obtained in 87% yield; mp 299°C; IR (KBr) ν 3289 (NH), 3223 (NH), 1698 (C=O), 1654 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.92 (s, 1H), 7.41–7.72 (m, 9H), 8.34 (s, 1H), 11.20 (s, 1H), 13.21 (s, 1H); MS *m/z*: 316, 315, 270, 185, 157, 143, 102, 77.

Anal. Calcd for $C_{19}H_{13}N_3O_2$: C, 72.37; H, 4.16; N, 13.33. Found: C, 72.19; H, 3.99; N, 13.05%.

*2-[(4-Phenylpyrazol-3-ylamino)methylene]-1,3-indenedione (**18d**)*

The compound was obtained in 82% yield; mp 263°C; IR (KBr) ν 3428 (NH), 3199 (NH), 1698 (C=O), 1656 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.31–7.72 (m, 9H), 8.11 (s, 1H), 8.42 (s, 1H), 11.30 (s, 1H), 13.21 (s, 1H); MS *m/z*: 316, 315, 314, 181, 143, 102, 50.

Anal. Calcd for $C_{19}H_{13}N_3O_2$: C, 72.37; H, 4.16; N, 13.33. Found: C, 72.24; H, 3.94; N, 13.15%.

*2-[(Benzimidazol-2-ylamino)methylene]-1,3-indenedione (**18e**)*

The compound was obtained in 80% yield; mp 209°C; IR (KBr) ν 3369 (NH), 3187 (NH), 1690 (C=O), 1651 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.21 (s, 2H), 6.82–7.13 (m, 8H), 7.60 (s, 1H); MS *m/z*: 290, 289, 271, 243, 203, 146, 134, 86, 52.

Anal. Calcd for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.53. Found: C, 70.29; H, 3.62; N, 14.35%.

*Synthesis of **19a–e***

Method A. A mixture of compound **1a** or **1b** (5 mmol) and one of **18a–e** (5 mmol) in acetic acid (30 ml) was refluxed for 4 h and left to cool. The solid product was collected by filtration and crystallized from dimethylformamide to give compounds **19a–e**, respectively.

Method B. A mixture of each compound **20a–e** (5 mmol) and 1,3-indene-dione (0.73 g, 5 mmol) in acetic acid (30 ml) was refluxed for 1 h and left to cool. The solid product was collected by filtration and crystallized from dimethylformamide to give compounds which were identical in all respects (mp, mmp, and spectral data) with **19a–e** obtained by Method A.

*11-Hydroindeno[2,3-e]1,2,4-triazolo[1,5-a]-pyrimidin-6-one (**19a**)*

The compound was obtained in 77% yield; mp 281°C; IR (KBr) ν 1711 (C=O) cm^{-1}; MS *m/z*: 223, 222, 194, 167, 142, 126, 111, 91, 53.

Anal. Calcd for $C_{12}H_6N_4O$: C, 64.86; H, 2.72; N, 25.22. Found: C, 64.65; H, 2.55, N, 24.96%.

*2-Methyl-11-hydroindeno[2,3-*e*]pyrazolo[1,5-*a*]-pyrimidin-6-one (***19b**)

The compound was obtained in 80% yield; mp 225°C; IR (KBr) ν 1712 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.61 (s, 3H), 6.72 (s, 1H), 7.72–7.75 (m, 4H), 8.60 (s, 1H); MS *m/z*: 236, 235, 207, 142, 81, 69.

Anal. Calcd for $C_{14}H_9N_3O$: C, 71.48; H, 3.86; N, 17.86. Found: C, 71.39; H, 3.81; N, 17.67%.

*2-Phenyl-11-hydroindeno[2,3-*e*]pyrazolo[1,5-*a*]-pyrimidin-6-one (***19c**)

The compound was obtained in 75% yield; mp 280°C; IR (KBr) ν 1713 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.31 (s, 1H), 7.41–8.32 (m, 9H), 8.53 (s, 1H); MS *m/z*: 298, 297, 268, 221, 148, 142, 88, 77.

Anal. Calcd for $C_{19}H_{11}N_3O$: C, 76.75; H, 3.73; N, 14.13. Found: C, 76.44; H, 3.44; N, 13.86%.

*3-Phenyl-11-hydroindeno[2,3-*e*]pyrazolo[1,5-*a*]-pyrimidin-6-one (***19d**)

The compound was obtained in 91% yield; mp 260°C; IR (KBr) ν 1713 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.31–8.42 (m, 9H), 8.91 (s, 1H), 9.20 (s, 1H); MS *m/z*: 298, 297, 296, 139, 107, 102, 73, 63, 51, 50.

Anal. Calcd for $C_{19}H_{11}N_3O$: C, 76.75; H, 3.73; N, 14.13. Found: C, 76.54; H, 3.34; N, 13.96%.

*14-Hydrobenzimidazolo[1,2-*a*]indeno[2,3-*e*]-pyrimidin-5-one (***19e**)

The compound was obtained in 78% yield; mp 315°C; IR (KBr) ν 1712 (C=O) cm^{-1}; MS *m/z*: 272, 271, 243, 215, 189, 139, 126, 102, 55.

Anal. Calcd for $C_{17}H_9N_3O$: C, 75.27; H, 3.34; N, 15.49. Found: C, 75.08; H, 3.05; N, 15.19%.

Synthesis of **20c,d***: General Method*

A mixture of the appropriate **17c,d** (5 mmol) and DMFDMA (0.66 g, 5 mmol) in dioxan (25 ml) was refluxed for 1 h. The reaction mixture was left to cool and triturated with ethanol (10 ml). The solid product, so formed, was collected by filtration and crystallized from ethanol to give products **20c,d** respectively.

*5-Phenyl-1*H*-pyrazol-3-yl-dimethylaminoformamidine (***20c**)

The compound was obtained in 80% yield; mp 180°C; IR (KBr) ν 3189 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.91 (s, 3H), 3.09 (s, 3H), 6.33 (s, 1H), 7.21–7.79 (m, 5H), 8.14 (s, 1H), 12.32 (s, 1H); MS *m/z*: 215, 214, 213, 172, 104, 83, 57.

Anal. Calcd for $C_{12}H_{14}N_4$: C, 67.26; H, 6.59; N, 26.15. Found: C, 67.15; H, 6.42; N, 26.04%.

*4-Phenyl-1*H*-pyrazol-3-yl-dimethylaminoformamidine (***20d**)

The compound was obtained in 80% yield; mp 184°C; IR (KBr) ν 3186 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.03 (s, 6H), 7.14–7.83 (m, 6H), 8.02 (s, 1H), 12.11 (s, 1H); MS *m/z*: 215, 214, 213, 172, 142, 115, 89, 57.

Anal. Calcd for $C_{12}H_{14}N_4$: C, 67.26; H, 6.59; N, 26.15. Found: C, 67.11; H, 6.52; N, 26.09%.

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