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Bischalcones—synthons for a new class of bis(heterocycles)

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Novel oxo-linked bis(heterocycles) containing two different heterocyclic rings, *viz*. pyrroles in combination with pyrazolines and isoxazolines, are synthesized.

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Introduction

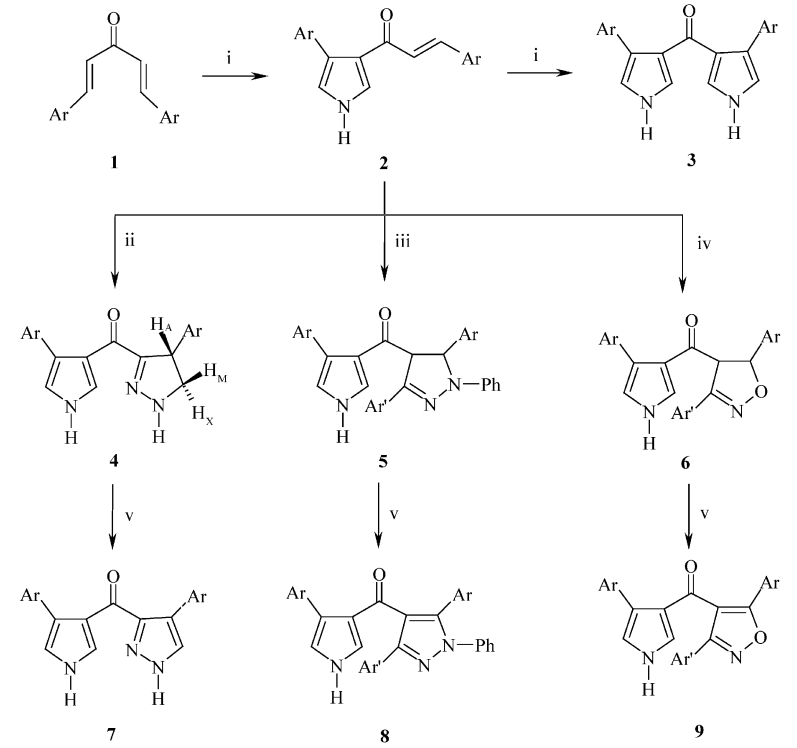
Amongst five-membered heterocycles, pyrroles, pyrazolines and isoxazolines represent a class of compounds of great importance in heterocyclic chemistry. These compounds have intrinsic biological activities and constitute the structural feature of many bioactive compounds. As constituents of cytotoxic drugs (such as netrospin and distamycin), 4-aminopyrrole-2-carboxylates have been used as the main compounds in the construction of a diverse series of DNA-binding ligands exhibiting antibiotic, antiviral and oncolytic properties.[1] The related 3-aminopyrroles also exhibit anticonvulsant activity by blocking sodium channels.[2] In addition, pyrazolines and isoxazolines have gained importance due to their various chemotherapeutic properties. In fact, Celecoxib, a pyrazole derivative, and Valdecoxib, an isoxazole derivative, are now widely used in the market as anti-inflammatory drugs.[3] Hence, it is considered worthwhile to prepare molecules having both pyrrole and pyrazole/isoxazole rings. In the literature, multistep synthetic routes to 3,4-disubstituted pyrroles have been reported either by coupling imines and nitroalkanes or by using Friedel–Crafts acylation in the presence of an electron-withdrawing group on the pyrrole nitrogen or on 3,4-silylated precursors.[4] However, these synthetic routes are often complicated and limited to only some substituents.

Previously, 3,4-disubstituted pyrroles have also been synthesized from Michael acceptors and tosyl methyl isocyanide (TosMIC).[5] Following this synthetic methodology, we reported recently a new regioselective one-step procedure using TosMIC, leading to a series of 3,4-disubstituted pyrroles in good yields.[6] Similarly, pyrazolines and isoxazolines have been synthesized by 1,3-dipolar cycloaddition of an ylide to an alkene involving the 3 + 2 principle.[7] Among the ylides, diazomethane, nitrile imines and nitrile oxides have been used extensively as reactive intermediates. These nitrile imines and nitrile oxides can be generated by the dehydrogenation of araldehyde phenylhydrazones and araldoximes with lead tetraacetate,[8] mercury acetate,[9] 1-chlorobenzotriazole,[10] chloramine-T,[11] *etc*. Use of the latter for *in situ* generation of dipolar reagents has enthused many organic chemists. In fact, we ourselves have reported in the past the 1,3-dipolar cycloaddition reaction of chloramine-T catalysed dipolar reagents with a variety of activated mono and bis(olefins).[12] The present communication deals with the synthesis of hitherto unknown oxo-linked bis(heterocycles) having pyrrole together with pyrazole or isoxazole units, from 1,3-dipolar cycloaddition of TosMIC, nitrile imines and nitrile oxides to activated olefins.

Results and discussion

The general synthetic pathway discussed hereafter is depicted in Scheme 1. Experimental data and spectroscopic analyses of compounds **2**–**9** are compiled in Tables 1 and 2. When bischalcone **1** is treated with TosMIC in the presence of sodium hydride in a solvent mixture of ether and DMSO, a solid is obtained and identified by NMR spectroscopy as 3′-aryl-1′-(4-aryl-1*H*-pyrrol-3-yl)-prop-2′-enone **2**. Compound **2a** exhibits two singlets at δ 6.80 and 6.96 ppm, assigned to H-2 and H-5 pyrrole ring protons. Two doublets are observed at δ 7.08 and 7.65 ppm corresponding to olefinic protons, in addition to the signals of aromatic protons. Thus, the formation of **2** indicates that the reaction is regiospecific. Attempts to prepare bis-(4-aryl-1*H*-pyrrol-3-yl)methanone **3** by refluxing **1** with 2 equiv. of TosMIC were not successful. However, **3** can be obtained by treating **2** with 1 equiv. of TosMIC, as confirmed by NMR spectroscopy. Compound **3a** presents two sharp singlets at δ 6.84 and 6.97 ppm corresponding to H-2,2′ and H-5,5′. This indicates that the molecule is highly symmetrical.

The olefinic group in **2** is used to develop different heterocyclic rings such as pyrazoles and isoxazoles. Treatment of **2** with diazomethane at −15 °C for 48 h gives a solid identified as (4′-aryl-4′,5′-dihydro-1′*H*-pyrazol-3′-yl)-(4-aryl-1*H*-pyrrol-3-yl) methanone **4** by spectral analysis. The ^{1}H NMR spectrum of **4a** shows an AMX splitting pattern for the pyrazoline ring protons at δ 4.53 (H_A), 3.64 (H_M) and 3.58 (H_X) ppm, respectively, in addition to the signals of the pyrrole ring protons. The observed coupling constant values J_{AM} = 12.6, J_{AX} = 5.5 and J_{MX} = 10.0 Hz indicate that H_A and H_M are cis, H_A and H_X are trans and H_M and H_X are geminal (see Table 2). Similarly, 1,3-dipolar cycloaddition of nitrile imines and nitrile oxides (generated from araldehyde phenylhydrazones and araldoximes, respectively) to **2** results in (4-aryl-1*H*-pyrrol-3-yl)-(1′,3′,5′- triaryl-4′,5′-dihydro-1′*H*-pyrazol-4′-yl)methanone **5** and (3′,5′-diaryl-4′,5′-dihydroisoxazol-4′-yl)-(4-aryl-1*H*-pyrrol-3-yl)methanone **6**, respectively. The ^{1}H NMR spectra of **5a** and **6a** display two doublets at δ 5.23, 5.61 ppm and 5.20, 5.65 ppm, respectively, which are assigned to H-4 and H-5, that is, the two methine protons of the pyrazoline and isoxazoline rings. The *J* values show that they are in a trans geometry (see Table 2). Compounds **4a**, **5a** and **6a**, upon oxidation with chloranil in xylene, give the corresponding pyrazoles and isoxazoles **7a**, **8a** and **9a**. The disappearance of the two doublets from the pyrazoline/isoxazoline ring protons in the ^{1}H NMR spectra confirms their formation. The structures of **2**–**9** were further confirmed by ^{13}C NMR spectroscopy (Table 2).



i) TosMIC, NaH, Et_2O + DMSO ii) CH_2N_2 / Et_2O iii) Ar'-CH=NNHPh / Chloramine-T.$3H_2O$ / MeOH

iv) Ar'-CH=NOH / Chloramine-T.$3H_2O$ / MeOH v) Chloranil, Xylene

	Ar	Ar'
2a,3a,4a,7a	Ph	-
2b,3b,4b	4-OMe.Ph	-
2c,3c,4c	4-Cl.Ph	-
5a,6a, 8a, 9a	Ph	Ph
5b,6b	4-OMe.Ph	Ph
5c,6c	Ph	4-Cl.Ph
5d,6d	4-Cl.Ph	4-Cl.Ph

Scheme 1

Compounds **3**–**6** were further tested for antimicrobial activity at three different concentrations (25, 75 and 100 μg per disc). The antibacterial activity was screened against the following microorganisms: *Staphylococcus aureus*, *Bacillus subtilis* (Gram-positive bacteria) and *Escherichia coli*, *Klebsiella pneumoniae* (Gram-negative bacteria), on nutrient agar plates at 37 °C for 24 h using Gentamycin as a reference drug. The compounds were also evaluated for their antifungal activity

Table 1 Experimental and IR spectroscopy data of compounds **2**–**9**

				Anal. calcd. (found)/wt %			IR ν/cm^{-1}			
	% Yield	M.p./°C	Molecular formula (MW/g mol^{-1})	C	H	N	NH	C=O	C=C	C=N
2a	74	201–202	$C_{19}H_{15}NO$ (273.33)	83.49 (83.56)	5.53 (5.50)	5.12 (5.17)	3169	1664	1636	—
2b	71	212–214	$C_{21}H_{19}NO_3$ (333.38)	75.66 (75.52)	5.74 (5.69)	4.20 (4.27)	3172	1658	1629	—
2c	68	236–238	$C_{19}H_{13}Cl_2NO$ (342.22)	66.68 (66.53)	3.83 (3.80)	4.09 (4.18)	3170	1665	1628	—
3a	78	209–211	$C_{21}H_{16}N_2O$ (312.36)	80.75 (80.81)	5.16 (5.12)	8.97 (9.04)	3180	1673	—	—
3b	82	203–205	$C_{23}H_{20}N_2O_3$ (372.42)	74.18 (74.11)	5.41 (5.38)	7.52 (7.59)	3175	1678	—	—
3c	79	243–245	$C_{21}H_{14}Cl_2N_2O$ (381.25)	66.16 (66.24)	3.70 (3.75)	7.35 (7.41)	3178	1669	—	—
4a	69	225–227	$C_{20}H_{17}N_3O$ (315.37)	76.17 (76.10)	5.43 (5.40)	13.32 (13.41)	3182	1685	—	1568
4b	72	217–219	$C_{22}H_{21}N_3O_3$ (375.42)	70.38 (70.32)	5.64 (5.68)	11.19 (11.24)	3174	1681	—	1571
4c	66	248–250	$C_{20}H_{15}Cl_2N_3O$ (384.26)	62.51 (62.44)	3.93 (3.88)	10.94 (10.99)	3169	1676	—	1570
5a	71	289–281	$C_{32}H_{25}N_3O$ (467.56)	82.20 (82.29)	5.39 (5.42)	8.99 (9.04)	3174	1680	—	1572
5b	66	277–279	$C_{34}H_{29}N_3O_3$ (527.61)	77.40 (77.51)	5.54 (5.50)	7.96 (8.00)	3180	1682	—	1569
5c	69	285–287	$C_{32}H_{24}ClN_3O$ (502.01)	76.56 (76.68)	4.82 (4.87)	8.37 (8.43)	3184	1685	—	1558
5d	72	298–300	$C_{32}H_{22}Cl_3N_3O$ (570.89)	67.32 (67.24)	3.88 (3.92)	7.36 (7.42)	3172	1680	—	1562
6a	70	269–271	$C_{26}H_{20}N_2O_2$ (392.45)	79.57 (79.43)	5.14 (5.19)	7.14 (7.19)	3168	1679	—	1581
6b	68	255–257	$C_{28}H_{24}N_2O_4$ (452.50)	74.32 (74.41)	5.35 (5.14)	6.19 (6.27)	3175	1684	—	1573
6c	72	249–251	$C_{26}H_{19}ClN_2O_2$ (426.89)	73.15 (73.28)	4.49 (4.43)	6.56 (6.64)	3180	1677	—	1571
6d	74	271–273	$C_{26}H_{17}Cl_3N_2O_2$ (495.78)	62.99 (62.81)	3.46 (3.51)	5.65 (5.62)	3182	1678	—	1562
7a	68	268–270	$C_{20}H_{15}N_3O$ (313.35)	76.66 (76.75)	4.82 (4.76)	13.41 (13.57)	3204	1664	1628	1572
8a	64	292–294	$C_{32}H_{23}N_3O$ (465.54)	82.56 (82.64)	4.98 (4.88)	9.03 (9.12)	3196	1656	1622	1560
9a	67	284–286	$C_{26}H_{18}N_2O_2$ (390.43)	79.98 (80.08)	4.65 (4.72)	7.17 (7.24)	3188	1655	1632	1559

Table 2 ^{1}H and ^{13}C NMR spectroscopic data and M^{+} values of compounds **2–9**

	^{1}H NMR ($CDCl_3$–DMSO-d_6) δ	^{13}C NMR ($CDCl_3$–DMSO-d_6) δ	M^{+}
2a	6.80 (s, 1H, H-2), 6.96 (s, 1H, H-5), 7.08 (d, 1H, H-2′, J = 18.0 Hz), 7.25–7.55 (m, 10H, H_{arom}), 7.65 (d, 1H, H-3′, J = 18.0 Hz), 8.79 (br s, 1H, NH)	118.3 (C-4), 122.2 (C-2′), 122.7 (C-3), 125.7 (C-5), 126.8 (C-2), 140.2 (C-3′), 195.3 (C=O)	273
2b	3.68 (s, 6H, OCH_3), 6.75 (s, 1H, H-2), 6.94 (s, 1H, H-5), 7.04 (d, 1H, H-2′, J = 18.2 Hz), 7.10–7.52 (m, 8H, H_{arom}), 7.68 (d, 1H, H-3′, J = 18.2 Hz), 8.84 (br s, 1H, NH)	54.9 (OCH_3), 118.0 (C-4), 123.7 (C-2′), 121.4 (C-3), 124.2 (C-5), 127.5 (C-2), 141.2 (C-3′), 194.4 (C=O)	—
2c	6.78 (s, 1H, H-2), 6.93 (s, 1H, H-5), 7.07 (d, 1H, H-2′, J = 18.3 Hz), 7.29–7.55 (m, 8H, H_{arom}), 7.70 (d, 1H, H-3′, J = 18.3 Hz), 8.78 (br s, 1H, NH)	118.7 (C-4), 121.4 (C-2′), 121.4 (C-3), 126.0 (C-5), 126.8 (C-2), 141.9 (C-3′), 194.9 (C=O)	—
3a	6.84 (s, 2H, H-2,2′), 6.97 (s, 2H, H-5,5′), 7.25–7.55 (m, 10H, H_{arom}), 8.79 (br s, 2H, NH)	115.2 (C-4,4′), 117.9 (C-3,3′), 124.5 (C-5,5′), 125.3 (C-2,2′), 188.0 (C=O)	312
3b	3.66 (s, 6H, OCH_3), 6.81 (s, 2H, H-2,2′), 6.94 (s, 2H, H-5,5′), 7.28–7.64 (m, 8H, H_{arom}), 8.81 (br s, 2H, NH)	55.7 (OCH_3), 116.7 (C-4,4′), 118.3 (C-3,3′), 124.9 (C-5,5′), 126.2 (C-2,2′), 189.7 (C=O)	—
3c	6.85 (s, 2H, H-2,2′), 6.92 (s, 2H, H-5,5′), 7.21–7.83 (m, 8H, H_{arom}), 8.77 (br s, 2H, NH)	117.0 (C-4,4′), 118.9 (C-3,3′), 123.9 (C-5,5′), 125.6 (C-2,2′), 188.6 (C=O)	—
4a	3.58 (dd, 1H, H_X), 3.64 (dd, 1H, H_M, J_{MX} = 10.0 Hz), 4.53 (dd, 1H, H_A, J_{AM} = 12.6; J_{AX} = 5.5 Hz), 6.46 (br s, 1H, NH), 6.82 (s, 1H, H-2), 6.94 (s, 1H, H-5), 6.97–7.64 (m, 10H, H_{arom}), 8.80 (br s, 1H, NH)	49.0 (C-4′), 57.0 (C-5′), 118.7 (C-4), 122.4 (C-3), 125.9 (C-5), 126.6 (C-2), 152.9 (C-3′), 188.8 (C=O),	315
4b	3.56 (dd, 1H, H_X), 3.65 (dd, 1H, H_M, J_{MX} = 10.1 Hz), 3.72 (s, 6H, OCH_3), 4.55 (dd, 1H, H_A, J_{AM} = 12.8; J_{AX} = 5.7 Hz), 6.48 (br s, 1H, NH), 6.79 (s, 1H, H-2), 6.88 (s, 1H, H-5), 6.85–7.59 (m, 8H, H_{arom}), 8.83 (br s, 1H, NH)	56.2 (OCH_3), 49.6 (C-4′), 57.5 (C-5′), 117.4 (C-4), 121.6 (C-3), 126.5 (C-5), 126.6 (C-2), 153.1 (C-3′), 189.9 (C=O),	—
4c	3.58 (dd, 1H, H_X), 3.67 (dd, 1H, H_M, J_{MX} = 10.2 Hz), 4.59 (dd, 1H, H_A, J_{AM} = 12.9; J_{AX} = 5.7 Hz), 6.51 (br s, 1H, NH), 6.82 (s, 1H, H-2), 6.87 (s, 1H, H-5), 6.94–7.63 (m, 8H, H_{arom}), 8.88 (br s, 1H, NH)	50.0 (C-4′), 58.6 (C-5′), 117.9 (C-4), 121.8 (C-3), 125.2 (C-5), 127.5 (C-2), 153.8 (C-3′), 190.5 (C=O),	—
5a	5.23 (d, 1H, H-4′, J = 6.0 Hz), 5.61 (d, 1H, H-5′, J = 6.0 Hz), 6.82 (s, 1H, H-2), 6.91 (s, 1H, H-5), 7.18–8.04 (m, 20H, H_{arom}), 8.80 (br s, 1H, NH)	64.6 (C-4′), 87.9 (C-5′), 118.6 (C-4), 122.9 (C-3), 125.4 (C-5), 126.7 (C-2), 155.1 (C-3′), 197.1 (C=O)	467
5b	3.75 (s, 6H, OCH_3), 5.19 (d, 1H, H-4′, J = 6.6 Hz), 5.62 (d, 1H, H-5′, J = 6.6 Hz), 6.80 (s, 1H, H-2), 6.93 (s, 1H, H-5), 7.04–7.79 (m, 18H, H_{arom}), 8.83 (br s, 1H, NH)	55.0 (OCH_3), 65.8 (C-4′), 88.5 (C-5′), 119.7 (C-4), 121.5 (C-3), 124.4 (C-2), 125.8 (C-5), 156.2 (C-3′), 198.8 (C=O)	—
5c	5.23 (d, 1H, H-4′, J = 6.9 Hz), 5.65 (d, 1H, H-5′, J = 6.9 Hz), 6.82 (s, 1H, H-2), 6.92 (s, 1H, H-5), 7.15–7.84 (m, 19H, H_{arom}), 8.80 (br s, 1H, NH)	66.7 (C-4′), 89.0 (C-5′), 120.0 (C-4), 122.9 (C-3), 124.9 (C-2), 126.1 (C-5), 157.4 (C-3′), 199.0 (C=O)	—
5d	5.24 (d, 1H, H-4′, J = 6.4 Hz), 5.62 (d, 1H, H-5′, J = 6.4 Hz), 6.85 (s, 1H, H-2), 6.93 (s, 1H, H-5), 7.21–7.90 (m, 17H, H_{arom}), 8.83 (br s, 1H, NH)	67.0 (C-4′), 88.4 (C-5′), 119.2 (C-4), 122.8 (C-3), 125.4 (C-2), 126.6 (C-5), 158.0 (C-3′), 199.5 (C=O)	—
6a	5.20 (d, 1H, H-4′, J = 5.9 Hz), 5.65 (d, 1H, H-5′, J = 5.9 Hz), 6.83 (s, 1H, H-2), 6.89 (s, 1H, H-5), 7.12–7.94 (m, 15H, H_{arom}), 8.80 (br s, 1H, NH)	64.6 (C-4′), 85.6 (C-5′), 118.3 (C-4), 122.6 (C-3), 125.7 (C-5), 126.6 (C-2), 153.8 (C-3′), 198.0 (C=O)	392
6b	3.71 (s, 6H, OCH_3), 5.23 (d, 1H, H-4′, J = 5.8 Hz), 5.63 (d, 1H, H-5′, J = 5.8 Hz), 6.85 (s, 1H, H-2), 6.91 (s, 1H, H-5), 7.02–7.88 (m, 13H, C_3–H and H_{arom}), 8.83 (br s, 1H, NH)	56.2 (OCH_3), 63.3 (C-4′), 85.2 (C-5′), 118.7 (C-4), 121.9 (C-3), 125.0 (C-5), 126.8 (C-2), 152.2 (C-3′), 196.1 (C=O)	—
6c	5.21 (d, 1H, H-4′, J = 6.0 Hz), 5.66 (d, 1H, H-5′, J = 6.0 Hz), 6.82 (s, 1H, H-2), 6.89 (s, 1H, H-5), 7.15–7.94 (m, 14H, H_{arom}), 8.87 (br s, 1H, NH)	62.9 (C-4′), 85.4 (C-5′), 117.9 (C-4), 121.4 (C-3), 124.6 (C-5), 126.1 (C-2), 153.1 (C-3′), 197.7 (C=O)	—
6d	5.26 (d, 1H, H-4′, J = 5.7 Hz), 5.68 (d, 1H, H-5′, J = 5.7 Hz), 6.79 (s, 1H, H-2), 6.92 (s, 1H, H-5), 7.22–7.89 (m, 12H, H_{arom}), 8.88 (br s, 1H, NH)	62.2 (C-4′), 84.5 (C-5′), 117.1 (C-4), 121.9 (C-3), 123.8 (C-5), 126.6 (C-2), 154.0 (C-3′), 198.1 (C=O)	—
7a	6.48 (br s, 1H, NH), 6.81 (s, 1H, H-2), 6.97 (s, 1H, H-5), 6.89–7.86 (m, 11H, C_5′–H and H_{arom}), 8.83 (br s, 1H, NH).	117.7 (C-4), 121.2 (C-3), 126.9 (C-5), 127.8 (C-2), 134.5 (C-5′), 141.0 (C-4′), 158.6 (C-3′), 187.6 (C=O)	313
8a	6.78 (s, 1H, H-2), 6.94 (s, 1H, H-5), 7.12–8.04 (m, 20H, H_{arom}), 8.84 (br s, 1H, NH)	149.7 (C-4′), 151.3 (C-5′), 117.4 (C-4), 123.2 (C-3), 124.8 (C-5), 126.4 (C-2), 146.3 (C-3′), 195.4 (C=O)	465
9a	6.78 (s, 1H, H-2), 6.85 (s, 1H, H-5), 7.09–7.92 (m, 15H, H_{arom}), 8.84 (br s, 1H, NH)	147.8 (C-4′), 152.8 (C-5′), 116.8 (C-4), 121.5 (C-3), 125.3 (C-5), 127.4 (C-2), 146.7 (C-3′), 193.2 (C=O)	390

against *Fusarium solani*, *Curvularia lunata*, *Aspergillus niger* and *Cunninghemella elegans*, using Nystatin (25 μg per disc) as a standard drug. Fungal cultures were grown on potato dextrose broth (PDA) at 25 °C for 3 days, then the spore suspension was adjusted to 10^6 pores ml^{-1} (fungi) at a mg ml^{-1} concentration by the Vincent and Vincent method.[13]

All test compounds were found to display moderate antimicrobial activity towards both Gram-positive and Gram-negative bacteria as well as antifungal activity towards all fungi. Compounds **4** and **5**, which have both pyrrole and pyrazoline rings, exhibit a relatively higher activity than the others. Further bioassay studies on these compounds are in progress.

In conclusion, novel oxo-linked bis(heterocycles) containing two different heterocyclic rings were developed from a simple substrate, bischalcone, by an elegant and well-versed methodology.

Experimental

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, 3 : 1 ethyl acetate–hexane). The IR spectra were recorded on KBr pellets on a Perkin–Elmer grating infrared spectrophotometer, model 337. ^{1}H NMR spectra were recorded in $CDCl_3$–DMSO-d_6 on a 300 MHz Varian EM-360 spectrophotometer. ^{13}C NMR spectra were recorded in $CDCl_3$–DMSO-d_6 on a Varian VXR spectrometer operating at 75.5 MHz. All chemical shifts are reported in ppm from TMS as an internal standard. Mass spectra were recorded on a Joel JMS-D 300 instrument at 70 eV. Elemental analyses were performed at Punjab University, Chandigarh, India. Starting materials, bischalcones, araldehyde phenylhydrazones and araldoximes, were prepared by standard procedures.[14]

Synthesis

3′-Aryl-1′-(4-aryl-1*H*-pyrrol-3-yl)-prop-2′-enone 2: general procedure. A mixture of TosMIC (5 mmol) and bischalcone **1** (5 mmol) in Et_2O–DMSO (2 : 1) is added dropwise under stirring to a suspension of NaH (50 mg) in Et_2O (10 ml) at room temperature. Stirring is continued for about 5 h. Then, water is added and the product is extracted with Et_2O. The ethereal fraction is dried over anhydrous Na_2SO_4. The solvent is removed *in vacuo*. The resulting solid is purified by recrystallization from methanol.

Bis(4-aryl-1*H*-pyrrol-3-yl)methanone 3: general procedure. A mixture of TosMIC (5 mmol) and 3′-aryl-1′-(4-aryl-1*H*-pyrrol-3-yl)-prop-2′-enone **2** (5 mmol) in Et_2O–DMSO (2 : 1) is added dropwise under stirring to a suspension of NaH (50 mg) in Et_2O (10 ml) at room temperature. Stirring is continued for about 5 h. Then, water is added and the product is extracted with Et_2O; the ethereal fraction is dried over anhydrous Na_2SO_4. The solvent is removed *in vacuo*. The resulting solid is purified by column chromatography [hexane–ethyl acetate (1 : 4)].

(4′-Aryl-4′,5′-dihydro-1′*H*-pyrazol-3′-yl)-(4-aryl-1*H*-pyrrol-3-yl)methanone 4: general procedure. To a cooled solution of **2** (5 mmol) in dichloromethane (20 m), an ethereal solution of diazomethane (40 ml, 0.4 M) and triethylamine (0.12 g) is added. The reaction mixture is kept at −20 to −15 °C for 40–48 h. The solvent is removed under reduced pressure. The resulting solid is purified by recrystallization from methanol.

(4-Aryl-1*H*-pyrrol-3-yl)-(1′,3′,5′-triaryl-4′,5′-dihydro-1′*H*-pyrazol-4′-yl)methanone 5: general procedure. A mixture of **2** (1 mmol), araldehyde phenylhydrazone (2 mmol) and chloramine-T (2 mmol) in methanol (20 ml) is refluxed for 18–20 h over a water bath. The precipitated inorganic salts are filtered off. The filtrate is concentrated and the residue is extracted with dichloromethane. The organic phase is washed with water, brine and dried over anhydrous Na_2SO_4. The solvent is removed under reduced pressure. Recrystallization of the crude product from ethanol resulted in pure **5**.

(3′,5′-Diaryl-4′,5′-dihydroisoxazol-4′-yl)-(4-aryl-1*H*-pyrrol-3-yl)methanone 6: general procedure. A mixture of **2** (1 mmol), araldoxime (2 mmol) and chloramine-T (2 mmol) in methanol (20 ml) is refluxed for 18–20 h over a water bath. The precipitated inorganic salts are filtered off. The filtrate is concentrated and the residue is extracted with dichloromethane. The organic phase is washed with water, brine and dried over anhydrous Na_2SO_4. The solvent is removed under reduced pressure. Recrystallization of the crude product from ethanol resulted in pure **6**.

(4′-Phenyl-1′*H*-pyrazol-3′-yl)-(4-phenyl-1*H*-pyrrol-3-yl)methanone 7a; (4-phenyl-1*H*-pyrrol-3-yl)-(1′,3′,5′-triphenyl-1′*H*-pyrazol-4′-yl)methanone 8a; (3′,5′-diphenylisoxazol-4′-yl) (4-phenyl-1*H*-pyrrol-3-yl)methanone 9a: general procedure. A solution of **4a** or **5a** or **6a** (1 mmol) and chloranil (1.04 mmol) in xylene (10 ml) is refluxed for 24–32 h. Then the reaction mixture is treated with a 5% NaOH solution. The organic layer is separated and repeatedly washed with water, dried over anhydrous Na_2SO_4 and the solvent is removed on a rotary evaporator. The solid obtained is purified by recrystallization in 2-propanol to give pure **7a**, **8a** or **9a**, respectively.

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