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REGULAR ARTICLE

Design, synthesis and characterization of functionalized pyrazole derivatives bearing amide and sulfonamide moieties from aza-aurones

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Abstract. In this work, we report the synthesis of new pyrazole derivatives bearing amide and sulfonamide frameworks from aza-aurones. Firstly, the intermediate spiropyrazolines were obtained through a highly regioselective 1,3-dipolar cycloaddition of nitrilimines with aza-aurones. Subsequently, the obtained cycloadducts were subjected to hydrochloric acid in hot ethanol which conducts to 5-(2-aminobenzoyl)-3,4-diaryl-1-phenylpyrazoles. Finally, the target compounds were obtained separately by the action of acetic anhydride, benzoyl chloride and tosyl chloride on the intermediates 2-aminobenzoylpyrazoles, respectively. Structures of all the synthesized compounds were established using IR, ^{1}H NMR and ^{13}C NMR and mass spectroscopy.

Keywords. Aza-aurone; nitrilimine; spiropyrazoline; pyrazole; amide; sulfonamide.

1. Introduction

Heterocyclic compounds are of great interest, owing to a wide variety of applications they possess in many fields.[1–6] Among the heterocyclic compounds, pyrazole derivatives constitute the most studied compounds due to its widespread applications.[7–15] In addition, pyrazole moiety is an active pharmacophore which enters into the design of a broad spectrum of natural and synthetic bioactive compounds.[16,17] Further, the pyrazole bearing sulfonamide and amide moieties are an important scaffold for therapeutic agents, namely celecoxib,[18] deracoxib,[19] rimonabant,[20] sulfaphenazole,[21] pyrazofurin,[22] difenamizole[23]…, etc. (Figure 1).

In general, the pyrazole compounds are prepared using two conventional approaches: cyclocondensation of hydrazine derivatives with 1,3-dielectrophilic compounds and 1,3-dipolar cycloaddition.[24,25] There is a general consensus that 1,3-dipolar cycloaddition reaction is employed as the most practical method to provide highly substituted pyrazoles.[26]

Aza-aurones, namely 2-arylideneindolin-3(2*H*)-ones are known to possess various biological activities,[27–31] including anticancer,[27,30] antimalarial,[28,29,31] and antibacterial.[32] It has also been found that these interesting compounds are used as key building blocks to develop many heterocyclic compounds.[33–38] In addition, indolin-3-one moiety is frequently found in natural products and biologically active molecules.[39–43] Hence, the introduction of this framework in the core of the designed compounds may lead to new heterocycles with promising pharmacological activity.

As part of our ongoing research, we aim to synthesize heterocyclic compounds for therapeutic

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purposes.[44–49] Here, we report the synthesis of poly-substituted pyrazole-bearing amide and sulfonamide frameworks from aza-aurones. The synthesis proceeds through two successive reactions: 1,3-dipolar cycloaddition and *N*-alkylation.

2. Experimental

2.1 *General information*

All reagents and solvents were of AR grade. These chemicals were purchased from Sigma-Aldrich and other commercial suppliers, and were used without further purification. The progress of the reactions was monitored by TLC, performed on pre-coated Merck silica gel 60 F254 plates. Column chromatography was carried out using Merck silica gel (70-230 mesh), eluting with n-hexane and ether solution. Melting points were determined using a Kofler Bench apparatus. IR spectra were recorded using a Fourier Transform Bruker Vertex 70 Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker Avance II 300 Ultra-Shield (300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometer using $CDCl_3$ and DMSO-d_6 solvents. ^{1}H and ^{13}C NMR chemical shifts (δ) are expressed in parts per million (ppm) with reference to the solvent used, and proton coupling constants (J) are reported in hertz (Hz). The spin multiplicities are reported as singlet (s), doublet (d), triplet (t), multiplet (m), doublet of doublets (dd), doublet of triplets (dt) and broad (br). Mass spectra were performed by the CESAMO (Bordeaux, France) on a Q Exactive Mass Spectrometer (Thermo). The instrument is equipped with an ESI source and the spectra were recorded in a positive mode. The spray voltage was maintained at 3200 V and capillary temperature was set at 320°C. Samples were introduced by injecting through a 20 μL sample loop into a 300 μL/min flow of methanol from the LC pump. Aza-aurones **1** was used as starting material in this work and were prepared according to the procedure described in the literature.[35,50,51]

2.2 *General procedures*

2.2a *Synthesis of aza-aurones (**1a–b**)*: In a 100 mL three-necked flask containing 50 mL of NaOH (2N), equipped with a condenser, dropping funnel and a nitrogen bubbler. The aqueous solution of NaOH was purged with a nitrogen stream under magnetic stirring for 10 min. Diacetylindoxyl (0.01 mol) was added to the solution and the mixture was heated under stirring for 20 min. Then, the proper aldehyde (0.015 mol) dissolved in 4 mL of ethanol was added dropwise through the dropping funnel. The mixture was refluxed until the formation of an orange solid which was filtered and washed thoroughly with water. The obtained solid was recrystallized in ethanol to afford aza-aurones in moderate to good yield, which was used without further purification.

2.2b *Synthesis of spiropyrazolines (**2aa–2db**)*: To a solution of appropriate aza-aurone **1** (1 mmol) in 20 mL of chloroform, the proper α-chloroarylidenep henylhydrazone (1.2 mmol) and trimethylamine (1.2 mmol) was added. The mixture was held under stirring at room temperature, and the progress of the reaction was monitored by TLC. After the reaction completed, the solvent was removed to provide a crude product. The obtained residue was crystallized in ethanol and the formed precipitate was filtered and washed with cold ethanol.

2.2c *Synthesis of 5-(2-aminobenzoyl)-3,4-diaryl-1-phenylpyrazoles (**3aa–3db**)*: In a 100 mL flask equipped with a condenser, cycloadduct **2** (1mmol) was dissolved in ethanol (40 mL), and three drops of hydrochloric acid was added to the solution. The mixture was refluxed until the completion of the reaction, as monitored by TLC. After the 3/4 of the solvent was removed by vacuum, 60 mL of cold water was added. The formed precipitate was filtered and washed thoroughly with water. The obtained solid was purified by recrystallization in ethanol.

2.2d *Synthesis of pyrazoles-bearing benzamide moiety (**4aa–4db**)*: To a solution of appropriate compound **3** (1 mol) in 20 mL of absolute DCM, triethylamine (2 mL) was added and the solution was stirred at 0°C in an ice bath. Benzoyl chloride (1 mol) was added in small portions while maintaining the temperature up to 0°C. Then, the reaction mixture was kept under magnetic stirring at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was transferred into a separatory funnel and washed several times with water. The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4) and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography using hexane–ether mixture (4:1).

2.2e *Synthesis of pyrazole bearing acetamide moiety (**5aa–5db**)*: In a 50 mL flask equipped with a

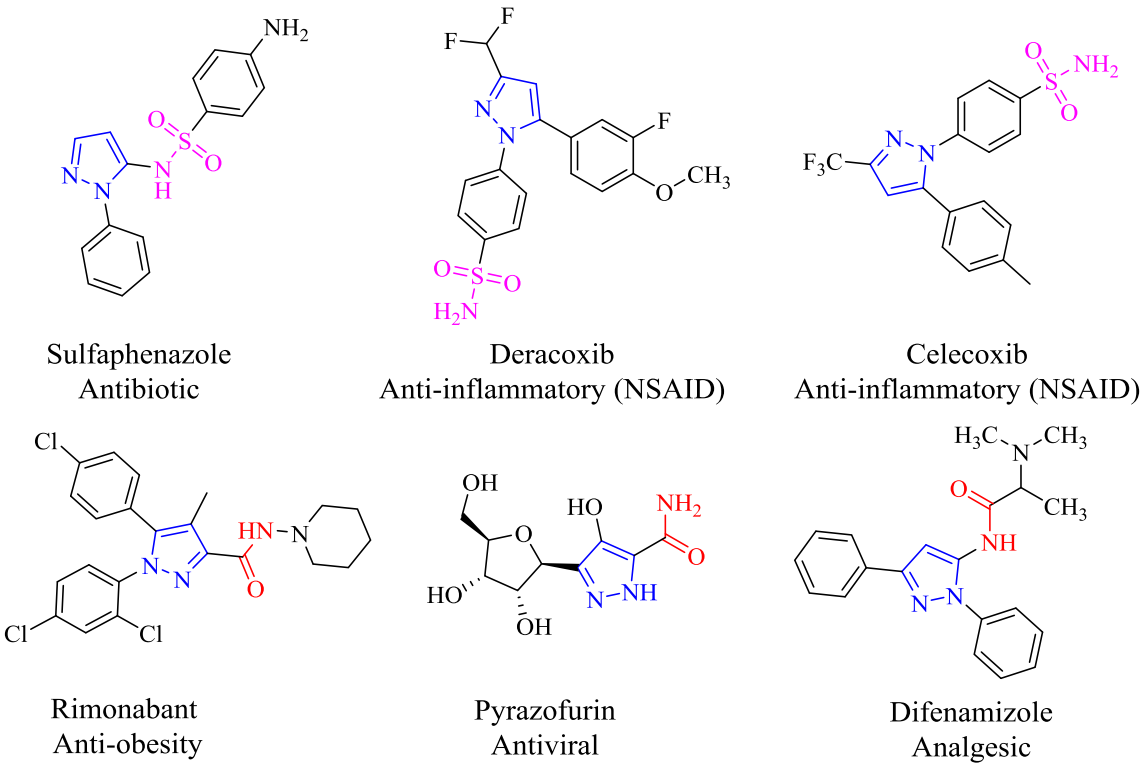


Figure 1. Pyrazoles bearing amide and sulfonamide moieties available as drugs.

condenser, 5-(2-aminobenzoyl)pyrazole (5 mmol) and acetic anhydride (20 mL) were introduced. The mixture was stirred at reflux until the completion of the reaction, as evidenced by TLC. The reaction mixture was poured into ice-cold water (200 mL) and extracted with DCM (3 x 20 mL). The DCM layer was washed thrice with a saturated solution of $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The crude product was crystallized in ethanol and the solid obtained was filtered and used.

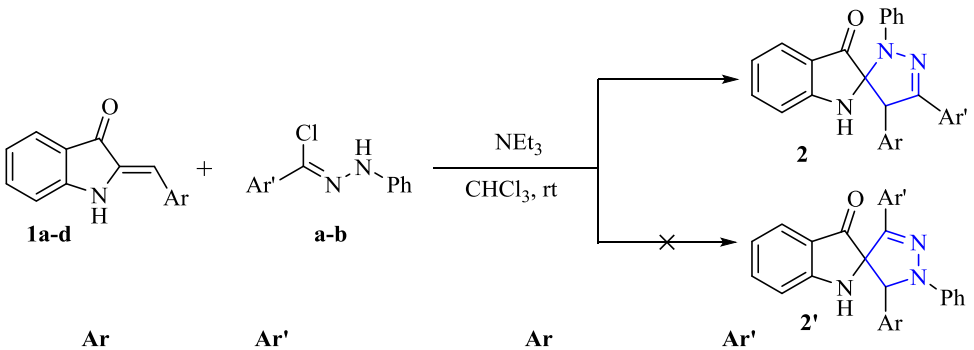
2.2f *Synthesis of pyrazole-bearing sulfonamide moiety (**6aa–6da**)*: In a 100 mL Erlenmeyer flask, pyridine (6 mL) was added to a solution of 5-(2-aminobenzoyl)pyrazole **3** (0.019 mol) in 2 mL dichloromethane. The mixture was stirred under ice-cold condition. Tosyl chloride (0.019 mol) was added by fractions, maintaining the temperature of the reaction mixture up to 0°C. When the addition was completed, the stirring was continued at room temperature until TLC revealed the completion of the reaction. The mixture was quenched in ice-cold water and neutralized dilute HCl (pH = 2) and extracted with DCM (3 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure. The resulting residue was crystallized in a mixture of EtOH–DCM (5:3).

3. Results and Discussion

3.1 *Synthesis of spiropyrazolines (**2**)*

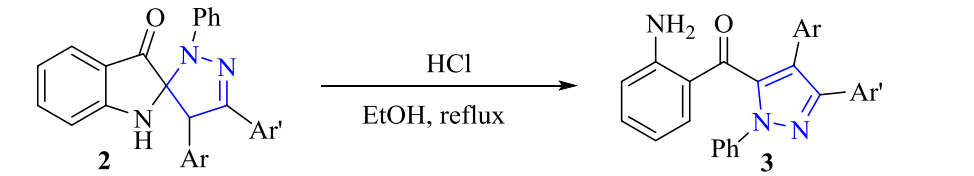
Spiropyrazolines **2** were prepared via 1,3-dipolar cycloaddition reaction of *N*-phenyl-*C*-arylnitrilimines with aza-aurones **1** in chloroform at room temperature. Nitrilimine derivatives were generated *in situ* from the α-chloroarylidenephenylhydrazones under the action of triethylamine. The reaction led to the formation of a spiranic cycloadduct **2** as a unique regioisomer with a good yield (Scheme 1).

The regiochemistry proposed in this reaction is comparable to that observed with similar dipolarophiles, namely 2-arylidene-indan-1-ones,[52] 2-arylidene-tetral-1(2*H*)-ones[53,54] and 3-arylidene-chromen-4(3*H*)-ones.[53] This regiochemistry was also checked with ^1H and ^{13}C NMR spectral data. Indeed, ^1H NMR spectra of cycloadducts **2** showed a broad singlet at 4.5 ppm exchangeable with D_2O corresponding to NH proton and a singlet around 5 ppm due to pyrazoline protons. Whereas, with a regioisomer **2′**, the chemical shift of the pyrazoline protons would normally be deshielded under the effect of the



	Ar	Ar'			Ar	Ar'	
2aa	C_6H_5	C_6H_5	90 %	**2ab**	C_6H_5	4-(Cl)C_6H_5	78 %
2ba	4-(OCH_3)C_6H_5	C_6H_5	88 %	**2bb**	4-(OCH_3)C_6H_5	4-(Cl)C_6H_5	67 %
2ca	4-(Cl)C_6H_5	C_6H_5	80 %	**2cb**	4-(Cl)C_6H_5	4-(Cl)C_6H_5	70 %
2da	4-(Br)C_6H_5	C_6H_5	89 %	**2db**	4-(Br)C_6H_5	4-(Cl)C_6H_5	73 %

Scheme 1. 1,3-Dipolar cycloaddition reaction affords spiropyrazolines **2**.



	Ar	Ar'			Ar	Ar'	
3aa	C_6H_5	C_6H_5	88 %	**3ab**	C_6H_5	4-(Cl)C_6H_5	80 %
3ba	4-(OCH_3)C_6H_5	C_6H_5	60 %	**3bb**	4-(OCH_3)C_6H_5	4-(Cl)C_6H_5	76 %
3ca	4-(Cl)C_6H_5	C_6H_5	70 %	**3cb**	4-(Cl)C_6H_5	4-(Cl)C_6H_5	63 %
3da	4-(Br)C_6H_5	C_6H_5	77 %	**3db**	4-(Br)C_6H_5	4-(Cl)C_6H_5	66 %

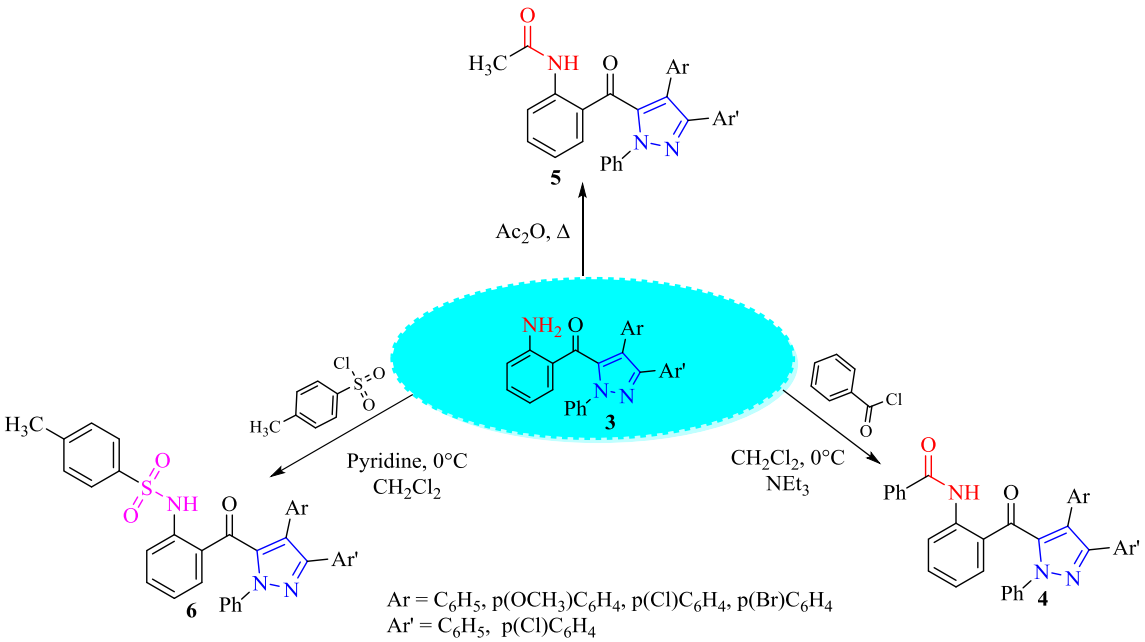
Scheme 2. Synthetic pathway of 5-(2-aminobenzoyl)-3,4-diaryl-1-phenylpyrazoles **3**.

neighboring nitrogen atom. Further, ^{13}C NMR spectra showed chemical shift around 87 ppm assigned to spiranic carbon $C_{52'}$; for the regioisomer **2'** lower chemical shift values should be expected for the spiranic carbon $C_{42'}$. These outcomes corroborate further the proposed regiochemistry. In addition, FT–IR spectra of the cycloadducts **2** revealed, in particular, the presence of absorption bands attributed around 3300 cm^{-1} and 1700 cm^{-1}, respectively, to N–H and C=O stretching bands while the absorption band at 1600 cm^{-1} was assigned to C=N stretching bands because of ring closure.

3.2 *Synthesis of 5-(2-aminobenzoyl)-3,4-diaryl-1-phenylpyrazoles (**3**)*

The prepared spiropyrazolines **2** were treated with concentrated hydrochloric acid in ethanol at reflux. The reaction undergoes ring-opening of the spiranic cycloadducts at the nitrogen atom of the indolin-3(2*H*)-one frameworks and leads to the formation of 5-(2-aminobenzoyl)-3,4-diaryl-1-phenylpyrazoles **3** with good yield (Scheme 2).[55]

The chemical structures of pyrazoles **3** were established by spectroscopic data (FT-IR, ^1H and ^{13}C NMR). Indeed, FT-IR spectra of compounds **3** exhibited two characteristic bands ranging between 3200 and 3420 $cm^{-1,}$ indicating the presence of a primary amine NH_2 group. Absorption band around 1600 cm^{-1} was assigned to C=O stretching band, which appear less than that observed on cycloadducts **2** spectra. The ^1H NMR spectra of compounds **3** showed in addition to signals corresponding to aromatic protons, a broad signal at 6.3 ppm assigned to NH_2 protons. Their ^{13}C NMR spectra displayed a signal at 189 ppm assigned to C=O carbon 10 ppm shielded, compared with the one observed on the spectra of the corresponding cycloadduct **2**. In addition, the disappeared signals at 5 ppm (pyrazoline proton) and 87 ppm (spiranic carbon), respectively, in ^1H and ^{13}C NMR spectra of compounds **3** provided the evidence for the ring-opening of spiranic cycloadducts **2**.



Scheme 3. Synthetic route of pyrazole derivatives.

Table 1. Physical and MS data of the synthesized pyrazoles.

Entry	Ar	Ar′	Time (h)	m.p. (°C)	Yield (%)	HRMS (m/z*)
4aa	C_6H_5	C_6H_5	10	162–164	84	542.1832
4ab	C_6H_5	4-(Cl)C_6H_5	12	186–188	67	576.1439
4ba	4-(OCH_3)C_6H_5	C_6H_5	20	112–114	59	572.1930
4bb	4-(OCH_3)C_6H_5	4-(Cl)C_6H_5	15	140–142	60	606.1538
4ca	4-(Cl)C_6H_5	C_6H_5	8	198–200	72	576.1437
4cb	4-(Cl)C_6H_5	4-(Cl)C_6H_5	11	214–216	61	610.1058
4da	4-(Br)C_6H_5	C_6H_5	24	168–170	55	620.0931
4db	4-(Br)C_6H_5	4-(Cl)C_6H_5	18	224–226	70	654.0544
5aa	C_6H_5	C_6H_5	6	170–172	61	480.1680
5ab	C_6H_5	4-(Cl)C_6H_5	3	196–198	53	514.1284
5ba	4-(OCH_3)C_6H_5	C_6H_5	4	184–186	66	510.1774
5bb	4-(OCH_3)C_6H_5	4-(Cl)C_6H_5	7	216–218	70	544.1383
5ca	4-(Cl)C_6H_5	C_6H_5	8	180–182	58	544.1279
5cb	4-(Cl)C_6H_5	4-(Cl)C_6H_5	6	212–214	77	548.0891
5da	4-(Br)C_6H_5	C_6H_5	2	190–192	72	558.0777
5db	4-(Br)C_6H_5	4-(Cl)C_6H_5	4	202–204	81	592.0387
6aa	C_6H_5	C_6H_5	5	180–182	60	592.16635
6ab	C_6H_5	4-(Cl)C_6H_5	9	172–174	54	626.1272
6ba	4-(OCH_3)C_6H_5	C_6H_5	4	188–190	76	622.1756
6bb	4-(OCH_3)C_6H_5	4-(Cl)C_6H_5	8	182–184	66	656.1364
6ca	4-(Cl)C_6H_5	C_6H_5	10	196–198	80	626.1262
6cb	4-(Cl)C_6H_5	4-(Cl)C_6H_5	7	208–210	71	660.0869
6da	4-(Br)C_6H_5	C_6H_5	5	200–202	74	670.0757

*Mass obtained for $[M+Na]^+$ ion.

3.3 *Synthesis of pyrazoles bearing amide and sulfonamide*

The synthetic pathway followed for the preparation of novel pyrazole derivatives is illustrated in Scheme 3. The 5-(2-aminobenzoyl)-3,4-diaryl-1-phenylpyrazoles **3** on treating with benzoyl chloride, acetic anhydride and para-toluenesulfonyl chloride formed the required pyrazole derivatives containing amide and sulfonamide scaffold, which are known for their biological activities (Scheme 3).[18,19,22]

The structures of compounds **4**, **5** and **6** were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry analysis. The FT–IR spectra of compounds **4**, **5** and **6**, in particular, showed the presence of absorption bands around 3300 cm^{-1} correspond to N–H bond stretching. Two absorption bands around 1700 cm^{-1} and 1600 cm^{-1} indicate the presence of C=O stretchings of carboxamide and carbonyl groups, respectively. Their ^{1}H NMR spectra revealed a singlet at a range of 9–12 ppm exchangeable with D_2O corresponding to NH proton. Two singlets at 2.25 ppm and 2.44 ppm related to CH_3 protons, respectively, of acetamide for compounds **5** and tosyl for compounds **6**. The ^{13}C NMR spectra of the same compounds exhibited a signal at 166 ppm attributed to C=O carbon of carboxamide for compounds **4** and **5** as well as a signal at 192 ppm corresponding to C=O carbon of ketone. In addition, the signals between 21 and 25 ppm were assigned to methyl carbon CH_3 for compounds **5** and **6**. About high-resolution mass spectrometry, spectra in positive mode have been recorded with an electrospray ionization chamber which led to $[M+Na]^+$ adducts. All first molecular mass peaks were close to the theoretical value ($\Delta_{mass\ peak} < 3$ppm). Finally, spectroscopic data were found to be in good agreement with the proposed structures (Table 1).

4. Conclusion

In this study, we prepared novel pyrazole derivatives-bearing amide and sulfonamide moieties through respective 1,3-dipolar cycloaddition and *N*-alkylation reactions. We have shown that the 1,3-dipolar cycloaddition reactions occur in a regiospecific manner and conduct to one regioisomer **2** in each studied case. The spiropyrazoline **2** are developed into pyrazole-containing 2-aminobenzoyle frameworks, which are engaged in *N*-alkylation reactions through the amino group. The structures and regiochemistry of the cycloadducts and other obtained products were justified by spectroscopic techniques, *viz*., IR, ^{1}H NMR, ^{13}C NMR and HR-mass. The structures of all synthesized products are in perfect agreement with spectroscopic data.

Supplementary Information (SI)

Spectroscopic data and copies of spectra (IR, ^{1}H NMR, ^{13}C NMR, and HR-mass) of all obtained compounds are given in the supplementary information, which are available at www.ias.ac.in/chemsci.

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References

1. Khan M F, Alam M M, Verma G, Akhtar W, Akhter M and Shaquiquzzaman M 2016 The therapeutic voyage of pyrazole and its analogs: A review *Eur. J. Med. Chem.* **120** 170
2. K Küçükgüzel Ş G and Şenkardeş S 2015 Recent advances in bioactive pyrazoles *Eur. J. Med. Chem.* **97** 786
3. García-Vanegas J J, Ramírez-Villalva A, Fuentes-Benites A, Martínez-Otero D, González-Rivas N and Cuevas-Yañez E 2019 Synthesis and in-vitro biological evaluation of 1,1-diaryl-2-(1,2,3)triazol-1-yl-ethanol derivatives as antifungal compounds flutriafol analogues *J. Chem. Sci*. **131** 27
4. Yadav P and Purohit N V 2013 Synthesis and evaluation of some bioactive compounds having oxygen and nitrogen heteroatom *J. Chem. Sci*. **125** 165
5. Shah N K, Shah N M, Patel M P and Patel R G 2013 Synthesis of 2-amino-4H-chromene derivatives under microwave irradiation and their antimicrobial activity *J. Chem. Sci*. **125** 525
6. Jeyaveeran J C, Praveen C, Arun Y, Prince A A M and Perumal P T 2016 Cycloisomerization of acetylenic oximes and hydrazones under gold catalysis: Synthesis and cytotoxic evaluation of isoxazoles and pyrazoles *J. Chem. Sci*. **128** 73
7. Burschka J, Dualeh A, Kessler F, Baranoff E, Cevey-Ha N L, Yi C, Nazeeruddin M K and Grätzel M 2011 Tris(2-(1H-pyrazol-1-yl)pyridine)cobalt(III) as p-Type dopant for organic semiconductors and its application in highly efficient solid-state dye-sensitized solar cells *J. Am. Chem. Soc*. **133** 18042
8. Giornal F, Pazenok S, Rodefeld L, Lui N, Vors J and Leroux F R 2013 Synthesis of diversely fluorinated pyrazoles as novel active agrochemical ingredients *J. Fluor. Chem*. **152** 2
9. Romero A, Ramos E, Ares I, Castellano V, Martinez M, Martiınez-Larranaga M R, Anadon A and Martinez M A 2016 Fipronil sulfone induced higher cytotoxicity than fipronil in SH-SY5Y cells: protection by antioxidants *Toxicol. Lett.* **252** 42
10. Hassan A S, Moustafa G O, Askar A A, Naglah A M and Al-Omar M A 2018 Synthesis and antibacterial evaluation of fused pyrazoles and Schiff bases *Synth. Commun.* **48** 2761
11. Chauhan S, Paliwal S and Chauhan R 2014 Anticancer activity of pyrazole via different biological mechanisms *Synth. Commun.* **44** 1333
12. Deshmukh S, Dingore K, Gaikwad V and Jachak M 2016 An efficient synthesis of pyrazolo[1,5-a]pyrimidines and evaluation of their antimicrobial activity *J. Chem. Sci*. **128** 1459

13. Parshad M, Verma V, Kumar D, Narasimhan B, Kour S, Singh S and Sangwan P L 2015 Iodobenzene diacetate-mediated isomerization of pyrazolyl chalcones and their cytotoxicity and anti-microbial activity *J. Chem. Sci*. **127** 413
14. Faisal M, Saeed A, Hussain S, Dar P and Larik F A 2019 Recent developments in synthetic chemistry and biological activities of pyrazole derivatives *J. Chem. Sci*. **131** 70
15. Swami S, Agarwala A, Malik B and Shrivastava R 2016 A new class of efficient 4-[(nitro substituted-phenyl)-hydrazonomethyl]-1-phenyl-1H-pyrazole-3-carboxylate derived colorimetric chemosensor for selective sensing of fluoride and other biologically important anions *J. Chem. Sci*. **128** 1451
16. Blair L M and Sperry J 2013 Natural products containing a nitrogen-nitrogen bond *J. Nat. Prod*. **76** 794
17. Kumar V, Kaur K, Gupta G K and Sharma A K 2013 Pyrazole containing natural products: Synthetic preview and biological significance *Eur. J. Med. Chem.* **69** 735–753
18. Hassan G S, Abou-Seri S M, Kamel G and Ali M M 2014 Celecoxib analogs bearing benzofuran moiety as cyclooxygenase-2 inhibitors: Design, synthesis and evaluation aspotential anti-inflammatory agents *Eur. J. Med. Chem.* **76** 482
19. Cox S K, Roark J, Gassel A and Tobias K 2005 Determination of deracoxib in feline plasma samples using high performance liquid chromatography *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* **819** 181
20. Boustany-Kari C M, Jackson V M, Gibbons C P and Swick A G 2011 Leptin potentiates the anti-obesity effects of rimonabant *Eur. J. Pharmacol.* **658** 270
21. Giancarlo G M, Venkatakrishnan K, Granda B W, Von Moltke L L and Greenblatt D J 2001 Relative contributions of CYP2C9 and 2C19 to phenytoin 4-hydroxylation in vitro: Inhibition by sulfaphenazole, omeprazole, and ticlopidine *Eur. J. Clin. Pharmacol.* **57** 31
22. Wyde P R, Gilbert B E and Ambrose M W 1989 Comparison of the anti-respiratory syncytial virus activity and toxicity of papaverine hydrochloride and pyrazofurin in vitro and in vivo *Antiviral Res.* **11** 15
23. Tsutomu K and Toshitaka N 1978 Effects of 1,3-diphenyl-5-(2-dimethylaminopropionamide)-Pyrazole[difenamizole] on a conditioned avoidance response *Neuropharmacology* **17** 249
24. Fustero S, Antonio S F and Sanz-Cervera J F 2009 Recent advances in the synthesis of pyrazoles. A review *Org. Prep. Proced. Int.* **41** 253
25. Fustero S, Sánchez-Roselló M, Barrio P and Simón-Fuentes A 2011 From 2000 to mid-2010: A fruitful decade for the synthesis of pyrazoles *Chem. Rev.* **111** 6984
26. Shawali A S 2014 Chemoselectivity in 1,3-Dipolar Cycloaddition Reactions of Nitrilimines with Multifunctionalized Dipolarophiles *Curr. Org. Chem.* **18** 598
27. Gerby B, Boumendjel A, Blanc M, Bringuier P P, Champelovier P, Fortuné A, Ronot X and Boutonnat J 2007 2-Arylidenedihydroindole-3-ones: Design, synthesis, and biological activity on bladder carcinoma cell lines *Bioorg. Med. Chem. Lett.* **17** 208
28. Carrasco M P, Machado M, Gonçalves L, Sharma M, Gut J, Lukens A K, Wirth D F, André V, Duarte M T, Guedes R C, dos Santos D J V A, Rosenthal P J, Mazitschek R, Prudêncio M and Moreira R 2016 Probing the Azaaurone Scaffold against the Hepatic and Erythrocytic Stages of Malaria Parasites *Chem. Med. Chem*. **11** 2194
29. Sharma M C, Sharma S, Sharma P and Kumar A 2014 Pharmacophore and QSAR modeling of some structurally diverse azaaurones derivatives as anti-malarial activity *Med. Chem. Res.* **23** 181
30. Zhang M, Li T, Qian M, Li K, Qin Y, Zhao T and Yang L.-Q 2018 Synthesis and Biological Activities of 1-Azaaurone Derivatives *J. Heterocycl. Chem.* **55** 1574
31. Souard F, Okombi S, Beney C, Chevalley S, Valentin A and Boumendjel A 2010 1-Azaaurones derived from the naturally occurring aurones as potential antimalarial drugs *Bioorg. Med. Chem.* **18** 5724
32. Campaniço A, Carrasco M P, Njoroge M, Seldon R, Chibale K, Perdigão J, Portugal I, Warner D F, Moreira R and Lopes F 2019 Azaaurones as potent antimycobacterial agents active against MDR- and XDR-TB *Chem. Med. Chem*. **14** 1537
33. Boughaleb A, Zouihri H, Gmouh S, Kerbal A and El Yazidi M 2011 (2RS,4′RS)-3′-(3-Chloro-4-methoxyphenyl)-4′-phenyl-4′H-spiro-[indene-2,5′-isoxazol]-1(3H)-one ethanol monosolvate *Acta Crystallogr. Sect. E Struct. Reports Online* **67** o2434.
34. Zhang L J, Wang Y, Hu X Q and Xu P F 2016 Hydrogen-Bonding Network Promoted [3+2] Cycloaddition: asymmetric catalytic construction of spiro-pseudoindoxyl Derivatives *Chem. An Asian J.* **11** 834
35. Daisley R W, Elagbar Z A and Walker J 1982 Reaction of indol-3(2H)-one derivatives with some active methylene compounds *J. Heterocycl. Chem*. **19** 1013
36. Yang L, Huang W, He X H, Yang M C, Li X, He G, Peng C and Han B 2016 Stereoselective synthesis of Hydropyrano[3,2-b]indoles via Organocatalytic Asymmetric Inverse-Electron-Demand Oxa-Diels–Alder Reaction *Adv. Synth. Catal.* **358** 2970
37. Wang M, Rong Z Q and Zhao Y 2014 Stereoselective synthesis of ε-lactones or spiro-heterocycles through NHC-catalyzed annulation: Divergent reactivity by catalyst control *Chem. Commun.* **50** 15309
38. Guo C, Schedler M, Daniliuc C G, Glorius F 2014 N-heterocyclic carbene catalyzed formal [3+2] annulation reaction of enals: An efficient enantioselective access to spiro-heterocycles *Angew. Chem. Int. Ed.* **53** 10232
39. Birch A J and Wright J J 1969 The brevianamides: A new class of fungal alkaloid *J. Chem. Soc. D* 644b
40. Paterson R R M, Simmonds M J S, Kemmelmeier C and Blaney W M 1990 Effects of brevianamide A, its photolysis product brevianamide D, and ochratoxin A from two Penicillium strains on the insect pests Spodoptera frugiperda and Heliothis virescens *Mycol. Res.* **94** 538
41. Williams R M, Glinka T, Kwast E, Coffman H and Stille J K 1990 Asymmetric, stereocontrolled total synthesis of (-)-brevianamide B *J. Am. Chem. Soc.* **112** 808

42. Pearson W H, Lee I Y, Mi Y and Stoy P 2004 Total synthesis of the Kopsia lapidilecta alkaloid (±)-lapidilectine B *J. Org. Chem.* **69** 9109
43. Ji Y, He X, Peng C and Huang W 2019 Recent advances in the synthesis of C2-spiropseudoindoxyls *Org. Biomol. Chem.* **17** 2850
44. Boughaleb A, Al Houari G, Bennani B, Daoudi M, Garrigues B, Kerbal A and El Yazidi M 2010 Cycloaddition des N-phényl-C-arylnitrilimines sur des dérivés de la 2-benzylidènebenzo[b]tiophèn-3(2H)-one (thioaurones) *J. la Société Chim. Tunisie* **12** 109
45. Boughaleb A, Akhazzane M, Al Houari G, Daoudi M, Garrigues B, Kerbal A and El Yazidi M 2011 Cycloaddition des arylnitriloxydes sur des dérivés de la 2-benzylidènebenzo[b]thiophèn-3(2H)- one (thioaurones) *J. la Société Chim. Tunisie* **13** 117
46. Mahfoud A, Al Houari G, El Yazidi M, Saadi M and El Ammari L 2015 Crystal structure of 3,4′-diphenyl-3′-*p* -tolyl-4′ *H* -spiro[indan-2,5′-[1,2]oxazol]-1-one *Acta Crystallogr. Sect. E Crystallogr. Commun*. **71** o873
47. Bakhouch M, Al Houari G, Daoudi M, Kerbal A and El Yazidi M 2015 Michael addition of active methylene compounds to (Z)-2-arylidenebenzo[b]thiophen-3(2H)-ones *Mediterr. J. Chem.* **4** 9
48. Bakhouch M, El Yazidi M, Al Houari G, Saadi M and El Ammari L 2017 3′-(4-Chlorophenyl)-4′-phenyl-3*H*,4′*H*-spiro[benzo[b]thiophene-2,5′-isoxazol]-3-one *IUCrData*. **2** x170677
49. Bakhouch M, El Yazidi M, Al Houari G, Saadi M and El Ammari L 2018 3′,4′-Diphenyl-3H,4′H-spiro[benzo[b]thiophene-2,5′-isoxazol]-3-one *IUCrData*. **3** x181019
50. Rössing A 1884 Beobachtungen über innere Condensationen bei Abkömmlingen des Salicylaldehyds *Berichte der Dtsch. Chem. Gesellschaft* **17** 2988–3010
51. Rodríguez-Domínguez J C, Balbuzano-Deus A, López-López M A and Kirsch G 2007 An improved synthesis of 1-acetyl-1H-indol-3-yl acetates *J. Heterocycl. Chem.* **44** 273
52. Kerbal A, Tshiamala K, Vebrel J and Laude B 1988 Cycloaddition de quelques diarylnitrilimines sur diverses arylidene-2-indanones-1. Regio- et diastereochimies des spiropyrazolines synthétisées *Bull. Soc. Chim. Belg*. **97** 149
53. Lévai A 2002 Synthesis of 2-pyrazolines by the reactions of α,β-unsaturated aldehydes, ketones, and esters with diazoalkanes, nitrile imines, and hydrazines *J. Heterocycl. Chem.* **39** 1
54. Kerbal A, Tshiamala K, Vebrel J, Laude B and Mercier M F 1991 Réaction de diarylnitrlimines sur des 2-arylidene-tetralin-1-ones substituées. Influence des facteurs conformationnels sur la diastéreochimie de la réaction *Bull. Soc. Chim. Belg*. **100** 159
55. Daou B, Soufiaoui M and Carrié R 1989 Régiospécificité de la cycloaddition des diarylnitrilimines sur quelques dérivés indoliques *J. Heterocycl. Chem.* **26** 1485