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Synthesis of Novel Heterocyclic Pyrazole-3-carboxamides using Nitrilimines

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Abstract: A new series of 1,3,4,5-tetrasubstituted pyrazole carboxamides have been synthesized by the 1,3-dipolar cycloaddition of nitrilimine with p-nito phenyl acetone. Both analytical and spectroscopic data of all the synthesized compounds are in full agreement with the proposed structures.
Key words: Nitrilimines, 1,3 dipolar cycloaddition, pyrazole-3-carboxylic acid, HATU.

Introduction

A large number of substituted pyridines have been reported to possess several biological activities[1]. Functionally substituted pyridines like Atorivodine is a potent anti HIV agent[2]. Pyrazoles are important class of compounds in the pharmaceutical industry. Compounds containing pyrazole motif are being developed for a wide range of therapeutic areas including CNS**,** metabolic diseases and endocrine functions and oncology[2]. Several pyrazoles have been successfully commercialized, such as the blockbuster drugs Sildenafil, Celecoxib and Rimonabant. Tetra substituted pyrazole derivatives bearing nitro substituent on phenyl ring shown binding affinity towards estrogen receptor (ER) subtypes ERα and ERβ[3]. In view of this, and in continuation of our work on new pyrazoles and pyridines, we report herein the synthesis of pyridinyl pyrazoles as a new class of pyridine based hetero aryl pyrazole templates. The synthesis of multi-substituted pyrazoles has been extensively studied, and the existing methods are not particularly suitable for the regioselective synthesis of tetra substituted pyrazoles. Two methods have certainly stood out in terms of generality and convenience. One is the venerable Knorr reaction involving the condensation of substituted hydrazines with 1, 3-diketones or their derivatives[4-5]. The other method is the 1,3–dipolar cycloaddition of diazoalkanes or nitrile imines with olefins or alkynes[6-8]. As successful as these two methods are in preparing pyrazoles with various substitution patterns, they are not particularly suited for the regioselective synthesis of 1,3,4,5 tetra substituted pyrazoles. These pyrazoles are pharmaceutically important, yet less represented in the literature, probably due to the synthetic difficulties. In recent years, 1,3 dipolar cycloaddition reactions have received considerable attention because they have been shown to be an efficient synthetic tool for the preparation of a wide variety of heterocyclic compounds. The reaction of nitrilimine 1,3 dipoles with dipolarophiles provide a source for the construction of substituted pyrazoles. The stereochemistry of the formation of pyrazoles from nitrilimines was reported in many studies[9-15]. In view of these facts and in continuation of our studies on the use of hydrazonyl halides as useful precursors for the synthesis of various heterocycles[16], we report the synthesis of new pyrazole derivatives via reaction of nitrilimine with 4-nitro phenyl acetone.

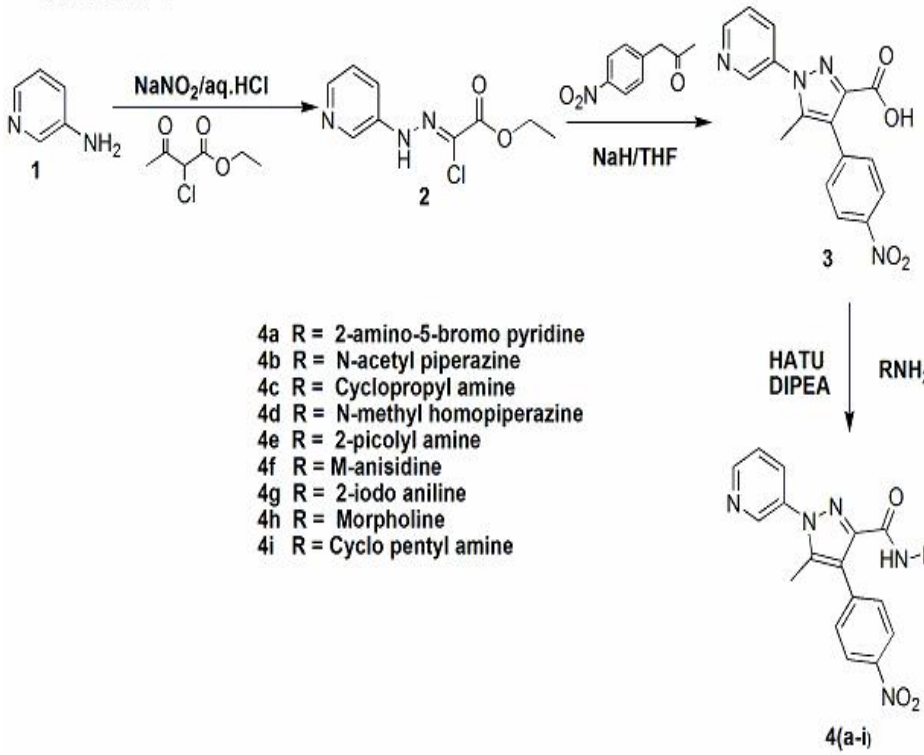
Chemistry

Herein, we report a regioselective synthesis of 1,3,4,5-tetra substituted pyrazoles from readily available hydrazone. In this case, the transformation involves the 1, 3-dipolar cycloaddition reaction of hydrazonoyl hydrochlorides with 4-niotro phenyl acetone in the presence of excess amount of sodium hydride to give pyrazole-3-carboxylic acid. In this 'one-flask' synthesis of 1,3-dipolar reaction, hydrazonoyl hydrochloride was concerned as the masked 1,3-dipole nitrilimine under basic condition. The target compounds were synthesized via the route shown in scheme-1. Diazotization of commercially available 3-Amino pyridine in presence of hydrochloric acid gave the diazonium salt, which was directly coupled with ethyl-2-chloroacetoacetate to afford the oxobutanoate[17-19] **2**. The one pot regioselective synthesis of pyrazole-3-carboxylic acid **3** was achieved by the 1, 3 dipolar cycloaddition reaction of **2** with 4-nitro phenyl acetone in presence of excess amount of sodium hydride. This key intermediate was converted to pyrazole-3-carboxamides **4(a-i)** with different aliphatic and aromatic primary and secondary amines in presence of HATU and DIPEA.

Experimental Methods

All reagents were purchased from Aldrich and used as received. Dry THF, Ethanol and DIPEA were supplied by Spectrochem. All chemistry was performed under a nitrogen atmosphere using standard techniques. All the NMR spectra were measured using either Bruker AMX 400 instrument with 5mm PABBO BB-1H tubes. ^{1}H and ^{13}C NMR spectra were measured for approximately 0.03M solutions in DMSO at 400MHZ with TMS as internal reference. The IR spectra were measured as potassium bromide pellets using a Perkin-Elmer 1600 series FTIR spectrometer. LCMS were obtained using Agilent 1200 series LC and Micro mass zQ spectrometer. Column chromatography was performed using a silica gel (230- 400 mesh). Combustion analysis was performed on a Costech Elemental, Combustion System CHN elemental analyzer.

scheme-1



Scheme 1. (a) i) $NaNO_2$, aq.HCl, O^oC; ii) Ethyl-2-chloroacetoacetate,NaOAc,EtOH,H_2O,O^0C; (b)NaH, THF, 4-Nitro phenyl acetone; (c) corresponding amines for 4(a-i), HATU, DIPEA, N_2 atm, DMF, 0^0C-RT.

General procedure:

Ethyl 2-chloro-2-(2-(3-pyridyl) hydrazono) acetate (2):

3-amino pyridine (25 g, 0.265 mol) was dissolved in 250ml of 6N HCl (250 ml) solution to give a clear solution and cooled to 0^0C. Sodium nitrite (18.2 g, 0.265 mol) in water (50 ml) was added drop wise to the reaction mass and stirred for 30 minutes at the same temperature. Later, ethyl-2-chloro actetoacetate (43.5 g, 0.265mol) in ethanol (100 ml) added drop wise for one hour at O^0C. After 30 minutes, sodium acetate (65g, 0.795mol) in water (200 ml) was added drop wise to the reaction mixture and stirred for 12 hrs. The precipitated solid was filtered, washed with water and dried under vacuum to afford pale yellow crystals of **2** (4g, 75%). M.P. = 124-127^{0}C. ^{1}HNMR (400MHZ, DMSO): δ 8.72 (d, 1H), 8.63(s, 1H), 7.63(d, 1H), 7.26(d, 2H), 4.54(q, 2H), 1.46(t, 3H); ^{13}C NMR (400 MHz, DMSO) δ 160.3, 156.7, 150.89, 146.2, 134.5, 133.3, 62.2 , 32.6, LCMS 229.04 (M^++1): 230.07, Anal.calcd for $C_9H_{10}ClN_3O_2$ (C, H, N). C: 47.48, H: 4.43, N: 18.46. Found: C: 47.28, H: 4.63, N: 18.30.

5-methyl-4-(4-nitrophenyl)-1-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (3)

4-nitro phenyl acetone (8.65 g, 0.0483mole) in THF(25ml) was added drop wise to a stirred solution of sodium hydride(2.1g, 0.0876mole) in THF(10ml) at 0^oc. Thirty minutes later, **2** (10 g, 0.0438mole) in THF (50ml) was added drop wise to the reaction media at 0^0C. The reaction mixture was heated to 70^0C for 12 hrs. After completion of the reaction, the reaction mixture quenched in ice water, the P^H of the solution was adjusted to 2-3 using AcOH, the precipitated solid was filtered and washed with water to afford pale brown solid of **3** (9.5g, 66%).

General procedure for the preparation of pyrazole-3-carboxamides 4(a-i)

A solution of **3** (1eq), (2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl- uronium hexafluorophosphate methanaminium [HATU] (1.5eq) and diisopropylethylamine (1.5eq) in dimethylformamide (5vol) was stirred at room temperature for 30 minutes. After stirring the reaction mixture for 30 minutes, the corresponding amine (1.2 eq) added and stirred the reaction for 2-3 hours. After completion of the reaction the reaction mixture diluted with ethyl acetate and wash with aqueous 1N HCl (10ml), brine (20ml), dried over $MgSO_4$, filtered and concentrated to give the crude amide. The crude product was purified by column chromatography to afford pyrazole-3-carboxamides 4(a-i) in 60-90% yield.

N-(5-bromopyridin-2-yl)-5-methyl-4-(4-nitrophenyl)-1-(pyridin-3-yl)-1H-pyrazole-3-carboxamide (4a)

Compound 4a was prepared from 3 (250 mg, 7mmol) and 2-amino-5-bromo pyridine (138 mg, 8mmole) then purified by column chromatography ($CHCl_3$/MeOH, 9.5/0.5) to afford 4a as pale yellow solid (84%). M.Pt. = 195–198°C; ^{1}H NMR (400 MHz, DMSO) δ 9.03 (s, 1H), 8.74 (d, 1H), 8.47 (s, 1H), 8.23-8.28 (m, 3H), 8.01-8.07 (m,2H), 7.64-7.72 (m,3H),2.36 (s,3H), ^{13}CNMR (400MHz, DMSO) δ 160.11, 150.07, 148.67, 146.37 ,145.79, 143.19, 140.74, 140.41, 138.77, 135.29, 132.55, 131.21, 124.16, 123.12, 120.53, 115.45, 114.04; MS (ESI) m/z: 481.1 (M^++1). Anal.Calcd for $C_{21}H_{15}BrN_6O_3$; C, 52.63; H, 3.15; N, 17.53. Found: C, 52.63; H, 3.15; N, 17.53.

(5-methyl-4-(4-nitrophenyl)-1-(pyridin-3-yl)-1H-pyrazol-3-yl)(4-acetylpiperazin-1-yl) methanone (4b)

Compound 4b was prepared from 3 (250 mg, 7mmol) and N-acetylpiperazine (102 mg, 8mmol), then purified by column chromatography (Pet. Ether/EtOAc, 4/6) to afford 4b as pale brown solid (80%) M.Pt. = 195–198°C; ^{1}H NMR (400 MHz, DMSO) δ 8.88 (s, 1H), 8.71 (d, 1H), 8.47 (s, 1H), 8.28 (d, 2H),8.01- 8.07 (m, 2H), 7.60-7.68 (m, 3H),2.36 (s, 3H), ^{13}C NMR (400MHz, DMSO) δ 168.43, 149.39, 146.11, 145.80, 145.27, 138.76, 135.30, 132.65, 129.73, 124.17, 123.84, 53.51, 46.56, 46.18, 45.91, 45.20, 41.23, 40.13, 39.92, 38.87, 21.17, 18.03, 16.69, 11.36. MS (ESI) m/z: 436.1 (M^++1). Anal.Calcd for $C_{22}H_{22}N_6O_4$ C, 60.82; H, 5.10; N, 19.34. Found: C, 60.83; H, 5.15; N, 19.30.

N-cyclopropyl-5-methyl-4-(4-nitrophenyl)-1-(pyridin-3-yl)-1H-pyrazole-3-carboxamide (4c)

Compound 4c was prepared from 3 (250 mg, 7mmol) and Cyclopropylamine (45 mg, 8mmol), then purified by column chromatography ($CHCl_3$/MeOH, 9.5/0.5) to afford 4c as pale brown solid.(90%) ; ^{1}H NMR (400 MHz, DMSO) ; δ 8.91 (s, 1H), 8.71 (s, 1H), 8.36 (s, 1H), 8.26 (d, 2H) , 8.13 (m, 2H), 7.62-7.67(m, 3H), 2.76(m, 1H), 2.30(s, 3H), 0.56-0.65(m, 4H). ^{13}CNMR(400MHz,DMSO) ; δ168.43, 149.39, 146.11, 145.80, 145.27, 138.76, 135.30, 132.65, 129.73, 124.17, 123.84, 53.51, 46.56, 46.18, 45.91, 45.20, 41.23, 40.13, 39.92, 38.87, 21.17, 18.03, 16.69, 11.36. MS (ESI) m/z: 364.1

(M^++1). Anal.Calcd. for $C_{19}H_{17}N_5O_3$ C, 62.80; H, 4.72; N, 19.27. Found: C, 62.83; H, 4.69; N, 19.28.

(4-methyl-1,4-diazepan-1-yl)(5-methyl-4-(4-nitrophenyl)-1-(pyridin-3-yl)-1H-pyrazol-3-yl)methanone (4d)

Compound 4d was prepared from 3 (250 mg, 7mmol) and N-methyl homo- piperazine (91 mg, 8mmol), then purified by column chromatography ($CHCl_3$/MeOH, 9.5/0.5) to afford 4d as brown solid.(65%) ; ^{1}H NMR (400 MHz, DMSO) δ 8.87 (s, 1H), 8.71 (s, 1H), 8.29 (t, 2H), 8.13 (d, 1H), 7.62-7.67 (m, 3H), 3.68 (d, 2H), 3.58(t, 2H), 3.49(t, 2H), 2.42(s, 3H), 2.30(s, 3H), 1.93(m, 2H), 1.82(m, 2H).; ^{13}CNMR (400MHz, DMSO) δ163.74, 149.32, 146.05, 145.68, 138.87, 135.32, 132.56, 129.74, 124.17, 123.84, 57.89, 56.37, 55.82, 55.21, 47.19, 44.43, 40.13, 39.92, 38.87, 11.36.. MS (ESI) m/z: 421.3 (M^++1). Anal.Calcd for $C_{22}H_{24}N_6O_3$ C, 62.84; H, 5.75; N, 19.99. Found: C, 62.83; H, 5.72; N, 19.96.

5-methyl-4-(4-nitrophenyl)-N-((pyridin-2-yl) methyl)-1-(pyridin-3-yl)-1H-pyrazole-3-carboxamide (4e)

Compound 4e was prepared from 3 (250 mg, 7mmol) and 2-Picolyl amine (86 mg, 8mmol), then purified by column chromatography ($CHCl_3$/MeOH, 9.5/0.5) to afford 4e as brown solid.(82%) ^{1}H NMR (400 MHz, DMSO) δ 8.95 (s, 2H), 8.73 (s, 1H), 8.49 (s, 1H), 8.24 (d, 2H),8.17(d, 1H),7.73 (t, 1H) 7.62-7.67 (m, 3H), 7.22-7.31(m, 2H), 4.48 (s, 2H), 2.31(s, 3H).; ^{13}CNMR (400MHz, DMSO) δ161.49, 158.27, 149.52,148.71, 145.94, 144.06, 139.89, 139.33, 136.64, 135.37, 132.68, 131.30, 124.12, 122.86, 122.00, 120.86. MS (ESI) m/z: 415.1 (M^++1). Anal.Calcd for $C_{22}H_{18}N_6O_3$ C, 63.76; H, 4.38; N, 20.28; Found: C, 63.73; H, 4.41; N, 20.25.

N-(3-methoxyphenyl)-5-methyl-4-(4-nitrophenyl)-1-(pyridin-3-yl)-1H-pyrazole-3-carboxamide (4f)

Compound 4f was prepared from 3 (250 mg, 7mmol) and m-Anisidine (98 mg, 8mmol), then purified by column chromatography (PE/EA, 5/5) to afford 4f as pale brown solid.(75%) . ^{1}H NMR (400 MHz, DMSO) δ 9.00 (s, 1H), 8.73 (s, 1H), 8.29 (d, 2H), 8.20 (d,1H), 7.62-7.67 (m, 3H), 7.41 (s, 1H) 7.33(d, 1H), 7.21(t, 1H), 6.65(d, 1H), 3.71(s, 3H), 2.34(s, 3H).; ^{13}CNMR (400MHz, DMSO) δ160.02, 159.39, 149.59,146.26, 146.03, 144.42, 140.09, 139.73, 139.21, 135.34, 132.75, 131.18, 129.32, 124.13, 123.09, 112.32, 109.28, 105.77. MS (ESI) m/z: 430.1 (M^++1). Anal.Calcd for $C_{23}H_{19}N_5O_4$; C, 64.33; H, 4.46; N, 16.31; Found: C, 64.30; H, 4.44; N, 16.33.

N-(2-iodophenyl)-5-methyl-4-(4-nitrophenyl) -1-(pyridin-3-yl)-1H-pyrazole-3-carboxamide (4g)

Compound 4g was prepared from 3 (250 mg, 7mmol) and 2-Iodoaniline (175 mg, 8mmol), then purified by column chromatography (PE/EA, 5/5) to afford 4g as Off white solid.(88%). ^{1}H NMR (400 MHz, DMSO) δ 9.72 (s, 1H), 8.99 (s, 1H), 8.76 (d, 1H), 8.29 (t, 3H), 8.22 (d, 1H), 7.86 (m, 2H), 7.62-7.78 (m, 3H), 7.38 (t, 1H), 6.95(t, 1H), 2.34(s, 3H).; ^{13}CNMR (400MHz, DMSO) δ 149.70,145.88, 138.85, 132.69, 131.46, 128.82, 126.92, 124.24, 124.14, 122.95. MS (ESI) m/z: 526.1 (M^++1). Anal.Calcd for $C_{22}H_{16}IN_5O_3$ C, 50.30; H, 3.07; N, 13.33; Found: C, 50.33; H, 3.11; N, 13.32.

(5-methyl-4-(4-nitrophenyl)-1-(pyridin-3-yl)-1H-pyrazol-3-yl) (morpholino) methanone (4h)

Compound 4h was prepared from 3 (250 mg, 7mmol) and Morpholine (70 mg, 8mmol), then purified by column chromatography ($CHCl_3$/MeOH, 9.5/0.5) to afford 4h as pale brown solid.(62%) ^{1}H NMR (400 MHz, DMSO) δ 8.87 (s, 1H), 8.71 (d, 1H), 8.32 (d, 2H), 8.10 (d, 1H), 7.62-7.67 (m, 3H), 3.48 (t,4H), 3.38 (t, 4H), 2.40(s, 3H).; ^{13}CNMR (400MHz, DMSO) δ162.20, 149.38, 146.11, 145.80, 138.79, 135.29, 132.66, 129.71, 124.16, 123.83, 118.83, 66.20, 65.89, 46.98, 41.80, 39.92, 39.08, 11.34.. MS (ESI) m/z: 395.1 (M^++1). Anal.Calcd for $C_{20}H_{19}N_5O_4$ C, 61.06; H, 4.87; N, 17.80. Found: C, 61.09; H, 4.85; N, 17.79.

N-cyclopentyl-5-methyl-4-(4-nitrophenyl)-1-(pyridin-3-yl)-1H-pyrazole-3-carboxamide (4i)

Compound 4i was prepared from 3 (250 mg, 7mmol) and Cyclopentyl amine (68 mg, 8mmol), then purified by column chromatography ($CHCl_3$/MeOH, 9.5/0.5) to afford 4i as pale yellow solid.(78%) . ^{1}H NMR (400 MHz, DMSO) δ 8.92 (s, 1H), 8.71 (d, 1H), 8.26 (d, 2H), 8.12-8.18 (m, 2H), 7.62-7.67 (d, 2H), 2.30(s, 3H), 1.82 (m, 2H), 1.65 (m, 2H), 1.48 (m, 4H), 4.13 (m, 1H); ^{13}CNMR (400MHz, DMSO) δ161.03, 149.42, 146.08, 145.96, 139.47, 135.38, 132.69, 131.10, 124.09, 122.94, 50.24, 40.13, 38.87, 31.95, 23.52, 1105. MS (ESI) m/z: 392.17 (M^++1). Anal.Calcd for $C_{21}H_{21}N_5O_3$ C, 64.44; H, 5.41; N, 17.89. Found: C, 64.47; H, 5.39; N, 17.88.

Conclusion

In conclusion, we prepared some tetra substituted pyrazole derivatives regioselectively in good yields via the reaction of nitrilimine derivative. Furthermore, this newly developed methodology can be applied to various acetone substrates including aliphatic, cyclic aliphatic and aromatic acetones. The above approach has been proved very useful for the construction of new heterocycles of potential pharmacological interest.

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