(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
08 December 2022 (08.12.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/256358 A1

(51) International Patent Classification:
C07D 231/38 (2006.01)

(21) International Application Number:
PCT/US2022/031685

(22) International Filing Date:
01 June 2022 (01.06.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/196,382 03 June 2021 (03.06.2021) US

(71) Applicant: **GENENTECH, INC.** [US/US]; 1 DNA Way, South San Francisco, California 94080-4990 (US).

(71) Applicant *(for all designated States except US)*: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, 4070 Basel (CH).

(71) Applicant *(for US only)*: **HOFFMANN-LA ROCHE INC.** [US/US]; 150 Clove Road, Overlook at Great Notch, Suite 8, Little Falls, New Jersey 07424 (US).

(72) Inventors: **STUMPF, Andreas**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, California 94080-4990 (US). **LAO, David**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, California 94080-4990 (US). **ANGELAUD, Remy**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, California 94080-4990 (US). **MARX, Andreas**; c/o F. Hoffmann-La Roche AG, Grenzacherstrasse 124, 4070 Basel (CH).

(74) Agent: **HALL, Robert C.** et al.; c/o Genentech, Inc., 1 DNA Way, South San Francisco, California 94080-4990 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) Title: PROCESS FOR PREPARING MEDICAMENTS

(57) Abstract: The present application affords an improved preparation of 3-(5-chloro-2-(difluoromethoxy)phenyl)-1H-pyrazol-4-amine hydrochloride qhich was a useful intermediate in the synthesis of JAK inhibitors.

WO 2022/256358 A1

PROCESS FOR PREPARING MEDICAMENTS

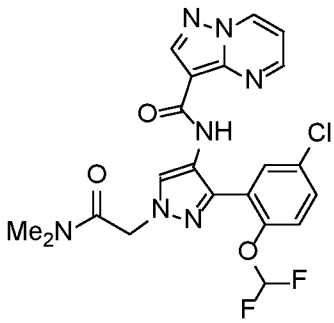
FIELD OF THE INVENTION

The present invention relates to a new and improved process for the preparation of synthetic intermediates useful for the synthesis of medicaments including JAK kinases of formula **1.** One object of the present invention is an improved process, which efficiently implemented on commercial scale.

BACKGROUND OF THE INVENTION

Janus kinases (JAK), including JAK1, JAK2, JAK3 and TYK2, are cytoplasmic protein kinases that associate with type I and type II cytokine receptors and regulate cytokine signal transduction. Cytokine pathways mediate a broad range of biological functions, including many aspects of inflammation and immunity.

A series of pyrazolo[1,5-a]pyrimidines afforded JAK inhibitors remarkably efficacious for the treatment of asthma and inflammatory diseases (E. Hanan *et al., J. Med. Chem.*, **2012** 55:10090-10107; M. Zak, *et al.* WO2015/177326; M. Zak, *et al.*, 2018/215389). Compound I was selected for additional testing which required larger quantities for further clinical evaluation.

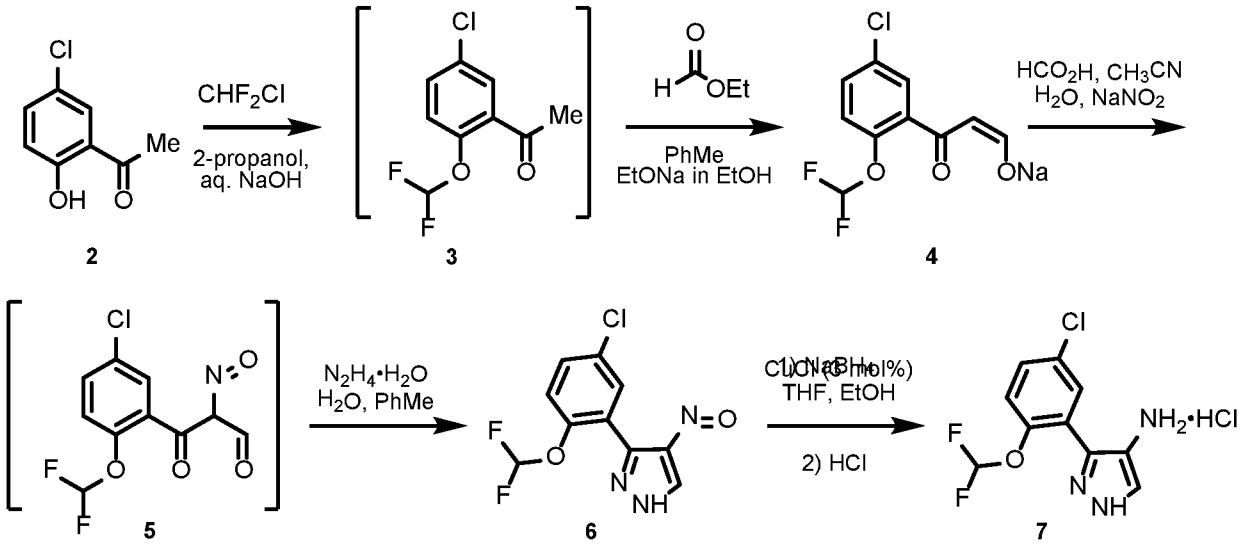


(I)

BRIEF SUMMARY OF THE INVENTION

The invention affords (*i*) a sequential difluoromethylation and Claisen condensation to afford enolate **4** without isolation of the intermediate, (*ii*) one-pot nitrosation of **4** followed by condensation with hydrazine to form nitrosopyrazole **6**, and (*iii*) subsequent reduction of the nitroso group using sodium borohydride and catalytic copper(I) chloride to produce target compound **7**. The optimized process delivered highly pure **7** (99.9 A% by HPLC) in overall 28% yield over 5 steps. (SCHEME 1)

SCHEME 1



The aminopyrazole intermediate 7 can be condensed with pyrazolo[1,5-a]pyrimidine-3-carboxylic acid a]pyrimidine-3-carboxylic acid (II) to afford 2-(4-amino-3-(5-chloro-2-(difluoromethoxy)phenyl)-1H-pyrazol-1-yl)-N,N-dimethylacetamide (III) and N-alkylated with N,N-dimethyl-bromoacetamide to afford **I.**

DETAILED DESCRIPTION OF THE INVENTION

The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The phrase “a” or “an” entity as used herein refers to one or more of that entity; for example, a compound refers to one or more compounds or at least one compound. As such, the terms “a” (or “an”), “one or more”, and “at least one” can be used interchangeably herein.

As used in this specification, whether in a transitional phrase or in the body of the claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound or composition, the term "comprising" means that the compound or composition includes at least the recited features or components, but may also include additional features or components.

A bond drawn into ring system (as opposed to connected at a distinct vertex) indicates that the bond may be attached to any of the suitable ring atoms.

The term “optional” or “optionally” as used herein means that a subsequently described event or circumstance may, but need not, occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, “optionally substituted” means that the optionally substituted moiety may incorporate a hydrogen or a substituent.

The term "about" is used herein to mean approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 20%.

As used herein, the term “treating”, “contacting” or “reacting” when referring to a chemical reaction means to add or mix two or more reagents under appropriate conditions to produce the indicated and/or the desired product. It should be appreciated that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added, i.e., there may be one or more intermediates which are produced in the mixture which ultimately leads to the formation of the indicated and/or the desired product.

An optionally substituted 2-hydroxyacetophenone refers to a compound which is optionally further substituted with one or two halogens, C_{1-3} alkyl, C_{1-3}-alkoxy, C_{1-3}-haloalkoxy moieties.

The term “alkyl” as used herein alone or in combination with other groups, denotes an unbranched or branched chain, saturated, monovalent hydrocarbon residue containing 1 to 10 carbon atoms. The term “lower alkyl” denotes a straight or branched chain hydrocarbon residue containing 1 to 6 carbon atoms. "C_{1-6} alkyl" as used herein refers to an alkyl composed of 1 to 6 carbons. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, i-propyl, n-butyl, i-butyl, t-butyl, neope The term “haloalkyl” as used herein denotes an alkyl group as defined above wherein at least one hydrogen atom is substituted by a halogen. Examples are 1-fluoromethyl, 1-chloromethyl, 1-bromomethyl, 1-iodomethyl, difluoromethyl, trifluoromethyl, trichloromethyl, 1-fluoroethyl, 1-chloroethyl, 2-

fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2,2-dichloroethyl, 3-bromopropyl or 2,2,2-trifluoroethyl.

The term "alkoxy" as used herein means an -O-alkyl group, wherein alkyl is as defined above, such as methoxy, ethoxy, n-propyloxy, i-propyloxy, n-butyloxy, i-butyloxy, t-butyloxy, pentyloxy, hexyloxy, including their isomers. "Lower alkoxy" as used herein denotes an alkoxy group with a "lower alkyl" group as previously defined. "C_{1-10} alkoxy" as used herein refers to an-O-alkyl wherein alkyl is C_{1-10}.

The term "haloalkoxy" as used herein refers to a group -OR where R is haloalkyl as defined herein. The term "haloalkylthio" as used herein refers to a group -SR where R is haloalkyl as defined herein.

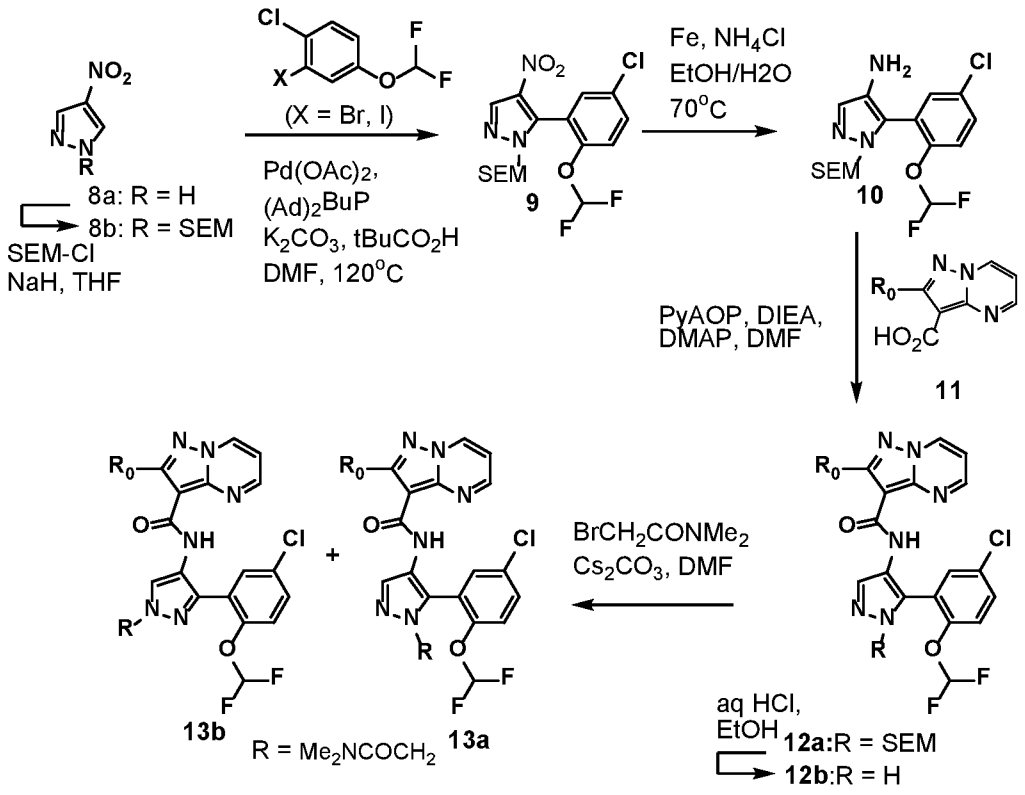
The term "halogen" or "halo" as used herein means fluorine, chlorine, bromine, or iodine. The term “halo”, “halogen”, and “halide” are used interchangeably herein and denote fluoro, chloro, bromo, or iodo.

Reduction of a nitro group to an amine can be accomplished with a metal reducing agent such as Fe, Sn or Zn, in a reaction inert solvent, *e.g.* MeOH, EtOH, EtOAc, benzene, toluene, xylene, *o*-dichlorobenzene, DCM, DCE, THF, dioxane, or mixtures thereof. If desired, when the reducing reagent is Fe, Sn or Zn, the reaction is carried out under acidic conditions in the presence of water. The reduction may be carried out by hydrogenation in the presence of a metal catalyst, e.g. nickel catalysts such as Raney nickel, palladium catalysts such as Pd/C, platinum catalysts such as PtO_2, or ruthenium catalysts such as $RuCl_2(Ph_3P)_3$ under H_2 atmosphere or in the presence of hydrogen sources such as hydrazine or formic acid. If desired, the reaction is carried out under acidic conditions, *e.g.,* in the presence of HCl or HOAc.

Carboxylic acids can be can be activated with agents such as EDC, DCC, benzotriazol-1 -yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PyBrOP), or 2-fluoro-1-methylpyridinium p-toluenesulphonate (Mukaiyama's reagent with or without a base such NMM, TEA or DIPEA in an inert solvent such as dimethylformamide (DMF) or dichloromethane at temperatures between 0 °C and 60 °C. Acylation of amines (J. March, *supra* pp.417-425; H. G. Benz, *Synthesis of Amides and Related Compounds* in *Comprehensive Organic Synthesis,* E.

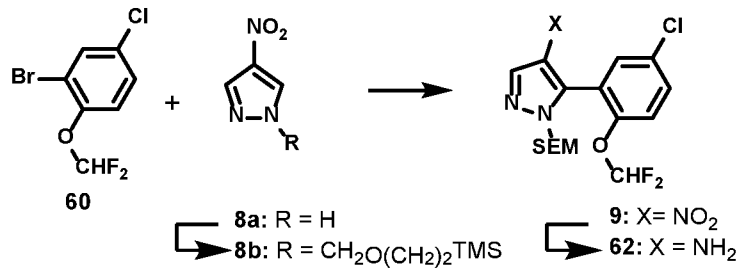
Winterfeldt, ed., vol. 6, Pergamon Press, Oxford **1991** pp. 381-411; see R. C. Larock, *Comprehensive Organic Transformations – A Guide to Functional Group Preparations*, 1989, VCH Publishers Inc., New York; pp. 972-976) has been reviewed.

SCHEME 2



The laboratory scale preparation of I is depicted in Scheme 2 (P. Gibbons *et al.*, *WO2011/003065*, p.43). Heretofore, the preparation of I was accomplished by protection of 4-nitro pyrazole (**8a**) with SEM-Cl to afford **8b** which was subjected to $Pd(OAc)_2$ catalyzed coupling with 2-difluoromethoxy-5-chloro bromobenzene to afford the amine **10** and condensed with **11** to afford the amide **12** which was subsequently deprotected. (Scheme 2)

SCHEME 3



The original process in Scheme 2 requires the protection and deprotection of the pyrazole nitrogen as a SEM ester that adds two steps to the process. In addition, the current process

telescopes the conversion of **2** to **4** and the conversion of **4** to **6** minimizing the costs associated with the extra steps.

Commonly used abbreviations include: acetyl (Ac), aqueous (aq.), di(1-adamantyl)-n-butylphosphine ((Ad)2BuP), tert-butoxycarbonyl (Boc), di-tert-butyl pyrocarbonate or Boc anhydride (BOC2O), benzyl (Bn), benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP), butyl (Bu), benzoyl (Bz), Chemical Abstracts Registration Number (CASRN), benzyloxycarbonyl (CBZ or Z), carbonyl diimidazole (CDI), N,N'-dicyclohexylcarbodiimide (DCC), 1,2-dichloroethane (DCE), dichloromethane (DCM), diethyl azodicarboxylate (DEAD), di-iso-propylazodicarboxylate (DIAD), iso-propylethylamine (DIPEA), N,N-dimethyl acetamide (DMA), 4-N,N-dimethylaminopyridine (DMAP), N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), 1,1'-bis-(diphenylphosphino)ethane (dppe), 1,1'-bis-(diphenylphosphino)ferrocene (dppf), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), ethyl (Et), ethyl acetate (EtOAc), ethanol (EtOH), diethyl ether (Et2O), O-(7-azabenzotriazole-1-yl)-N, N,N'N'-tetramethyluronium hexafluorophosphate acetic acid (HATU), acetic acid (HOAc), 1-N-hydroxybenzotriazole (HOBt), (3-Hydroxy-3H-1,2,3-triazolo[4,5-b]pyridinato-O)tri-1-pyrrolidinyl-phosphorus hexafluorophosphate (PyAOP),high pressure liquid chromatography (HPLC), iso-propanol (IPA), methanol (MeOH), melting point (mp), $MeSO_2$- (mesyl or Ms), methyl (Me), acetonitrile (MeCN), mass spectrum (ms), methyl tert-butyl ether (MTBE), N-methylmorpholine (NMM), N-methylpyrrolidone (NMP), petroleum ether (pet ether, i.e. hydrocarbons),)phenyl (Ph), propyl (Pr), iso-propyl (*i*-Pr), pounds per square inch (psi), bromo-*tris*-pyrrolidinophosphonium hexafluorophosphate (PyBrOP), pyridine (pyr), room temperature (rt or RT), satd. (saturated), 2-(Trimethylsilyl)ethoxymethyl (SEM), *tert*-butyldimethylsilyl or t-BuMe2Si (TBDMS), triethylamine (TEA or Et_3N), triflate or CF_3SO_2-(Tf), trifluoroacetic acid (TFA), thin layer chromatography (TLC), tetrahydrofuran (THF), tetramethylethylenediamine (TMEDA), trimethylsilyl or Me_3Si (TMS), 2-(trimethylsilyl)ethoxymethyl (SEM), p-toluenesulfonic acid monohydrate (TsOH or pTsOH), 4-Me-$C_6H_4SO_2$- or tosyl (Ts) Conventional nomenclature including the prefixes normal (n), iso (i-), secondary (sec-), tertiary (tert- or -t) and neo- have their customary meaning when used with an alkyl moiety. (J. Rigaudy and D. P. Klesney, Nomenclature in Organic Chemistry, IUPAC 1979 Pergamon Press, Oxford.).

COMPOUNDS AND PREPARATION

Unless otherwise noted all reactions were run under a nitrogen atmosphere, solvents and reagents were used without further purification. ^{1}H NMR (300 MHz, 500 MHz, 600 MHz), ^{13}C NMR (125 MHz) were recorded on a Bruker Avance 3 spectrometer. Chemical shifts are reported in ppm (δ units) downfield of internal tetramethylsilane [$(CH_3)_4Si$] or residual $CHCl_3$; coupling constants are reported in hertz (Hz). Multiplicities are as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet.

1-(5-chloro-2-(difluoromethoxy)phenyl)ethan-1-one

A reactor was charged with 1-(5-chloro-2-hydroxyphenyl)ethan-1-one (**2,** 135 kg, 791 mol, 100 mol%), 2-propanol (541 kg), aqueous sodium hydroxide (539 kg, 4043 mol, 511 mol%, 30 wt%), and heated to 49 °C. Dichlorofluoromethane (248 kg, 2410 mol, 305 mol%) was bubbled into the reaction mixture and heated at 49 °C for >20 min until reaction was complete (<0.5 A% HPLC). The mixture was cooled to 20 °C and filtered. The cake was washed with 2-propanol (135 kg), and the combined filtrates charged back into the reactor. The reactor was heated to 27 °C for 15 min, let stand for 40 min without stirring to achieve phase separation and the aqueous phase was drained. The remaining organic phase was concentrated to ~ 200 L under reduced pressure at 45 °C, toluene (652 kg) was charged and heated to 27 °C for 40 min. The mixture was filtered and the cake washed with toluene (132 kg). The combined filtrates were recharged into the reactor followed by a rinse with toluene (50 kg). The reactor content was concentrated to ~200 L under reduced pressure at 45 °C, toluene (268 kg) was charged and the solution of 1-(5- chloro-2-(difluoromethoxy)phenyl)ethan-1-one (**3**) in toluene was discharged to drums for subsequent use in the next step (83% corrected yield, 84.5 A% HPLC, 26.1% assay, KF = 0.1%, 2-propanol = 0.01%).

sodium (Z)-3-(5-chloro-2-(difluoromethoxy)phenyl)-3-oxoprop-1-en-1-olate (**4**)

A reactor was charged with ethyl formate (159.0 kg, 2146 mol, 328 mol%), a solution of 1-(5-chloro-2-(difluoromethoxy)phenyl)ethan-1-one (**3**) in toluene (144.5 kg assay corrected from the precursor step, 655 mol, 100 mol%), toluene (392 kg), ethyl formate (10.0 kg, 135 mol, 21 mol%), and heated to 41 °C. A solution of NaOEt in EtOH (360.0 kg, 952 mol, 145 mol%, 18 wt%) and toluene (16 kg) was charged and heated to 46 °C for 4 h. HPLC analysis showed **2** to be 2.1 A%. The reactor content was concentrated to ~1100 L at ≤40 °C under reduced pressure, heptane (578 kg) was added and the mixture was concentrated to ~800 L at ≤40 °C under reduced pressure, heptane (346 kg) was added again and the mixture

concentrated to ~800 L at ≤40 °C. This cycle was repeated 2 more times (using 346 kg of heptane each) followed by a last charge of heptane (340 kg). The reactor contents were then heated to 44 °C for 1 h, and cooled over 3 h to -3 °C, and stirred at this temperature for 2 h. The mixture was filtered, the cake washed with heptane (145 kg) and dried under vacuum for 24 h at 37 °C to give 196.4 kg of sodium (Z)-3-(5-chloro-2-(difluoromethoxy)phenyl)-3-oxoprop-1-en-1-olate (**4**, 76% corrected yield, 85.2 A% HPLC purity; 68.4% assay): mp = 181 °C; ^{1}H NMR (500 MHz, DMSO-d6) δ 9.36 (d, J = 9.5 Hz, 1H), 8.50 (s, 1H), 8.43 (d, J = 10.1 Hz, 1H), 7.77 – 7.68 (m, 1H), 7.35 (dt, J = 8.7, 2.4 Hz, 2H), 7.14 (dd, J = 5.8, 3.0 Hz, 3H), 7.04 (s, 1H), 4.88 (d, J = 9.6 Hz, 1H), 4.82 (d, J = 10.2 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d6) δ 197.47, 185.61, 185.51, 166.97, 146.57, 146.54, 146.52, 139.80, 133.46, 133.07, 130.18, 129.77, 129.27, 128.11, 122.17, 121.94, 119.49, 117.44, 116.89, 105.64, 31.31. HRMS $[M+H]^+$ calcd for $C_{10}H_6ClF_2NaO_3$ 249.0125; found 249.0126.

3-(5-chloro-2-(difluoromethoxy)phenyl)-4-nitroso-1H-pyrazole)

A reactor was charged with formic acid (354 kg), acetonitrile (156 kg), water (44 kg) and cooled to -3 °C. Sodium (Z)-3-(5-chloro-2-(difluoromethoxy)phenyl)-3-oxoprop-1-en-1-olate (**4**) (67.0 kg assay corrected, 248 mol, 100 mol%) was added in one charge, and a solution of aqueous $NaNO_2$ (110 kg, 303 mol, 122 mol%, 19 wt%) was dosed into the solution over 1 h, followed by a rinse with water (4 kg), and stirred for 3 h. HPLC analysis showed **4** was undetected. The reactor was heated to 2 °C, aqueous hydrazine monohydrate (102 kg, 326 mol, 131 mol%, 16 wt%) was added over 1 h and stirred for 3 h at 6 °C. HPLC analysis showed **5** to be 1.0 A%. The reactor was charged with toluene (57 kg), followed by water (468 kg) over 1 h, and cooled to - 7 °C for 4 h. The mixture was filtered, the cake washed with water (248 kg) and dried under vacuum at 33 °C for 33 h to give 42.7 kg of 3-(5-chloro-2-(difluoromethoxy)phenyl)-4-nitroso-1H-pyrazole (**6**) as a green solid (61% yield, 97.2 A% HPLC, 96.0% assay): mp = 149 °C; ^{1}H NMR (500 MHz, DMSO-d6) δ 7.81 (s, 1H), 7.72 (dd, J = 8.8, 2.7 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.31 (s, 1H), 7.17 (s, 1H), 7.02 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d6) δ 161.74, 148.77, 132.26, 131.44, 129.61, 120.67, 118.78, 116.72, 114.66.

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.81 (s, 1H), 7.72 (dd, J = 8.8, 2.7 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.31 (s, 1H), 7.17 (s, 1H), 7.02 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.74, 148.77, 132.26, 131.44, 129.61, 120.67, 118.78, 116.72, 114.66. HRMS $[M+H]^+$ calcd for $C_{10}H_6ClF_2N_3O_2$ 274.0190; found 274.0194.

3-(5-chloro-2-(difluoromethoxy)phenyl)-1H-pyrazol-4-amine hydrochloride

A reactor was charged with $NaBH_4$ (92.9 kg, 2455 mol, 1681 mol%), CuCl (1.10 kg, 11 mol, 69 mol%), THF (440 kg) and heated to 26 °C. A solution of **6** (41.6 kg, 146 mol, 100 mol%) in EtOH (360 kg) was added over 15 h, followed by two rinses with EtOH (50 kg, 48 kg), and continued to stir for 24 h. HPLC analysis showed **6** to be 0.5 A%. A solution of HCl gas in EtOH (653 kg, 4966 mol, 3400 mol%, 6 M) was added over 16 h and stirred at 22 °C for 3 h. Diatomaceous earth (86.2 kg, diatomite) and EtOH (11 kg) was added and stirred for 2 h at 26 °C . The mixture was filtered and the cake washed with five portions of EtOH (256 kg each). The combined filtrate was charged to a reactor and concentrated to ~270 L at ≤ 45 °C under reduced pressure. The reactor was cooled to 26 °C, charged with MeOH (600 kg) and concentrated to ~230 L at ≤ 45 °C under reduced pressure. The reactor was cooled to 26 °C, charged with MeOH (486 kg) and concentrated to ~230 L at ≤ 45 °C under reduced pressure. The reactor was cooled to 26 °C, charged with MeOH (102 kg),title compound seeds and concentrated to ~230 L at ≤ 45 °C under reduced pressure. The reactor was cooled to 26 °C, charged with MTBE (700 kg) and cooled over 4 h to 2 °C and held at this temperature for 8 h. The mixture was filtered, the cake washed three times with MTBE (235 kg each) and dried under vacuum at 70 °C for 44 h to give 72.2 kg of 3-(5-chloro-2-(difluoromethoxy)phenyl)-1H-pyrazol-4-amine hydrochloride (**7**, 72% yield, 99.9 A% HPLC, 97.7% assay) as a yellow solid: mp = 181 °C; ^{1}H NMR (500 MHz, DMSO-d6) δ 13.52 (s, 1H), 10.00 (s, 3H), 7.95 (s, 1H), 7.71 (d, J = 2.7 Hz, 1H), 7.61 (dd, J = 8.8, 2.7 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.17 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d6) δ 147.52, 131.20, 129.95, 121.67, 118.71, 116.64, 114.56, 112.52; HRMS calcd for $C_{10}H_8ClF_2N_3O$ 260.0397; found *m/z* 260.0396.

The features disclosed in the foregoing description, or the following claims, expressed in their specific forms or in terms of a means for performing the disclosed function, or a method or process for attaining the disclosed result, as appropriate, may, separately, or in any combination of such features, be utilized for realizing the invention in diverse forms thereof.

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the

following appended claims, along with the full scope of equivalents to which such claims are entitled.

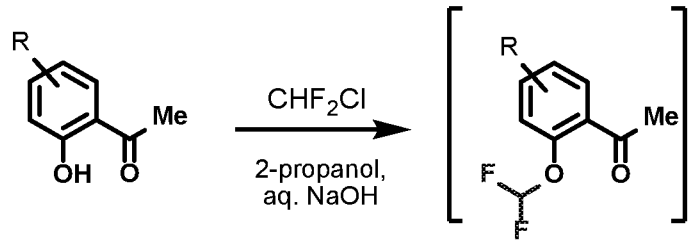
The patents, published applications, and scientific literature referred to herein establish the knowledge of those skilled in the art and are hereby incorporated by reference in their entirety to the same extent as if each was specifically and individually.

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We claim:

1. A process for the preparation of 3-(5-chloro-2-(difluoromethoxy)phenyl)-1H-pyrazol-4-amine (**6**) which process comprises the steps of:

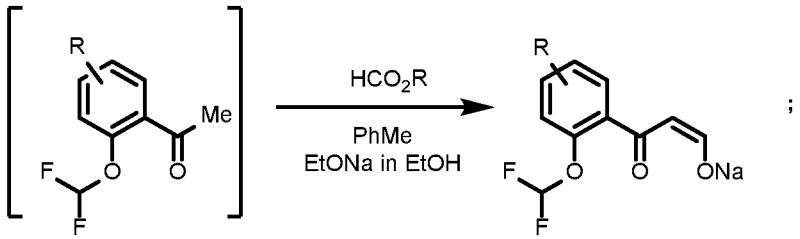
(i) treating an optionally substituted 2-hydroxy-acetophenone with chlorodifluoromethane to afford the difluoromethyl ether **3**



2 **3**

;

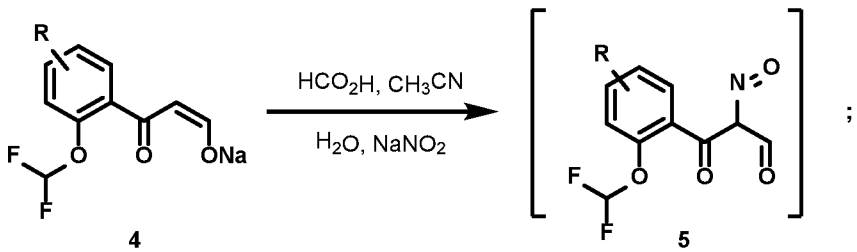
(ii) **3,** without purification, is treated with formic acid ester and base to afford the enolate **4**



3 **4**

;

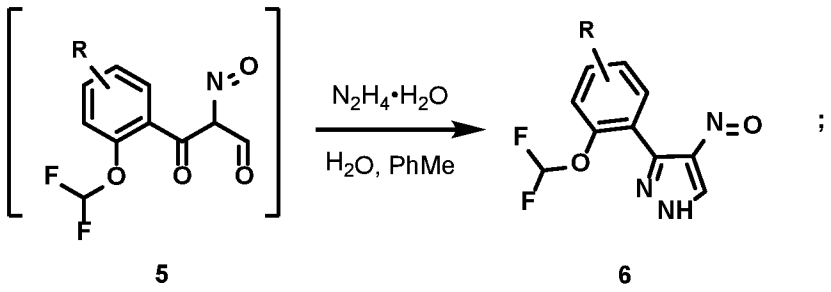
(iii) treating the enolate *in situ* with a nitrosating agent sodium nitrite to afford the nitroso compound **5**



4 **5**

;

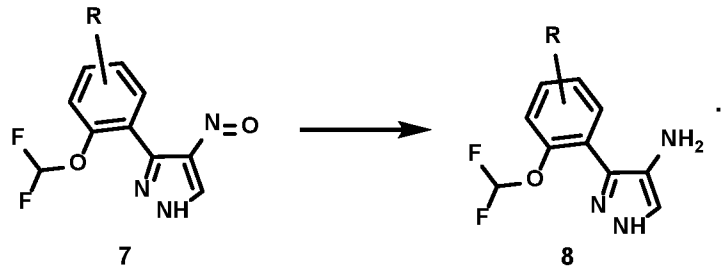
(iv) treating the nitroso-β-dicarbonyl **5**, without further purification, with hydrazine to afford a nitroso-pyrazole **6**



5 6

;

(v) and, reducing the a nitroso group to afford the aminopyrazole and optionally converting the amine to a salt with an organic acid



7 8

2. The process of claim 1 wherein the optionally substituted 2-hydroxyacetophenone is 2-hydroxy-5-chloro-acetophenone, the reducing agent is $NaBH_4$/CuCl and the formate ester, the base is ethyl formate and sodium ethoxide, the nitrosating agent is sodium nitrite.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/031685

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D231/38
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2015/177326 A1 (HOFFMANN LA ROCHE [CH]; GENENTECH INC [US]) 26 November 2015 (2015-11-26) cited in the application Reactions Scheme 4; page 214 - page 215	1,2
A	WO 2018/166993 A2 (HOFFMANN LA ROCHE [CH]; GENENTECH INC [US]) 20 September 2018 (2018-09-20) Reaction Scheme 4; page 58	1,2

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2022	05/08/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bissmire, Stewart

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2022/031685

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