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Regioselective synthesis of 1,3,5- and 1,3,4,5-substituted pyrazoles via acylation of *N*-Boc-*N*-substituted hydrazones

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ABSTRACT

Acylation of *N*-Boc-*N*-methylhydrazones followed by TFA treatment affords regioselective access to substituted pyrazoles. Both regioisomers of 1-methyl-3,5-disubstituted-1H-pyrazoles can be selectively obtained. This procedure can also be employed for the regioselective preparation of fully substituted 1*H*-pyrazoles.

1. Introduction

Pyrazoles are an important class of heteroaromatic ring systems that find extensive use in the pharmaceutical industry. Examples are Viagra,[1] an inhibitor of 5-phosphodiesterase used for the treatment of erectile dysfunction, Celebrex, an inhibitor of cyclo-oxygenase-2 (COX-2) used as potent anti-inflammatory,[2] and Acomplia, antagonist of the CB-1 cannabinoid receptor,[3] used for the treatment of obesity. General methods for the preparation of pyrazoles include the condensation between hydrazines and 1,3-dicarbonyl compounds[4] and 1,3-dipolarcycloadditions.[5] These methods often present problems that range from low selectivities, multistep sequences, and drastic conditions. Therefore, there are still many efforts directed toward the selective preparation of substituted pyrazoles: recent examples include the repeated metalation-electrophile trapping of unsubstituted pyrazoles,[6] low-temperature strong-base mediated reaction of hydrazones with nitroolefins,[7] and condensation of hydrazines with yne-ones.[8]

Recently, researchers at GlaxoSmithKline reported[9] a regioselective synthesis of the pyrazole moiety of compound **1** (Fig. 1), a highly potent and selective dopamine D_3 receptor antagonist.[10]

In that case, the regioselective synthesis of the pyrazole moiety was achieved via acylation of acetone *N*-Boc-*N*-methylhydrazone

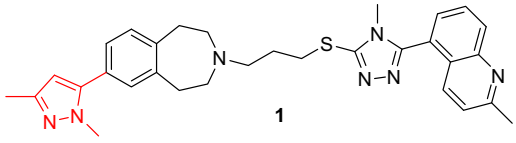
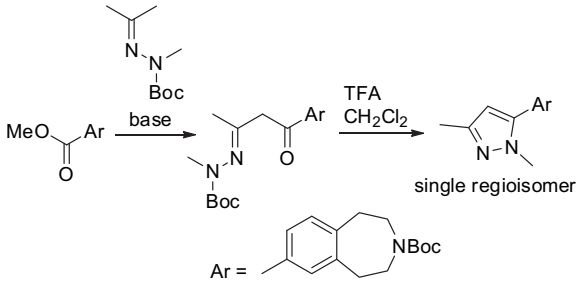


Fig. 1. A potent and selective dopamine D_3 receptor antagonist.

with a methyl benzoate derivative, followed by exposure to trifluoroacetic acid (TFA), as depicted in Scheme 1.



Scheme 1. Regioselective preparation of the pyrazole moiety adopted for the synthesis of compound **1**.

The acylation of hydrazones followed by pyrazole ring closure is known in the literature[11] but the reported procedures often show drawbacks, such as the requirement of strong bases and low temperatures[11a,b] or that they allow no direct access to 4-substituted

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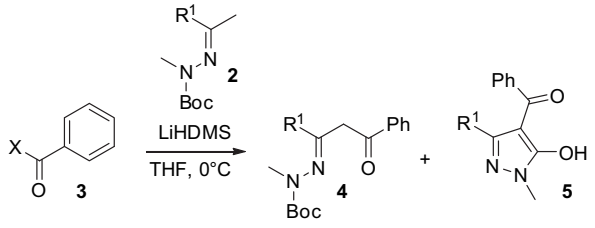
pyrazoles.[8,11c] In this paper, we wish to report the results of our work aimed at investigating the scope of the strategy depicted in Scheme 1, in order to obtain a new and general regioselective preparation of 1,3,5-trisubstituted and 1,3,4,5-tetrasubstituted pyrazoles.

2. Results and discussion

From the very beginning of our study it was clear that the methodology depicted in Scheme 1 was not generally applicable. In fact, when methyl benzoate (**3**, X=OMe) was reacted under the same conditions with a different *N*-Boc-*N*-methylhydrazone[12,13] anion **2a**, generated by the addition of lithium bis(trimethylsilyl)amide (LiHDMS) in THF at 0 °C, a mixture of two compounds was obtained, where the desired ketoimine[14] **4a** was the minor one (Scheme 2). The major product was identified to be the 5-hydroxy-4-acylpyrazole derivative **5a**, which can be present in several tautomeric forms, hampering its NMR spectroscopic characterization.[15]



Scheme 2. Acylation of *N*-Boc-*N*-methylhydrazones (**2**).

When we repeated the reaction using a series of hydrazones **2** (Table 1) we observed that in most of the cases large amounts of **5** are obtained. In some cases as with the *N*-Boc-*N*-methylhydrazones **2c**, **2d**, and **2f** (Table 1) the reaction afforded only the corresponding hydroxypyrazole **5**, with no trace of the desired ketoimine **4**.

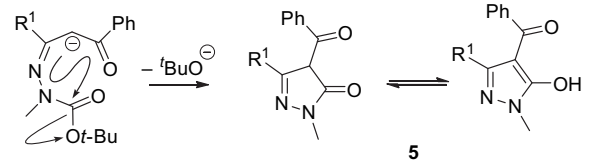
Table 1
Acylation of hydrazones **2** with methyl benzoate **3** (Scheme 2, X=OMe)

Entry	R^1	Time (h)	Yield of **4**[a] (%)	Yield of **5**[a] (%)
a	Ph	1	12	42
b	2-Tolyl	0.25	85	0
c	2-Pyridinyl[b]	15	0	60
d	4-Pyridinyl[b]	15	0	45
e	Me	1	80	0
f	*t*-Bu	0.30	0	66

[a] Isolated yields.
[b] Reaction performed at rt.

The formation of **5** could be explained assuming that the anion of ketoimine **4** undergoes an intramolecular cyclization by addition to the Boc group, followed by *tert*-butoxide elimination (Scheme 3).

Following this hypothesis, formation of hydroxypyrazoles **5** arises from a consecutive reaction of the ketoimine product: before the reaction is complete, the ketoimine starts to undergo the intramolecular cyclization to the unwanted **5**. In fact, HPLC profiles obtained by monitoring at regular intervals the reaction depicted in Scheme 2 clearly shows that at the beginning the ketoimine **4** is the only product, and as reaction proceeds, the hydroxypyrazole **5** starts to form and soon becomes the major product. A second confirmation came when we observed that subjecting isolated ketoimine **4a** to the same reaction conditions depicted in Scheme 2, leads to its clean conversion into hydroxypyrazole **5a**.



Scheme 3. Formation of by-products **5**.

In an attempt to minimize hydroxypyrazole formation, we tried to replace methyl benzoate with (a) stronger acylating agents, such as anhydrides or acyl chlorides, to make the first step to ketoimine much faster than the subsequent conversion to the corresponding hydropyrazole; (b) Weinreb's amides in order to stabilize the tetrahedral intermediate, that is, initially formed through attack of the hydrazone anion to the acylating agent, thus slowing down its conversion into **5**.[16]

In this regard, we tested hydrazones **2a**, **2c**, and **2f**, the ones that with methyl benzoate gave significant amounts of **5**, by reacting them with different acylating agents. Table 2 reports the results of this study.

Table 2
Effect of the nature of the acylating agent on product distribution of the reaction in Scheme 2

Acylating agent **3** (X) [yield of **4** (%)/yield of **5** (%)][a]				
Hydrazone	OMe	N(Me)OMe	PhCOO	Cl[b]
2a	12/42	78/0	15/50	69/0
2f	0/66	8/45[c,d]	15/65	70/0
2c	0/60[d]	n.a.	n.a.	71/0[e]

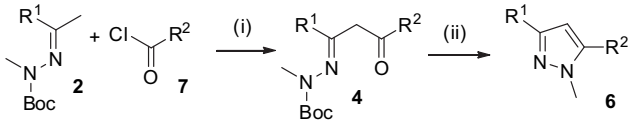
[a] Isolated yields.
[b] Reactions performed at −10 °C.
[c] Chromatographic yields.
[d] Reaction performed at rt.
[e] Crude yields.

The use of the Weinreb amide of benzoic acid [Scheme 2, X=N(Me)OMe] in the reaction with hydrazone **2a** (Table 2, entry a) gave the desired ketoimine **4a** in a 78% isolated yield, while in the same reaction with hydrazone **2f** (Table 2, entry b) we observed only a slight improvement over the results obtained with methyl benzoate. This is probably due to the fact this latter reaction is very slow because of steric hindrance: at rt it takes 15 h to complete, and under such conditions the tetrahedral intermediate may no longer be stable generating the ketoimine product during the reaction, well before it is complete, which then can undergo the degradation process to hydroxypyrazole **5**.

The use of benzoic anhydride (**3**, X=PhCOO) led to slightly improved results: both hydrazones **2a** and **2f** afforded higher amounts of the desired ketoimines **4a** and **4f**, respectively. However, **5** was still the major product.

Finally, the reaction of hydrazones **2a** and **2f** with benzoyl chloride gave ketoimines **4a** and **4f** as the only products, with no trace of the unwanted hydroxypyrazole by-products. Also hydrazone **2c**, that was very reluctant to react with methyl benzoate (Table 1) affording only **5**, when reacted with benzoyl chloride (Table 2) afforded only ketoimine **4c**.

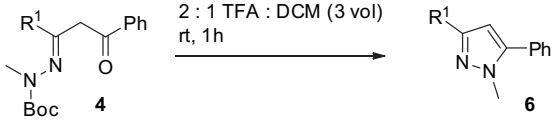
We investigated if this regioselective methodology to 1-methyl-3,5-disubstituted-1*H*-pyrazoles could be employed to obtain either of two possible regioisomers of a specific pyrazole ring. From the general procedure depicted in Scheme 4, it is possible to see that to obtain either regioisomer would require the exchange of groups R^1



Scheme 4. General regioselective preparation of 1-methyl-3,5-disubstituted-1*H*-pyrazoles: (I) LiHDMS, THF, 0 °C; (ii) TFA/DCM (2:1; 3 vol), rt, 1 h.

and R^2. For example, the reaction between the hydrazone derived from ketone **2f** (R^1=*t*-Bu) and benzoyl chloride (R^2=Ph) affords, after the TFA treatment, 1-methyl-3-*t*ert-butyl-5-phenyl-1*H*-pyrazole (**6f**, Table 3). According to Scheme 2, its regioisomer, 5-(*tert*-butyl)-1-methyl-3-phenyl-1*H*-pyrazole (**6h**), might be obtained by using the hydrazone derived from benzophenone (**2a**, R^1=Ph) and an acylating agent derived from pivalic acid (R^2=*t*-Bu).

Table 3
Conversion of ketoimines **4** into 1-methyl-3,5-disubstituted-1*H*-pyrazoles **6**

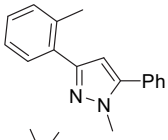
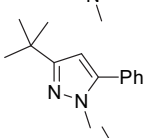
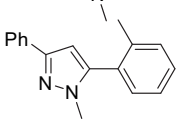
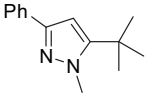


Entry	R^1	Yield
a	Ph	98
b	2-Tolyl	Quant.
c	2-Pyridinyl	70[a]
e	Me	Quant.
f	*t*-Bu	95

[a] overall yield over two steps, starting from benzoyl chloride (**3**; X=Cl). See Scheme 4.

We therefore attempted to selectively obtain the other regioisomer of pyrazoles **6b** and **6f** using acyl chlorides as acylating agents. Table 4 reports the results.

Table 4
Results of the synthesis of Scheme 4

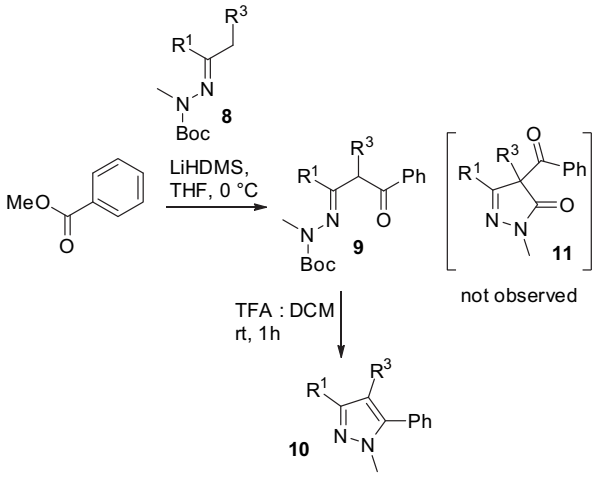
Entry	R^1	R^2	Pyrazole **6**[a]	Overall yield[b] (%)
b	2-Tolyl	Ph		79
f	*t*-Bu	Ph		69
g	Ph	2-Tolyl		77
h	Ph	*t*-Bu		65

[a] Regioisomer structure confirmation through NOE experiments.
[b] Isolated yield over the two steps depicted in Scheme 4.

By reacting the anion of hydrazone **2a** (R^1=Ph) with 2-methylbenzoyl chloride(**7**, R^2=2-tolyl) a smooth reaction occurred and the desired ketoimine **4g** was obtained after 30 min at 0 °C, in a 78% isolated yield. (Table 4, entry g). The reaction between the anion of hydrazone **2a** and pivaloyl chloride (**7**, R^2=*t*-Bu) afforded ketoimine **4h**, after 20 min at 0 °C, in 68% isolated yield (Table 4, entry h).

By rapid exposure to TFA at rt, both ketoimines **4g** and **4h** were readily converted in nearly quantitative yields, into the corresponding 1-methyl-3,5-disubstituted-1*H*-pyrazoles **6g** and **6h**, which are the regioisomers of **6b** and **6f**, respectively.

We also investigated the possibility to apply our methodology to the regioselective synthesis of fully substituted 1-methyl-3,4,5-trisubstituted-1*H*-pyrazole systems **10** (Scheme 5). This requires the use of hydrazones derived from 'methylene' ketones **8**.

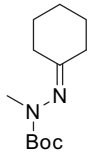
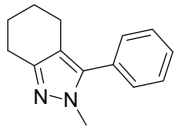
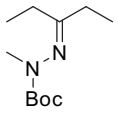
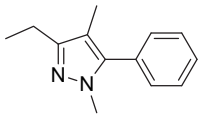
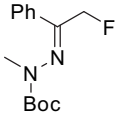
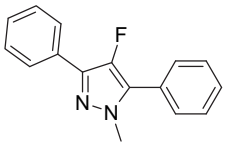
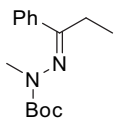
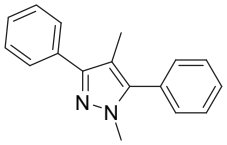


Scheme 5. Regioselective synthesis of fully substituted pyrazole systems **10**.

We were glad to find that reacting the anion derived from hydrazones **8**[12] with methyl benzoate, cleanly afforded the corresponding ketoimines **9**.[14] In this case, we do not observe the formation of by-products. The corresponding substituted 1*H*-pyrazol-5(4*H*)-ones **11**, that would arise from an intermolecular cyclization of ketoimines **9**, similar to that reported in Scheme 3, were never observed. Ketoimines **9** were cleanly converted by treatment with TFA into the corresponding fully substituted pyrazoles **10** and where regioisomeric products are possible, only one was obtained.

Table 5 shows the results obtained and the tolerance of this methodology to different substituents. In fact, it allows the synthesis of pyrazoles with fused rings, with fluorine atoms, alkyl and aromatic groups.

Table 5
Results of the regioselective synthesis of fully substituted pyrazole systems **10** (Scheme 5)

Entry	Hydrazone **8**	Pyrazole **10**	Overall yield[a] (%)
a			89
b			69
c			74
d			79

[a] Overall isolated yields over the two steps depicted in Scheme 5.

3. Conclusions

In conclusion, we have presented a methodology for the regioselective preparation of 1-methyl-3,5-disubstituted-1*H*-pyrazoles **6**. This is achieved by a reaction through the anion of hydrazones **2** with an acylating agent **3**, followed by TFA treatment of the ketoimine **4** obtained. The choice of the appropriate acylating agent

is critical. While methyl benzoate often affords hydroxypyrazoles **5** as the major or only product, Weinreb amides, anhydrides, and acyl chlorides offer higher ketoimine yields, with acyl chlorides being the reagents of choice since they gave no by-product in all the cases.

The procedure is also amenable to be controlled and by the appropriate choice of the reactant substituents either of the two regioisomers of a given 1-methyl-3,5-disubstituted-1*H*-pyrazole could be obtained in good overall yields.

Finally, the methodology was also extended to obtain the fully substituted pyrazole systems **10** incorporating a wide range of substituents.

4. Experimental section

All hydrazones were prepared from commercially available ketones according to Refs. 11 or 12. The fluoromethyl phenyl ketone necessary to obtain hydrazone **8c** was prepared according to a literature method.[17]

All moisture-sensitive reactions were performed in an inert, dry atmosphere of argon or nitrogen in oven-dried glassware. Reagent grade solvents were used for chromatographies and extractions. THF was distilled from Na/benzophenone under argon; CH_2Cl_2, was distilled from CaH_2 under argon. Analytical thin-layer chromatography (TLC) was performed using Merck precoated TLC plates (Silica gel 60 GF_{254} 0.25 mm). Flash chromatography was performed using Merck Silica gel 60 (230–400 mesh). The solvent compositions reported for all separations are on a volume/volume basis. Gas chromatography (GC) was performed using a Hewlett Packard HP6890 or an Agilent 6850 instruments using an Agilent 19091Z-413E, HP-1 Methyl siloxane column, 30 m×320 μm×0.25 μm.

High performance liquid chromatography (HPLC) was performed using an Agilent 1100 instrument equipped with a C18 Hypersil column (25×4.6 cm), eluent 40% channel A (ACN); 60% channel B (ACN/water 1:1); 1 ml/min; UV 254 nm; *T* 25 °C.

^{1}H NMR spectra were recorded at 300, 400 or 600 MHz at 25 °C with either tetramethylsilane (δ 0.00) or chloroform (δ 7.26) as the internal standard. ^{13}C NMR spectra were recorded at 75, 100 or 150 MHz at 25 °C with $CDCl_3$ (δ 77.0) as the internal standard. Carbon assignments were based on DEPT and/or HMQC experiments. ^{19}F NMR spectra were recorded at 376 MHz at 25 °C using hexafluorobenzene as external standard (δ −163.5 ppm). Melting points were determined through a Büchi instrument.

Mass spectra were obtained with positive electron spray ionization on Waters Micromass ZQ4000 instrument. High resolution mass spectra for new pyrazoles products were obtained by electronic impact on a Thermo Finnigan MAT95XP instrument.

4.1. General procedure for the synthesis of ketoimines 4 and 9

A solution of LiHDMS (1 M in THF; 2.4 equiv) was added, under a nitrogen atmosphere, to a stirred solution of the hydrazone (2 mmol) in dry THF (4 vol with respect to hydrazone weight) and stirred at 0 °C for 1 h. After this time the resulting solution was added via syringe to a solution of the acylating agent (1 mmol) in dry THF (8 vol), under N_2, at 0 °C. The reaction progress was monitored by HPLC analysis and the mixture was stirred at 0 °C for the indicated time. The reaction was quenched with water (10 vol) and extracted with ethyl acetate (3×5 vol). The organic phase was dried and evaporated. The crude product was purified by FC eluting with a mixture of cyclohexane/AcOEt to obtain the desired compound.

*4.1.1. tert-Butyl 1-methyl-2-(3-oxo-1,3-diphenylpropylidene)hydrazinecarboxylate (**4a**).* Hydrazone **2a** and methyl benzoate: 1 h at 0 °C, 42 mg of **4a** (yield 12%) and 125 mg of **5a** (yield 45%). Hydrazone **2a** and benzoyl chloride 20 min, at −10 °C, 243 mg of **4a** (yield 69%); Hydrazone **2a** and benzoic anhydride: 1 h, 0 °C, 53 mg of **4a** (yield 15%) and 139 mg of **5a** (yield 50%). Hydrazone **2a** and benzoic acid Weinreb's amide: 30 min, 0 °C, 275 mg of **4a** (yield 78%). The crude was purified by FC with Cyclohexane/ethyl acetate 9:1. The compound was obtained as a yellow oil.

Compound **4a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.37 (s, 9H), 3.02 (s, 3H), 5.97 (s, 1H), 7.45 (m, 8H), 7.92 (m, 2H), 11.8 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.1 (CH_3), 38.6 (CH_3), 81.4 (C), 95.6 (CH), 127.4 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 129.8 (CH), 131.4 (CH), 134.8 (C), 139.4 (C), 155.2 (C), 166.9 (C), 190.1 (C).

Compound **5a**: The compound was obtained as a brownish foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.50 (br s, 3H), 6.92 (br m, 11H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 31.2 (CH_3), 103.2 (C), 127.0 (CH), 127.4 (CH), 128.8 (CH), 129.0 (CH), 130.6 (CH), 133.9 (CH), 138.4 (C), 151.5 (C), 165.1 (C), 191.2 (CH).

*4.1.2. tert-Butyl 1-methyl-2-(3-oxo-3-phenyl-1-o-tolylpropylidene) hydrazinecarboxylate (**4b**).* From hydrazone **2b** and methyl benzoate: 10 min, at 0 °C. The crude was purified by FC with cyclohexane/ethyl acetate 9:1. The compound was obtained as a yellow oil (293 mg; yield 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (s, 9H), 2.22 (s, 3H), 3.19 (s, 3H), 5.82 (s, 1H), 7.25 (m, 4H), 7.89 (m, 3H), 7.89 (m, 2H), 11.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.4 (CH_3), 28.8 (CH_3), 38.5 (CH_3), 82.6 (C), 96.7 (CH), 127.6 (CH), 127.7 (CH), 128.2 (CH), 128.4 (CH), 130.0 (CH), 131.4 (CH), 131.9 (CH), 134.8 (C), 139.6 (C), 155.4 (C), 167.0 (C), 190.7 (C).

*4.1.3. tert-Butyl 1-methyl-2-(3-oxo-3-phenyl-1-(pyridin-2-yl)propylidene)hydrazinecarboxylate (**4c**).* From hydrazone **2c** and methyl benzoate: 15 h at rt, 168 mg of **5c** (yield 60%). From hydrazone **2c** and benzoyl chloride: 30 min, −10 °C, 246 mg of **4c** (yield 70%). The crude was purified by FC with Cyclohexane/ethyl acetate from 95:5 to 70:30. The compound was obtained as a brown oil.

Compound **4c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (s, 9H), 3.14 (s, 3H), 6.16 (s, 1H), 7.34 (m, 1H), 7.44 (m, 2H), 7.58 (m, 1H), 7.74 (m, 1H), 7.95 (m, 2H), 8.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.0 (CH_3), 37.5 (CH_3), 81.4 (C), 96.0 (CH), 123.2 (CH), 124.2 (CH), 127.4 (CH), 128.2 (CH), 131.4 (CH), 136.1 (C), 139.2 (CH), 148.9 (CH), 150.7 (C), 155.0 (C), 164.34 (C), 190.5 (C).

Compound **5c**: The compound was obtained as brown foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.80 (s, 3H), 7.19 (m, 1H), 7.45 (m, 5H), 7.71 (m, 1H), 7.95 (m, 1H), 8.68 (m, 1H), 9.86 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.2 (CH_3), 107.3 (C), 122.5 (CH), 123.8 (CH), 128.4 (CH), 129.8 (CH), 132.2 (CH), 136.2 (CH), 137.8 (C), 145.6 (CH), 148.9 (C), 153.3 (C), 167.1 (C), 190.2 (C).

*4.1.4. tert-Butyl 1-methyl-2-(4-oxo-4-phenylbutan-2-ylidene)hydrazinecarboxylate (**4e**).* From hydrazone **2e** (2 mmol) and methyl benzoate (1 mmol): 1 h, 0 °C. The crude was purified by FC with cyclohexane/ethyl acetate from 95:5 to 90:10. The compound was obtained as a yellow oil (232 mg; yield 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40 (s, 9H), 2.26 (s, 3H), 3.22 (s, 3H), 5.97 (s, 2H), 7.38 (m, 3H), 7.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1 (CH_3), 28.1 (CH_3), 34.9 (CH_3), 36.6 (CH_2) 83.0 (C), 128.6 (CH), 129.1 (CH), 132.6 (CH), 137.1 (C), 150.3 (C), 155.2 (C), 190.1 (C).

*4.1.5. tert-Butyl 2-(4,4-dimethyl-1-oxo-1-phenylpentan-3-ylid-ene)-1-methylhydrazinecarboxylate (**4f**).* From hydrazone **2f** and methyl benzoate: 30 min at 0 °C, 170 mg of **5f** (yield 66%). From hydrazone **2f** and benzoyl chloride: 10 min at −10 °C, 233 mg of **4f** (yield 70%). From hydrazone **2f** and benzoic anhydride: 30 min, 0 °C, 50 mg of **4f** (yield 15%). The crude product was purified by FC with cyclohexane/ethyl acetate from 95:5 to 90:10.

Compound **4f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26 (s, 9H), 1.31 (s, 9H), 2.78 (s, 3H), 3.94 (s, 2H), 7.46 (m, 2H), 7.57 (m, 1H), 7.89 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.2 (CH_3), 28.1 (CH3), 35.8 (CH_3),

37.9 (CH2), 38.9 (C), 80.2 (C), 127.6 (CH), 128.5 (CH), 132.9 (CH), 137.0 (C), 156.0 (C), 136.1 (C), 181.6 (C), 194.1 (C).

Compound **5f**: The compound was obtained as a white solid (66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.14 (s, 9H), 3.56 (s, 3H), 7.49 (m, 5H), 9.34 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.3 (CH_3), 32.5 (C), 34.0 (CH_3) 102.6 (C), 127.7 (CH), 128.4 (CH), 130.1 (CH), 140.6 (C), 158.7 (C), 159.6 (C), 193.6 (C).

*4.1.6. tert-Butyl 1-methyl-2-(3-oxo-1-phenyl-3-o-tolylprop-1-enyl) hydrazinecarboxylate (**4g**).* From hydrazone **2a** and 2-methylbenzoyl chloride: 10 min, at −10 °C, The crude was purified by FC with cyclohexane/ethyl acetate 9:1. The compound was obtained as yellow oil (293 mg; yield 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36 (s, 9H), 2.52 (s, 3H), 3.05 (s, 3H), 5.62 (s, 1H), 7.31 (m, 9H), 11.70 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.5 (CH_3), 28.1 (CH_3), 38.8 (CH_3), 81.1 (C), 99.2 (CH), 125.4 (CH), 127.5 (CH), 127.7 (CH), 128.1 (CH), 129.6 (CH), 129.8 (CH), 131.1 (CH), 134.5 (C), 136.0 (C), 141.0 (C), 155.1 (C), 166.4 (C), 195.0 (C).

*4.1.7. tert-Butyl 2-(4,4-dimethyl-3-oxo-1-phenylpentylidene)-1-methylhydrazinecarboxylate (**4h**).* From hydrazone **2a** and pivaloyl chloride: 20 min, at −10 °C. The crude was purified by FC with cyclohexane/ethyl acetate from 95:5 to 90:10. The compound was obtained as a yellow oil (226 mg; 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.15 (s, 9H), 1.61 (s, 9H), 3.30 (s, 3H), 3.72 (s, 2H), 7.48 (m, 3H), 7.71 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.8 (CH_3), 29.3 (CH_3), 36.6 (CH_3), 41.9 (CH_2), 44.2 (C), 84.4 (C), 127.4 (CH), 128.4 (CH), 130.2 (CH), 136.1 (C), 146.2 (C), 154.6 (C), 198.6 (C).

*4.1.8. tert-Butyl 2-(2-benzoylcyclohexylidene)-1-methylhydrazinecarboxylate (**9a**).* From Hydrazone **8a** and methyl benzoate: 20 min, at −0 °C. The crude was purified by FC with cyclohexane/ethyl acetate from 95:5 to 85:15. The compound was obtained as a yellow oil (281 mg; 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.46 (s, 9H), 1.52 (m, 2H), 1.68 (m, 2H), 2.25 (t, 2H, J=6.4 Hz), 2.40 (t, 2H, J=6.4 Hz), 3.17 (s, 3H), 7.36 (m, 5H), 12.12 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.4 (CH_2), 23.1 (CH_2), 24.7 (CH_2), 27.5 (CH_2), 28.1 (CH_3) 38.5 (CH_3), 81.1 (C), 101.9 (C), 126.4 (CH), 127.7 (CH), 128.7 (CH), 132.7 (C), 142.3 (C), 155.3 (C), 163.7 (C), 196.7 (C).

*4.1.9. tert-Butyl 1-methyl-2-(2-methyl-1-oxo-1-phenylpentan-3-ylidene)hydrazinecarboxylate (**9b**).* From hydrazone **8b** and methyl benzoate: 20 min, at −0 °C. The crude was purified by FC with cyclohexane/ethyl acetate from 95:5 to 85:15. The compound was obtained as a yellow oil (255 mg; 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.01 (t, 3H, J=8.08 Hz) 1.46 (s, 9H), 1.87 (s, 3H), 3.07 (s, 3H), 7.48 (m, 5H), 12.51 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.4 (CH_3) 11.0 (CH_3), 23.3 (CH_2), 29.5 (CH_3) 38.4 (CH_3), 82.3 (C), 101.4 (C), 127.2 (CH), 128.0 (CH), 128.9 (CH), 132.9 (C), 140.2 (C), 156.1 (C), 163.0 (C), 197.1 (C).

*4.1.10. tert-Butyl 2-(2-fluoro-3-oxo-1,3-diphenylpropylidene)-1-methylhydrazinecarboxylate (**9c**).* From hydrazone **8c** and methyl benzoate: 40 min, at 0 °C, (282 mg; yield 76%). The crude product was purified by FC with cyclohexane/ethyl acetate from 95:5 to 90:10. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.39 (s, 9H), 2.96 (s, 3H), 7.45 (m, 8H), 7.92 (m, 2H), 10.56 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.0 (CH_3), 38.8 (CH_3), 81.2 (C), 128.0 (CH), 128.7–128.7 (CH), 128.8 (CH), 129.5 (CH), 129.8 (CH), 131.8 (CH), 137.1–137.2 (C), 138.2 (C), 140.5 (C), 152.7–152.9 (C), 155.3 (C), 186.9–187.2 (C).

*4.1.11. tert-Butyl 1-methyl-2-(2-methyl-3-oxo-1,3-diphenylpropylidene)hydrazinecarboxylate (**9d**).* From hydrazone **8d** (2 mmol) and methyl benzoate (1 mmol): 10 min, at 0 °C. The crude was purified by FC with cyclohexane/ethyl acetate from 95:5 to 90:10. The compound was obtained as a yellow oil (286 mg; yield 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 9H), 2.01 (s, 3H), 3.15 (s, 3H), 7.55 (m, 8H), 7.91 (m, 2H), 11.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.4 (s, CH_3), 28.3 (CH_3), 38.9 (CH_3), 81.5 (C), 108.2 (C), (CH), 127.4 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 129.8 (CH), 131.4 (CH), 134.8 (C), 139.4 (C), 155.2 (C), 165.2 (C), 189.2 (C).

4.2. General procedure for the synthesis of substituted pyrazoles 6 and 10

A solution of the ketoimine intermediate (**4** or **9**; 0.3 mmol) in dry DCM (0.4 ml) was added dropwise to TFA (0.8 ml) at rt. The reaction mixture was stirred at rt for 1 h and then evaporated. The residue was dissolved in DCM and NaOH 1 N was added until a basic pH. The organic layer was separated and the aqueous layer was further extracted with DCM (3×2 ml). The combined organic phases were dried over $MgSO_4$ and evaporated under vacuum to obtain the desired pyrazole as a single regioisomer.

*4.2.1. 1-Methyl-3,5-diphenyl-1H-pyrazole (**6a**)*[18]. The title compound was obtained as an off-white solid (69 mg; 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.94 (s, 3H), 6.62 (s, 1H), 7.41 (m, 8H), 7.83 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.5 (CH_3), 103.4 (CH), 125.5 (CH), 127.7 (C), 128.0 (CH), 128.6 (CH), 128.7 (CH), 128.7 (CH), 128.9 (CH), 129.8 (C), 130.5 (C), 133.2 (C), 145.1 (C), 150.4 (C). Mp 54–57 °C (lit.[18] 58–60 °C). IR (Nujol): 1590, 689 cm^{-1}. MS: (ESI$^+$, m/z): 235 (M+H)$^+$; 257 (M+Na)$^+$.

*4.2.2. 1-Methyl-5-phenyl-3-o-tolyl-1H-pyrazole (**6b**).* The title compound was obtained in quantitative yield (74 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.53 (s, 3H), 3.94 (s, 3H), 6.47 (s, 1H), 7.24 (m, 3H), 7.44 (m, 5H), 7.62 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.3 (CH_3), 37.5 (CH_3), 106.4 (CH), 125.7 (CH), 127.5 (C), 128.3 (CH), 128.6 (CH), 128.7 (CH), 129.1 (CH), 130.6 (CH), 132.2 (C), 135.8 (C), 144.0 (C), 150.7 (C). MS: (ESI$^+$, m/z): 249 (M+H)$^+$; 271 (M+Na)$^+$. HRMS (EI): calcd for $C_{17}H_{16}N_2$: 248.13135; found: 248.13140 (+0.2 ppm).

*4.2.3. 2-(1-Methyl-5-phenyl-1H-pyrazol-3-yl)pyridine (**6c**).* The title compound was obtained in 70% overall (49 mg) yield from hydrazine **2c**. ^{1}H NMR ($CDCl_3$) δ: 3.95 (s, 3H), 6.94 (s, 1H), 7.19 (m, 1H), 7.45 (m, 5H), 7.71 (m, 1H), 7.95 (m, 1H), 8.68 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 37.4 (CH_3), 112.0 (CH), 118.8 (CH), 122.3 (CH), 127.8 (CH), 128.6 (CH), 131.3 (C), 135.4 (CH), 144.2 (C), 148.2 (CH), 151.0 (C), 153.0 (C). MS: (ESI$^+$, m/z): 236 (M+H)$^+$; 258 (M+Na)$^+$. HRMS (EI): calcd for $C_{15}H_{13}N_3$: 235.11095; found: 235.11105 (+0.4 ppm).

*4.2.4. 1,3-Dimethyl-5-phenyl-1H-pyrazole (**6e**).* The title compound was obtained in quantitative yield (52 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 3.83 (3H), 6.10 (s, 1H), 7.45 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.3 (CH_3), 37.1 (CH_3), 105.6 (CH), 128.3 (CH), 128.6 (CH), 130.7 (C), 144.6 (C), 147.5 (C). MS: (ES$^+$, m/z): 173 (M+H)$^+$; 195 (M+Na)$^+$.

*4.2.5. 3-tert-Butyl-1-methyl-5-phenyl-1H-pyrazole (**6f**)*[8]. The title compound was obtained in 95% yield (61 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 3H), 3.84 (s, 3H), 6.16 (s, 1H), 7.42 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.7 (CH3), 32.0 (C), 37.2 (CH_3), 102.4 (CH), 126.9 (C), 128.1 (CH), 128.5 (CH), 128.6 (CH), 131.1 (C), 143.9 (C), 161.1 (C). MS: (ESI$^+$, m/z): 215 (M+H)$^+$; 237 (M+Na)$^+$. IR (neat): 1591, 1498, 779, 701 cm^{-1}.

*4.2.6. 1-Methyl-3-phenyl-5-o-tolyl-1H-pyrazole (**6g**).* The title compound was obtained in quantitative yield (75 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.23 (s, 3H), 3.69 (s, 3H), 6.51 (s, 1H), 7.33 (m, 7H), 7.84 (m, 2H), 7.62 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.8 (CH_3), 23.6 (CH_3), 103.6 (CH), 125.4 (CH), 125.7 (C), 127.5 (CH), 128.5 (CH), 129.1 (CH), 130.2 (CH), 130.2 (CH), 133.4 (C), 137.4 (C), 143.9

(C), 150.3 (C). MS: (ESI$^+$, *m*/*z*): 249 (M+H)$^+$; 271 (M+Na)$^+$. HRMS (EI): calcd for $C_{17}H_{16}N_2$: 248.13135; found: 248.13128 (−0.3 ppm).

*4.2.7. 5-tert-Butyl-1-methyl-3-phenyl-1H-pyrazole (**6h**).* The title compound was obtained in quantitative yield (64 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.41 (s, 9H), 4.00 (s, 1H), 6.33 (s, 1H), 7.35 (m, 4H), 7.94 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.6 (CH_3), 31.1 (C), 39.4 (CH_3), 100.9 (CH), 125.2 (CH), 127.0 (CH), 128.4 (CH), 133.5 (C), 148.9 (C), 152.4 (C). MS: (ESI$^+$, *m*/*z*): 215 (M+H)$^+$; 237 (M+Na)$^+$. HRMS (EI): calcd for $C_{14}H_{18}N_2$: 214.14700; found: 214.14686 (−0.6 ppm).

*4.2.8. 2-Methyl-3-phenyl-4,5,6,7-tetrahydro-2H-indazole (**10a**)*[19]. The title compound was obtained in quantitative yield (64 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.78 (m, 4H), 2.48 (t, 2H, *J*=6.44 Hz), 2.72 (t, 2H, *J*=6.42 Hz), 3.79 (s, 3H), 7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.1 (CH_2), 23.3 (CH_2), 23.4 (CH_2), 23.5 (CH_2), 37.1 (CH_3), 114.6 (C), 127.9 (CH), 128.5 (CH), 129.0 (CH), 130.7 (C), 139.4 (C), 148.1 (C). IR (neat) 3052, 1669, 1485, 749, 698 cm^{-1}. MS: (ESI$^+$, *m*/*z*): 213 (M+H)$^+$; 235 (M+Na)$^+$. HRMS (EI): calcd for $C_{14}H_{16}N_2$: 212.13135; found: 212.13127 (−0.4 ppm).

*4.2.9. 3-Ethyl-1,4-dimethyl-5-phenyl-1H-pyrazole (**10b**).* The title compound was obtained in quantitative yield (60 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (t, 3H, *J*=7.74 Hz), 1.95 (s, 3H), 2.64 (q, 2H, *J*=7.72−15.34 Hz), 3.71 (s, 3H), 7.30 (m, 2H), 7.42 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.3 (CH_3), 13.5 (CH_3), 20.0 (CH_2), 36.6 (CH_3), 111.7 (C), 128.0 (CH), 128.5 (CH), 129.6 (CH), 130.8 (C), 141.3 (C), 151.7 (C). MS: (ESI$^+$, *m*/*z*): 201 (M+H)$^+$; 223 (M+Na)$^+$. HRMS (EI): calcd for $C_{13}H_{16}N_2$: 200.13135; found: 200.13144 (+0.5 ppm).

*4.2.10. 4-Fluoro-1-methyl-3,5-diphenyl-1H-pyrazole (**10c**).* The title compound was obtained in quantitative yield (76 mg). ^{1}H NMR (400 MHz, CDCl3) δ: 3.88 (s, 3H), 7.48 (m, 8H), 7.90 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 38.5 (CH_3), 125.8 (CH), 127.3 (C), 127.7 (CH), 128.6 (CH), 128.9 (CH), 129.8 (C), 131.1 (C), 134.5 (C), 144.3 (C). ^{19}F NMR (376 MHz, CDCl3) δ: −174.6. MS: (ESI$^+$, *m*/*z*): 253 (M+H)$^+$; 275 (M+Na)$^+$. HRMS (EI): calcd for $C_{16}H_{13}FN_2$: 252.10628; found: 252.10633 (+0.2 ppm).

*4.2.11. 1,4-Dimethyl-3,5-diphenyl-1H-pyrazole (**10d**)*[20]. The title compound was obtained in quantitative yield as a yellowish solid (74 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.15 (s, 3H), 3.87 (s, 3H), 7.41 (m, 8H), 7.72 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.9 (CH_3), 37.2 (CH_3), 112.0 (C), 127.2 (CH), 127.6 (CH), 128.4 (CH), 128.4 (CH), 128.6 (CH), 129.8 (CH), 130.4 (C), 134.1 (C), 142.5 (C), 149.2 (C). Mp 110−112 °C (lit.[20] 112.5−116 °C). MS: (ESI$^+$, *m*/*z*): 249 (M+H)$^+$; 271 (M+Na)$^+$.

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Supplementary data

Actual ^{1}H, ^{13}C, and ^{19}F NMR spectra of pyrazoles **6** and **10**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.11.057. These data include MOL files and InChIKeys of the most important compounds described in this article.

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12. All hydrazones 2 and 8 were obtained by condensation of commercially available 1-(*tert*-butyloxycarbonyl)-1-methylhydrazine and the corresponding ketone.
13. A general preparation of N-BOC-N-substituted hydrazones is reported: Meyer, K. G. *Synlett* **2004**, 2355 Some of these hydrazones were tested and gave very similar results to those obtained with 1-BOC-1-methylhydrazones.
14. Most of the ketoimine products were isolated as the corresponding enaminones. See Supporting data for details.
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