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ORIGINAL PAPER

Evaluation of the synthesis of 1-(pentafluorophenyl)-4,5-dihydro-1*H*-pyrazoles using green metrics

Marcos A. P. Martins · Paulo H. Beck · Lilian Buriol · Clarissa P. Frizzo · Dayse N. Moreira · Mara R. B. Marzari · Marcileia Zanatta · Pablo Machado · Nilo Zanatta · Helio G. Bonacorso

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Abstract 1-(Pentafluorophenyl)-4,5-dihydro-1*H*-pyrazoles were synthesized from the cyclocondensation reactions of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones ($CX_3C(O)CH=C(R^1)OR$, where X = F, Cl; R = Me, Et; R^1 = H, Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Pent, Ph, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4) with pentafluorophenyl hydrazine. Pyrazoles were obtained under microwave irradiation in solvent-free conditions or under conventional heating in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate, [BMIM][BF_4]. These procedures furnished products in moderate to good yields in a short reaction time. Atom economy, reaction mass efficiency (RME), and environmental factor (E-factor) were determined for the cyclocondensation reaction performed under microwave (MW)/solvent-free and under conventional thermal heating/[BMIM][BF_4] conditions. RME and E-factor indicated that the solvent-free procedure is invariably less green than [BMIM][BF_4] when the isolated product was considered.

Keywords Pyrazoles · Atom economy · Reaction mass efficiency · E-factor · Green chemistry

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M. A. P. Martins · P. H. Beck · L. Buriol · C. P. Frizzo (✉) · D. N. Moreira · M. R. B. Marzari · M. Zanatta · P. Machado · N. Zanatta · H. G. Bonacorso
Núcleo de Química de Heterociclos (NUQUIMHE), Departament of Chemistry, Federal University of Santa Maria, Santa Maria, RS 97105-900, Brazil
e-mail: clarissa.frizzo@yahoo.com.br

M. A. P. Martins
e-mail: mmartins@base.ufsm.br

Introduction

Efforts to minimize the environmental impacts of a synthetic process should commence in the earliest stage of the product/process development. Some tools have been developed to support less aggressive processes [1–10], such as selecting solvents taking into account environmental, health, and safety aspects as well as the life cycle assessment (LCA) and economic criteria. Kralisch et al. [11, 12] evaluated and optimized an approach considering ecological and economic aspects of the production of some reactants and solvents used in synthesis, workup, recycling, and disposal. To evaluate the greenness of a product or process the authors used three main criteria: energy factor (EF), environmental and human health factor (EHF), and cost factor (CF). Such criteria describe the energy demand, toxicity, and the cost of chemicals, auxiliaries, and equipment used during a product or process of life cycle stages. There are some other metrics which can also be used such as atom economy (AE) [13, 14], reaction mass efficiency (RME) [15], environmental factor (E-factor) [16–19], effective mass yield [20], mass intensity [21], and the process profile [22].

For about 20 years, our research group has been working with cyclocondensation reactions to obtain useful heterocyclic compounds from inexpensive starting materials and clean methodologies [23–29] and recently we published two reviews in the field [30, 31]. Thus, the aim of this study was to determine the AE, RME, and E-factor of the synthesis of 3-alkyl(aryl)-1-(pentafluorophenyl)-5-(trihalomethyl)-4,5-dihydro-5-hydroxy-1*H*-pyrazoles through a cyclocondensation reaction of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones with pentafluorophenyl hydrazine in solvent-free conditions under microwave irradiation and in ionic liquid under conventional thermal heating conditions.

Results and discussion

Reaction and conditions

Pyrazoles are the main or secondary parts of important drugs such as rimonabant [32] and celecoxib [33, 34]. Cyclocondensation is the most common, rapid, and simple method to synthesize pyrazoles. This reaction is particularly useful in medicinal chemistry when associated with microwave (MW) assisted organic synthesis and/or use of solvents that accelerate the reaction, such as ionic liquids. There are several reports related to cyclocondensation reactions using ionic liquid [30] or MW irradiation in solvent-free conditions [31], whose process is considered green in qualitative terms.

In this study, 1-(pentafluorophenyl)-4,5-dihydro-1*H*-pyrazoles **4**, **5** were synthesized from the cyclocondensation reaction of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones **1**, **2** with pentafluorophenyl hydrazine **3**. A series of novel 3-alkyl(aryl)-1-(pentafluorophenyl)-5-(trihalomethyl)-4,5-dihydro-1*H*-pyrazol-5-ols (**4a–4e**, **4h**, **4j**, **4k**, **5a–5g**, **5i–5k**) were synthesized under MW irradiation in solvent-free conditions (Scheme 1). In addition, a series of 3-alkyl (aryl)-1-(pentafluorophenyl)-5-(trihalomethyl)-4,5-dihydro-1*H*-pyrazol-5-ols (**4b–4d**, **4f**, **4j–4m**) were synthesized under conventional thermal heating in ionic liquid [BMIM] [BF_4] conditions (Scheme 2).

Atom economy and reaction mass efficiency

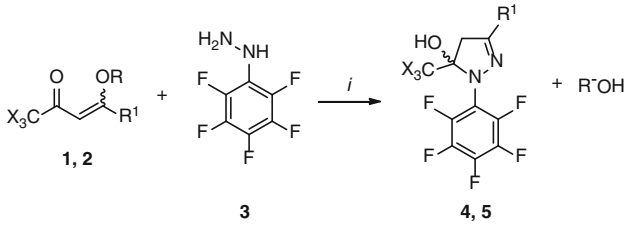
Atom economy is a calculation of how much of the reactant remains in the desired product regardless of the steps to obtain it. The method to calculate AE ignores the reaction yield as well as the use of solvents, auxiliaries, and molar excesses of reactants. Thus, AE is the ratio of the molecular weight of the target molecule to the sum total of the molecular weights of all substances produced in the stoichiometric equation for the reaction involved [15]. An ideal reaction has an AE of 100 %. For most reactions, a 100 % economy can never be reached owing to the nature of the reaction. On the other hand, RME takes into account yields, the actual molar quantities of reactants, and the concepts of AE. In other words, RME is the percentage of the mass of the reactants that remains in the product [15]. In this work, AE and RME for the cyclocondensation reactions were calculated by Eqs. (1) and (2), respectively [15].

$$\mathrm{AE} = \left(\frac{\mathrm{mw_P}}{\mathrm{mw_{R1}} + \mathrm{mw_{R2}}}\right) \times 100 \qquad (1)$$

$$\mathrm{RME} = \left(\frac{\text{mass of P(g)}}{\text{mass of R1(g)} + \text{ mass of R2(g)}}\right) \times 100 \qquad (2)$$

In Eq. (1), $\mathrm{mw_P}$ is the molecular weight of product P, $\mathrm{mw_{R1}}$ is the molecular weight of reactant R1, and $\mathrm{mw_{R2}}$ is the molecular weight of reactant R2. In Eq. (2), mass of P is the mass of product isolated, and mass R1 and mass of R2 are the mass of reactants R1 and R2, respectively, input to obtain mass of P.

Scheme 1



i: Solvent-free, MW, 100 °C, 6 min

Entry	X	R	R^1	Product	Yield (%)[a]
1	F	Et	H	**4a**	90
2	F	Me	Me	**4b**	94
3	F	Me	Et	**4c**	92
4	F	Me	Pr	**4d**	85
5	F	Me	*i*-Pr	**4e**	78
6	F	Me	Ph	**4h**	80
7	F	Me	4-Br-C_6H_4	**4j**	83
8	F	Me	4-F-C_6H_4	**4k**	75
9	Cl	Et	H	**5a**	88
10	Cl	Me	Me	**5b**	85
11	Cl	Me	Et	**5c**	93
12	Cl	Me	Pr	**5d**	94
13	Cl	Me	*i*-Pr	**5e**	90
14	Cl	Me	Bu	**5f**	73
15	Cl	Me	*i*-Pent	**5g**	80
16	Cl	Me	4-Cl-C_6H_4	**5i**	89
17	Cl	Me	4-Br-C_6H_4	**5j**	90
18	Cl	Me	4-F-C_6H_4	**5k**	78

[a]Isolated product

AE and RME were computed for some products in both solvent-free/MW and [BMIM][BF_4]/conventional thermal heating methods (Table 1). In all cases, AE is less than 100 % owing to the formation of ROH (R = Me, Et) as a by-product. In addition, since the product is formed in only one step, this synthesis is efficient in maintaining the reagent atoms in the product. There is a small variation in the AE for different products because the by product formed was methanol in all cases studied (Table 1). As expected, RME calculation, which provides a more realistic assessment of the synthetic procedures, takes into account the yield of reaction and molar excess of pentafluorophenyl hydrazine (20 %) required for the total conversion of the

products. Because RME accounts for all reactant mass (i.e., actual stoichiometric quantities used), yield, and AE, the combined metric AE/RME is probably the most helpful metric for chemists to focus attention on how far from 'green' the current processes are being operated [15]. From the results in Table 1, it is possible to rationalize that although the reaction occurs with good AE, the poor yields of the products in [BMIM][BF_4]/conventional thermal heating conditions contributed to lower RME.

E-factor

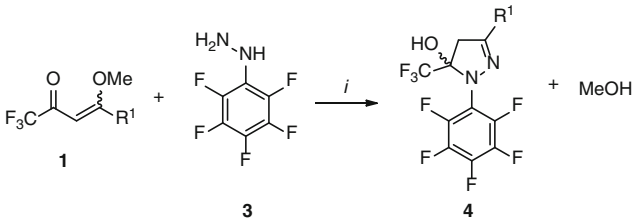
The E-factor is the ratio of generated waste weight and end product total weight. It is a useful tool for the evaluation of rapid processes and is based on generated waste [16–19]. The E-factor may be obtained for (1) the synthesis step (SYS); (2) for the synthesis and product isolation steps (SYS + PIS); and (3) for the synthesis and workup steps (SYS + PIS + PPS) (Fig. 1) [31].

For each case in this study, E-factors were calculated on the basis of the amount of reactant and the volume of solvent used in the synthesis (SYS) and synthesis and isolation (SYS + PIS). For the synthesis under MW conditions, where purification was needed, E-factors were calculated for synthesis, isolation, and purification (SYS + PIS + PPS). The E-factor was calculated by Eq. (3). Ionic liquid and water are not computed in the E-factor because they can be recovered after the separation of the product [16–18]. The values of the E-factors for the reaction in solvent-free/MW and [BMIM][BF_4]/conventional thermal heating are shown in Table 2.

$$\mathrm{E-factor} = \frac{m_{\mathrm{reactants}} - m_{\mathrm{product}}}{m_{\mathrm{product}}} = \frac{m_{\mathrm{input\ materials}} - m_{\mathrm{product}}}{m_{\mathrm{product}}} \quad (3)$$

As expected, the best E-factor values were found in the reactions performed in solvent-free/MW conditions when the SYS step is considered in the calculation. When the product extraction solvent was computed, E-factor values increased dramatically. This increase reflects the huge amount of ethyl acetate and drying agent used in the extraction, despite the MW reaction being solvent-free. Products of the reaction in [BMIM][BF_4] were extracted with dichloromethane and a smaller amount of solvent was necessary. However, the E-factor values in relation to solvent-free/MW synthesis were similar. Note that dichloromethane and [BMIM][BF_4] are as toxic as ethyl acetate, but this fact is not considered in the E-factor. When considering the purification step (necessary only for the solvent-free reaction), the E-factor for the solvent-free/MW synthesis has higher values. The great amount of solvent used in the product extraction in both methods was more important than the yield in determining the E-factor values. Consequently, the inclusion of solvents and drying

Scheme 2



i: [BMIM][BF_4], 80 °C, 1h

Entry	R^1	Product	Yield (%)[a]
1	Me	**4b**	74
2	Et	**4c**	82
3	Pr	**4d**	56
4	Bu	**4f**	61
5	4-Br-C_6H_4	**4j**	72
6	4-F-C_6H_4	**4k**	43
7	*i*-Bu	**4l**	79
8	4-Me-C_6H_4	**4m**	58

[a]Isolated product

Table 1 AE and RME for solvent-free/MW and [BMIM][BF_4]/conventional thermal heating

Compound	Solvent-free/MW			[BMIM][BF_4]/conventional thermal heating	
	AE (%)	Yield (%)[a]	RME (%)	Yield (%)[a]	RME (%)
4b	91.3	94	77	74	61
4c	91.6	92	76	82	68
4d	91.9	85	71	56	47
4j	93.5	83	72	72	62
4k	92.8	75	64	43	37

[a] Isolated product

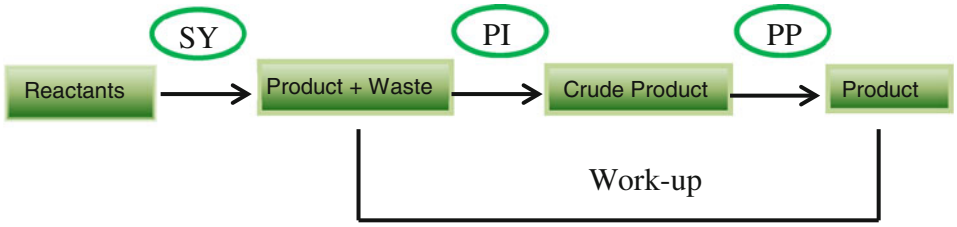


Fig. 1 Procedure to obtain products: synthesis step (SYS), product isolation steps (PIS), and product purification step (PPS)

Table 2 E-factor for the reaction in solvent-free/MW and [BMIM][BF_4]/conventional thermal heating

Compound	E-factor solvent-free/MW				E-factor [BMIM][BF_4]/conventional thermal heating		
	Yield (%)[a]	SYS	SYS + PIS	SYS + PIS + PPS	Yield (%)[a]	SYS	SYS + PIS
4b	94	0.29	124.8	250.6	74	0.64	84.3
4c	92	0.31	122.4	245.8	82	0.47	72.9
4d	85	0.41	127.4	255.8	56	1.14	103.1
4j	83	0.39	99.7	200.1	72	0.6	61.2
4k	75	0.56	126.4	253.6	43	1.73	117.8

[a] Isolated product

agent when computing the E-factor values give us an idea of the importance of this step in generating waste on the laboratory scale. In addition, these results show that when we take into account the isolated product, the solvent-free/MW procedure is invariably less green than [BMIM][BF_4]/conventional thermal heating.

Thus, we also observed that the solvent-free/MW method furnished higher values of RME, whereas higher E-factor values (considering isolated product) reflected the large amounts of waste produced. On the other hand, the reaction in the [BMIM][BF_4]/conventional thermal heating method furnished lower RME, whereas lower E-factor values reflected a lower waste production.

In summary, this study showed that AE is more useful to compare alternative routes to obtain the same products; however, it may also be useful as an organizing concept in combination with other metrics. RME and E-factor take into account the yield of reaction and the need for a molar excess. In particular, E-factor takes into account the solvent and drying agents (and other inputs) that are not computed in RME. In this work, RME and E-factor indicated that the solvent-free/MW method is invariably less green than the [BMIM][BF_4]/conventional thermal heating method when we consider the isolated product. Thus, RME and E-factor appear to be a useful metric to focus on deriving chemical procedures that may lead to more sustainable business practices.

Experimental

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 (^{1}H at 400.13 MHz and ^{13}C at 100.62 MHz) or Bruker DPX 200 (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz) in $CDCl_3$ or $(CD_3)C=O$/TMS solutions at 298 K. The general reproducibility of chemical shift data was estimated to be not greater than ±0.01 ppm. All spectra were acquired in a 5-mm tube, at natural abundance. *J* values are given in Hz. Mass spectra were registered on an HP 5973 MSD connected to an HP 6890 GC system and interfaced to a Pentium PC. The gas chromatograph was equipped with a split/split less injector, cross-linked to an HP-5 capillary column (30 m, 0.32 mm internal diameter), and helium was used as the carrier gas. The melting points were measured using a Microquímica MQAPF 301. The experiments were performed in an MW Discover CEM using the simultaneous cooling operation mode. The ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate, [BMIM][BF_4], was prepared according to procedures from the literature [23]. 4-Alkoxy-1,1,1-trihalo-3-alken-2-ones **1**, **2** were obtained from the acylation reaction of enol ether or acetal with trifluoroacetic anhydride or trichloroacetyl chloride in accordance with the methodology developed in our laboratory [29]. Pentafluorophenyl hydrazine was obtained commercially.

*Typical procedure for the synthesis of 4,5-dihydro-1H-pyrazoles **4**, **5** in solvent-free/MW conditions*

A mixture of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones **1**, **2** (1 mmol) and pentafluorophenyl hydrazine (1.2 mmol) was irradiated by a Discover CEM microwave for 6 min at 100 °C. Water (10 cm^3) was added to the reaction mixture

and products **4**, **5** were extracted with ethyl acetate (2×20 cm^3) and dried with 3.25 g $MgSO_4$ (27 mmol). The solvent was removed in a rotary evaporator and the product was obtained in high purity. When necessary, the product was recrystallized from cyclohexane (40 cm^3) or hexane (60 cm^3).

*Typical procedure for the synthesis of 4,5-dihydro-1H-pyrazoles **4** in [BMIM][BF$_4$]/conventional thermal heating*

A mixture of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones **1** (1 mmol), pentafluorophenyl hydrazine (1.2 mmol), and [BMIM][BF_4] (1 mmol) was stirred at 80 °C for 1 h. Products **4** were extracted with dichloromethane (10 cm^3), washed with water (3×10 cm^3), and dried with 7.40 g Na_2SO_4 (52 mmol). The solvent was removed in a rotary evaporator to afford the product in high purity and further purification was not necessary.

*1-(Pentafluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**4a**, $C_{10}H_4F_8N_2O$)*
Yield 90 %; oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.33$ (d, 1H, $^2J = 18$ Hz, H4a), 3.51 (d, 1H, $^2J = 18$ Hz, H4b), 7.16 (s, 1H, H3) ppm; ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta = 46.0$ (C4), 93.8 (q, $^2J = 31$ Hz, C5), 125.5 (q, $^1J = 282$ Hz, CF_3), 149.8, 147.3, 140.7, 140.8, 138.8, 150.0 (PhF_5), 147.3 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 320 (M^+, 35), 303 (1), 251 (100), 84 (5).

3-Methyl-1-(pentafluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**4b**, $C_{11}H_6F_8N_2O$)
Yield 94 % (MW), 74 % (conventional); m.p.: 130–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.04$ (s, 3H, H7), 3.21 (d, 1H, $^2J = 18$ Hz, H4a), 3.47 (d, 1H, $^2J = 18$ Hz, H4b) ppm; ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta = 16.3$ (C7), 48.2 (C4), 95.4 (q, $^2J = 31$ Hz, C5), 125.4 (q, $^1J = 282$ Hz, CF_3), 149.8, 147.3, 144.2, 141.6, 140.8, 138.2 (PhF_5), 152.9 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 334 (M^+, 30), 317 (10), 265 (100), 98 (1).

3-Ethyl-1-(pentafluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**4c**, $C_{12}H_8F_8N_2O$)
Yield 92 % (MW), 82 % (conventional); m.p.: 93–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.19$ (t, 3H, H8), 2.41 (q, 2H, H7), 3.24 (d, 1H, $^2J = 18$ Hz, H4a), 3.47 (d, 1H, $^2J = 18$ Hz, H4b) ppm; ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta = 11.9$ (CH_3), 24.7 (CH_2), 46.7 (C4), 95.2 (q, $^2J = 31$ Hz, C5), 125.5 (q, $^1J = 282$ Hz, CF_3), 149.9, 147.3, 144.1, 140.9, 140.8, 138.3 (PhF_5), 157.3 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 348 (M^+, 95), 331 (15), 279 (100), 181 (100), 112 (10).

1-(Pentafluorophenyl)-3-propyl-5-(trifluoromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**4d**, $C_{13}H_{10}F_8N_2O$)
Yield 85 % (MW), 56 % (conventional); m.p.: 103–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.98$ (t, 3H, H9), 1.63 (q, 2H, H8), 2.38 (t, 2H, H7), 3.25 (d, 1H, $^2J = 18$ Hz, H4a), 3.45 (d, 1H, $^2J = 18$ Hz, H4b) ppm; ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta = 14.9$ (CH_3), 21.2, 33.1 (CH_2), 46.9 (C4), 95.1 (q, $^2J = 31$ Hz, C5), 125.5 (q, $^1J = 282$ Hz, CF_3), 149.8, 147.3, 144.1, 140.7, 138.3, 119.5 (PhF_5), 156.2 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 362 (M^+, 25), 345 (1), 293 (100), 196 (15).

3-(1-Methylethyl)-1-(pentafluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**4e**, $C_{13}H_{10}F_8N_2O$)
Yield 78 %; m.p.: 120–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.19$ (d, 6H, H8), 2.69 (m, 1H, H7), 3.03 (d, 1H, $^2J = 18$ Hz, H4a), 3.37 (d, 1H, $^2J = 18$ Hz, H4b) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.7$ (CH_3), 19.9 (CH_3), 29.4 (CH), 43.7 (C4), 92.9 (q, $^2J = 31$ Hz, C5), 122.0 (q, $^1J = 282$ Hz, CF_3), 147.7, 145.2, 142.6, 140.1, 138.9, 136.4 (PhF_5), 158.8 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 362 (M^+, 90), 345 (1), 303 (10), 293 (100), 195 (15).

3-Butyl-1-(pentafluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**4f**, $C_{14}H_{12}F_8N_2O$)
Yield 61 %; oil; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.95$ (t, 3H, CH_3), 2.40 (st, 2H,CH_2), 2.60 (qui, 2H, CH_2), 3.04 (t, 2H, CH_2), 3.90 (d, 1H, $^2J = 19$ Hz, H4a), 4.41 (d, 1H, $^2J = 19$ Hz, H4b) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.6$ (CH_3), 22.2 (CH_2), 28.4 (CH_2), 29.4 (CH_2), 45.5 (C4), 92.4 (q, $^2J = 32$ Hz, C5), 122.7 (q, $^1J = 283$ Hz, CF_3), 149.1, 144.9, 140.1, 135.5 (PhF_5), 154.4 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 376 (M^+, 22), 317 (74), 307 (100), 181 (43).

1-(Pentafluorophenyl)-3-phenyl-5-(trifluoromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**4h**, $C_{16}H_8F_8N_2O$)
Yield 80 %; m.p.: 98–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.47$ (d, 1H, $^2J = 18$ Hz, H4a), 3.74 (d, 1H, $^2J = 18$ Hz, H4b), 7.38–7.41 (m, 3H, H–Ar), 7.59–7.62 (m, 2H, H–Ar) ppm; ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta = 44.5$ (C4), 95.7 (q, $^2J = 33$ Hz, C5), 125.2 (q, $^1J = 283$ Hz, CF_3), 128.1, 130.5, 131.6, 133.2 (C Ph), 119.1, 137.1, 142.0, 145.9, 150.9, 156.1 (PhF_5), 152.5 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 396 (M^+, 100), 379 (20), 327 (80), 141 (5).

3-(4-Bromophenyl)-1-(pentafluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**4j**, $C_{16}H_7BrF_8N_2O$)
Yield 83 % (MW), 72 % (conventional); m.p.: 143–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.76$ (d,

1H, $^2J = 18$ Hz, H4a), 3.87 (d, 1H, $^2J = 18$ Hz, H4b), 7.59 (d, 2H, H–Ar), 7.67 (d, 2H, H–Ar) ppm; ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta = 44.3$ (C4), 95.7 (q, $^2J = 33$ Hz, C5), 122.6 (q, $^1J = 283$ Hz, CF_3), 147.6, 145.1, 142.8, 140.7, 136.5, 132.0 (PhF_5), 140.3, 129.5, 127.4, 124.5 (PhBr), 151.5 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 476 (M + 2, 20), 474 (M^+, 70), 472 (30), 395 (10), 308 (10), 152 (10).

3-(4-Fluorophenyl)-1-(pentafluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**4k**, $C_{16}H_7F_9N_2O$)
Yield 75 % (MW), 43 % (conventional); m.p.: 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.69$ (d, 1H, $^2J = 18$ Hz, H4a), 4.09 (d, 1H, $^2J = 18$ Hz, H4b), 7.09 (dd, 2H, H–Ar), 7.64 (dd, 2H, H–Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 43.6$ (C4), 93.7 (q, $^2J = 32$ Hz, C5), 116.1 (d, $^2J = 23$ Hz, CAr), 122.6 (q, $^1J = 283$ Hz, CF_3), 126.8 (d, $^4J = 3$ Hz, C Ar), 128.0 (d, $^3J = 8$ Hz, CAr), 136.5, 139.0, 140.3, 142.8, 146.1, 147.7 (PhF_5), 148.9 (C3), 163.9 (d, $^1J = 251$ Hz, CAr) ppm; MS (EI, 70 eV): *m/z* (%) = 414 (M^+, 20), 319 (10), 247 (10), 152 (10).

3-(2-Methylpropyl)-1-(pentafluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**4l**, $C_{14}H_{12}F_8N_2O$)
Yield 79 %; oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.98$ (d, 6H, CH_3), 1.92–1.95 (m, 1H, CH), 2.26 (d, 2H, CH_2), 3.02 (d, 1H, $^2J = 18$ Hz, H4a), 3.37 (d, 1H, $^2J = 18$ Hz, H4b) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.1$ (CH_3), 22.2 (CH_3), 26.5 (CH_2), 38.4 (CH), 45.4 (C4), 92.9 (q, $^2J = 32$ Hz, C5), 122.7 (q, $^1J = 283$ Hz, CF_3), 153.8, 148.7, 143.9, 139.1, 135.0, 132.6 (PhF_5), 154 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 376 (M^+, 43), 317 (51), 307 (100), 181 (26).

3-(4-Methylphenyl)-1-(pentafluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**4m**, $C_{17}H_{10}F_8N_2O$)
Yield 58 %; m.p.: 120–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.37$ (s, 3H, CH_3), 3.47 (d, 1H, $^2J = 18$ Hz, H4a), 3.75 (d, 1H, $^2J = 18$ Hz, H4b), 7.19 (d, 2H, H–Ar), 7.50 (d, 2H, H–Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$ (CH_3), 43.5 (C4), 93.5 (q, $^2J = 23$ Hz, C5), 122.6 (q, $^1J = 283$ Hz, CF_3), 149.0, 145.6, 142.1, 137.7, 135.2, 132.3 (PhF_5), 140.6, 129.5, 127.6, 126.0 (PhMe), 150.2 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 410 (M^+, 48), 392 (100), 341 (37), 181 (10).

1-(Pentafluorophenyl)-5-(trichloromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**5a**, $C_{10}H_4Cl_3F_5N_2O$)
Yield 88 %; m.p.: 125–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.33$ (d, 1H, $^2J = 19$ Hz, H4a), 3.81 (d, 1H, $^2J = 19$ Hz, H4b), 6.99 (s, 1H, H-3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 49.7$ (C4), 101.6 (C5), 103.2 (CCl_3), 138.9, 136.4, 130.9, 130.9, 128.8, 116.7 (PhF_5), 151.7 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 351 (M^+ – OH, 1), 316 (60), 315 (100), 251 (1).

3-Methyl-1-(pentafluorophenyl)-5-(trichloromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**5b**, $C_{11}H_6Cl_3F_5N_2O$)
Yield 85 %; m.p.: 109–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.33$ (s, 3H, H7), 3.27 (d, 1H, $^2J = 18$ Hz, H4a), 3.75 (d, 1H, $^2J = 19$ Hz, H4b) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.4$ (CH_3), 49.7 (C4), 101.6 (C5), 103.3 (CCl_3), 145.7, 142.8, 138.9, 136.4, 140.5, 117.1 (PhF_5), 151.3 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 381 (M^+, 1), 330 (100), 264 (100), 83 (2).

3-Ethyl-1-(pentafluorophenyl)-5-(trichloromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**5c**, $C_{12}H_8Cl_3F_5N_2O$)
Yield 93 %; m.p.: 75–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.19$ (t, 3H, H8), 2.42 (q, 2H, H7), 3.25 (d, 1H, $^2J = 20$ Hz, H4a), 3.74 (d, 1H, $^2J = 20$ Hz, H4b) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.6$ (CH_3), 23.2 (CH_2), 48.1 (C4), 101.4 (C5), 103.4 (CCl_3), 145.8, 142.8, 138.9, 136.4, 114.8 (PhF_5), 156.1 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 396 (M + H^+, 1), 380 (M^+ – OH, 1), 279 (M^+ – CCl_3, 100).

1-(Pentafluorophenyl)-3-propyl-5-(trichloromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**5d**, $C_{13}H_{10}Cl_3F_5N_2O$)
Yield 94 %; m.p.: 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.99$ (t, 3H, H9), 1.64 (q, 2H, H8), 2.36 (t, 2H, H7), 3.25 (d, 1H, $^2J = 20$ Hz, H4a), 3.72 (d, 1H, $^2J = 20$ Hz, H4b) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.5$ (CH_3), 19.8 (CH_2), 31.6 (CH_2), 48.3 (C4), 101.4 (C5), 103.4 (CCl_3), 148.6, 142.9, 140.3, 139.0, 136.5, 117.2 (PhF_5), 155.0 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 410 (M^+, 1), 364 (100), 358 (63), 293 (M^+ – CCl_3, 20), 83 (2).

3-(1-Methylethyl)-1-(pentafluorophenyl)-5-(trichloromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**5e**, $C_{13}H_{10}Cl_3F_5N_2O$)
Yield 90 %; m.p.: 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.19$ (d, 6H, 2 CH_3), 2.69 (m, 1H, H7), 3.26 (d, 1H, $^2J = 18$ Hz, H4a), 3.73 (d, 1H, $^2J = 20$ Hz, H4b) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.9$ (CH_3), 20.0 (CH_3), 29.6 (CH), 46.4 (C4), 101.4 (C5), 103.5 (CCl_3), 148.2, 146.4, 145.6, 138.9, 136.4, 117.2 (PhF_5), 159.6 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 365 (M^+ – *i*-Pr, 20), 293 (M^+ – CCl_3,100), 83 (5).

3-Butyl-1-(pentafluorophenyl)-5-(trichloromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**5f**, $C_{14}H_{12}Cl_3F_5N_2O$)
Yield 73 %; m.p.: 59–61 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.94$ (t, 3H, H10), 1.41 (s, 2H, H9), 1.58 (q, 2H, H8), 2.38 (t, 2H, H7), 3.25 (d, 1H, $^2J = 20$ Hz, H4a), 3.74 (d, 1H, $^2J = 20$ Hz, H4b) ppm; ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta = 15.0$ (CH_3), 23.8, 29.2, 32.6 (CH_2), 49.1 (C4), 103.5 (C5), 106.0 (CCl_3), 148.3, 144.3, 141.8, 138.2,

130.6, 120.5 (PhF_5), 156.8 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 406 (M^+ – OH, 1), 264 (100), 257 (1).

3-(3-Methylbutyl)-1-(pentafluorophenyl)-5-(trichloromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**5g**, $C_{15}H_{14}Cl_3F_5N_2O$)

Yield 80 %; m.p.: 91–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, 6H, 2 CH_3), 1.50 (m, 2H, H8), 1.54 (m, 1H, H9), 2.37 (d, 2H, H7), 3.25 (d, 1H, ^2J = 18 Hz, H4a), 3.74 (d, 1H, ^2J = 20 Hz, H4b) ppm; ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ = 23.5, 23.6 (CH_3), 29.3, 29.3 (CH_2), 36.9 (CH), 49.7 (C4), 103.6 (C5), 106.0 (CCl_3), 144.3, 141.8, 140.6, 138.2, 133.8, 120.5 (PhF_5), 156.9 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 320 (M^+ – CCl_3, 10), 304 (5), 278 (5), 264 (100), 97 (15).

3-(4-Chlorophenyl)-1-(pentafluorophenyl)-5-(trichloromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**5i**, $C_{16}H_7Cl_4F_5N_2O$)

Yield 89 %; m.p.: 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.66 (d, 1H, ^2J = 18 Hz, H4a), 4.09 (d, 1H, ^2J = 18 Hz, H4b), 7.35 (d, 2H, H–Ar), 7.55 (d, 2H, H–Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.2 (C4), 102.8 (CCl_3), 106.9 (C5), 148.1, 145.5, 143.1, 140.5, 138.9, 116.8 (PhF_5), 136.0, 129.2, 127.3, 102.1 (PhCl), 149.1 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 443 (M^+ – Cl, 40), 409 (100), 373 (10), 344 (1).

3-(4-Bromophenyl)-1-(pentafluorophenyl)-5-(trichloromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**5j**, $C_{16}H_7BrCl_3F_5N_2O$)

Yield 90 %; m.p.: 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.69 (d, 1H, ^2J = 18 Hz, H4a), 4.10 (d, 1H, ^2J = 18 Hz, H4b), 7.50 (m, 4H, H–Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.2 (C4), 102.8 (CCl_3), 106.9 (C5), 148.0, 145.6, 143.1, 140.5, 138.9, 116.8 (PhF_5), 136.0, 129.0, 127.3, 102.1 (PhBr), 151.4 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 505 (M^+ – OH, 1), 367 (75), 338 (1), 298 (100).

3-(4-Fluorophenyl)-1-(pentafluorophenyl)-5-(trichloromethyl)-4,5-dihydro-5-hydroxy-1H-pyrazole (**5k**, $C_{16}H_7Cl_3F_6N_2O$)

Yield 78 %; m.p.: 134–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.69 (d, 1H, ^2J = 18 Hz, H4a), 4.12 (d, 1H, ^2J = 18 Hz, H4b), 7.50 (s, 4H, H–Ar) ppm; ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ = 47.5 (C4), 104.3 (C5), 105.4 (CCl_3), 145.7, 141.8, 140.7, 136.9, 119.9, 108.9 (PhF_5), 167.7, 151.3, 130.1, 117.6, 105.4, 104.2 (PhF), 164.2 (C3) ppm; MS (EI, 70 eV): *m/z* (%) = 346 (M^+ – CCl_3, 30), 345 (100), 295 (1), 83 (5).

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References

1. Curzons AD, Constable DJC, Cunningham VL (1999) Clean Prod Process 1:82
2. Alfonsi K, Colberg J, Dunn PJ, Fevig T, Jennings S, Johnson TA, Kleine HP, Knight C, Nagy MA, Perry DA, Stefaniak M (2008) Green Chem 10:31
3. Fleischer G, Schmidt W-P (1997) Int J Life Cycle Assess 2:20
4. Gani R (2004) Comput Chem Eng 28:2441
5. Gani R, Jimenez-Gonzalez C, Constable DJC (2005) Comput Chem Eng 29:1661
6. Li M, Harten PF, Cabezas H (2002) Ind Eng Chem Res 41:5867
7. Elgue S, Prat L, Cognet P, Cabassud M, Le Lann M, Cezerac J (2004) J Sep Purif Technol 34:273
8. Jimenez-Gonzales C, Curzons AD, Constable JC, Cunningham VL (2005) Clean Technol Environ Policy 7:42
9. Capello C, Fischer U, Hungerbuhler K (2007) Green Chem 9:927
10. Elgue S, Prat L, Cabassud M, Cezerac J (2006) Chem Eng J 117:169
11. Kralisch D, Stark A, Körsten S, Ondruschka B, Kreisel G (2005) Green Chem 7:301
12. Kralisch D, Reinhardt D, Kreisel G (2007) Green Chem 9:1308
13. Trost BM (1991) Science 254:1471
14. Trost BM (2002) Acc Chem Res 35:695
15. Constable DJC, Curzons AD, Cunningham VL (2002) Green Chem 4:521
16. Sheldon RA (1992) Chem Ind (London) 903
17. Sheldon RA (1994) Chemtech 38–47
18. Sheldon RA (1997) J Chem Technol Biotechnol 68:381
19. Dunn PJ, Galvin S, Hettenbach K (2004) Green Chem 6:43
20. Hudlicky T, Frey DA, Koroniak L, Claeboe CD, Brammer LE (1999) Green Chem 1:57
21. Curzons AD, Constable DJC, Mortimer DN, Cunningham VL (2001) Green Chem 3:1
22. Berkoff CE, Kamholz K, Rivard DE, Wellman G, Winicov H (1986) Chemtech 552–559
23. Frizzo CP, Marzari MRB, Buriol L, Moreira DN, Rosa FA, Vargas PS, Zanatta N, Bonacorso HG, Martins MAP (2009) Catal Commun 10:1967
24. Buriol L, Frizzo CP, Prola LDT, Moreira DN, Marzari MRB, Scapin E, Zanatta N, Bonacorso HG, Martins MAP (2011) Catal Lett 141:1130
25. Guarda EA, Marzari MRB, Frizzo CP, Guarda PM, Zanatta N, Bonacorso HG, Martins MAP (2011) Tetrahedron Lett 53:170
26. Buriol L, Frizzo CP, Moreira DN, Prola LDT, Marzari MRB, München TS, Zanatta N, Bonacorso HG, Martins MAP (2011) Monatsh Chem 142:515
27. Buriol L, Frizzo CP, Marzari MRB, Moreira DN, Prola LDT, Zanatta N, Bonacorso HG, Martins MAP (2010) J Braz Chem Soc 21:1037
28. Vargas PS, Rosa FA, Buriol L, Rotta M, Moreira DN, Frizzo CP, Bonacorso HG, Zanatta N, Martins MAP (2012) Tetrahedron Lett 53:3131
29. Martins MAP, Cunico W, Pereira CMP, Flores AFC, Bonacorso HG, Zanatta N (2004) Curr Org Synth 1:391
30. Martins MAP, Frizzo CP, Moreira DN, Bonacorso HG, Zanatta N (2008) Chem Rev 108:2015

31. Martins MAP, Frizzo CP, Moreira DN, Buriol L, Machado P (2009) Chem Rev 109:4140
32. Donohue SR, Halldin C, Pike VW (2008) Tetrahedron Lett 49:2789
33. Szabó G, Fischer J, Kis-Varga Á, Gyires K (2008) J Med Chem 51:142
34. Penning TD, Talley JJ, Bertenshaw SR, Carter JS, Collins PW, Docter S, Graneto MJ, Lee LF, Malecha JW, Miyashiro JM, Rogers RS, Rogier DJ, Yu SS, Anderson GD, Burton EG, Cogburn JN, Gregory SA, Koboldt CM, Perkins WE, Seibert K, Veenhuizen AW, Zhang YY, Isakson PC (1997) J Med Chem 40:1347