Tetrahedron Letters 53 (2012) 5488–5491

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

New one-pot, efficient, and regioselective method for the synthesis of 3-Trifluoromethyl-1*H*-1-phenylpyrazoles and alkyl 3-carboxylate analogs

Helio G. Bonacorso *, Michele S. Correa, Liliane M. F. Porte, Everton P. Pittaluga, Nilo Zanatta, Marcos A. P. Martins

Núcleo de Química de Heterociclos–NUQUIMHE, Departamento de Química, Universidade Federal de Santa Maria, 97105-900 Santa Maria, RS, Brazil

ARTICLE INFO

Article history:
Received 5 July 2012
Revised 24 July 2012
Accepted 26 July 2012
Available online 3 August 2012

Keywords:
Phenylpyrazoles
3-Trifluoromethylpyrazoles
Esterification reactions
Cyclization reactions
Phenylsemicarbazides

ABSTRACT

An efficient and regioselective procedure for the synthesis of a series of alkyl(aryl/heteroaryl) substituted 3-trifluoromethyl-1*H*-1-phenylpyrazoles and alkyl 3-carboxylate analogs, from the cyclocondensation reactions of 4-alkoxy-1,1,1-trihaloalk-3-en-2-ones [$CX_3C(O)CR^2{=}CR^1(OMe/OEt)$, where R^1 = H, Me, Ph, 2-Furyl; R^2 = H; R^1-R^2 = -C_4H_8- and X = F, Cl] and 1-phenylsemicarbazide in an acidified alcoholic medium (R^3OH/H_2SO_4), where R^3 = Me, Et, Pr^i was successfully applied and is described here in detail.

The synthesis of pyrazole derivatives has been extensively explored by our research group through the cyclocondensation reaction of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones and different hydrazines contemplating their biological activities as analgesic and anti-inflammatory,[1] antimycobacterial,[2] antimicrobial,[3] antinociceptive,[4] and antioxidant agents.[5] The method to introduce a trihalomethyl group into heterocycles based on the above cited trihalomethylated building block approach, in most cases regioselectively leads to the C-5 trihalomethyl-substituted pyrazoles or to mixtures of 1,3- and 1,5-isomers.[6]

Variously substituted pyrazoles and their derivatives bearing a diversity of functional groups are important biological agents and a significant amount of research activity has been directed toward this class. Special interest has been devoted to developing efficient approaches to introduce a CF_3 group at a pyrazole ring in a regioselective manner, mostly because trifluoromethyl-substituted pyrazoles at the C-3 position often show pharmacological activities such as the anti-inflammatory[7] Celecoxib® and the anticoagulant Razaxaban®.[8] Moreover, the phenylpyrazole structure is the scaffold of common worldwide over-the-counter drugs as a potent antipyretic and analgesic[9a,b] Dipyrone® and the insecticide Fipronil®.[9c]

A literature survey revealed that mixtures of 1,3- and 1,5-regioisomers are frequently obtained by various synthetic procedures.[10–12] Studies which increase the regioselectivity in the product formation usually implement one or more steps from β-diketones, hydrazines, and derivatives thereof,[10] high-cost solvents[11] or present a limited scope of substituents in the pyrazole ring.[12]

Therefore, because of the above mentioned importance and our ongoing research interest in introducing CX_3 groups in heterocycles, we have decided to investigate the regioselectivity in the cyclocondensation reaction of 4-alkoxy-1,1,1-trihaloalk-3-en-2-ones [$CX_3C(O)\ CR^2{=}CR^1$ (OMe/OEt), where R^1 = H, Me, Ph, 2-Furyl; R^2 = H; R^1-R^2 = -C_4H_8- and X = F, Cl] and 1-phenylsemicarbazide in order to regioselectively obtain 3-trihalomethyl-substituted 1-phenylpyrazoles as the main isomer.

So, in this Letter, we report first a new, simple, and efficient method for the regio insertion of CF_3 group in 1-phenylpyrazoles. By this new method, the C-3 position of pyrazoles can be selectively trifluormethylated with a good yield under a mild and simple reaction step, employing facile solvent and catalyst access. In addition, we also describe the indirect carboxyalkylation reaction from 3-trichloromethyl-substituted pyrazole analogs under similar conditions.

The optimized synthesis of 3-trifluoromethyl pyrazoles (**4a**–**e**) from the cyclocondensation reaction of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones (**1a**–**e**) and 1-phenylsemicarbazide (**3**) was done in the presence of sulfuric acid, methanol as the reaction solvent in a 1:1.5 molar ratio.[13,14] In comparison to other polar solvents, methanol was shown to be more suitable to solubilize the 1-phenylsemicarbazide at room temperature, as well as contributing more to achieve the desired regioisomer product. The reactions were performed by stirring the mixtures at 60 °C for 24 h

* Corresponding author. Tel.: +55 55 3220 8867; fax: +55 55 3220 8031.
E-mail address: heliogb@base.ufsm.br (H.G. Bonacorso).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.07.119

(Scheme 1). Compounds **4a**–**e** were obtained as dark-yellow colored oils with 50–85% yields.[15,16]

This methodology resulted in a series of 5-alkyl(aryl/heteroaryl)-3-trifluoromethyl-1*H*-1-phenylpyrazoles (**4a**–**e**) in a one-step reaction without the isolation of 3-hydroxy-pyrazoline ring intermediate. It is probable that the drops of concentrated sulfuric acid used as catalyst promoted the in situ dehydration of the intermediate and lead to the aromatic pyrazoles (**4**). Besides, it is widely known that similar acidic condition promotes the hydrolysis of *C(O)-N* function with the respective elimination of the carbamoyl group.[17]

The structures of all compounds **4a**–**e** were confirmed by ^{1}H and ^{13}C $\{^{1}H\}$ NMR, mass spectrometry (GC–MS) data analysis where the mixture of synthesized regioisomers of this work and the 5-trifluormethyl-1*H*-pyrazoles previously acquired were compared.[18] The GC chromatograms showed unequivocal specific retention times for each regioisomer. This comparison permitted to identify the desired product and proved that the 3-CF_3-substituted pyrazole regioisomers were fully isolated by employing this new methodology (Table 1).[14–16]

All the results are in agreement to the literature where it is well-known that the amino group linked to the phenyl ring of 1-phenylsemicarbazide (*N*1) is the best nucleophile of the precursor, while the second amino group (*N*2) has its nucleophilicity decreased due the resonance with the strong electron withdrawing of the carbamoyl group.[19]

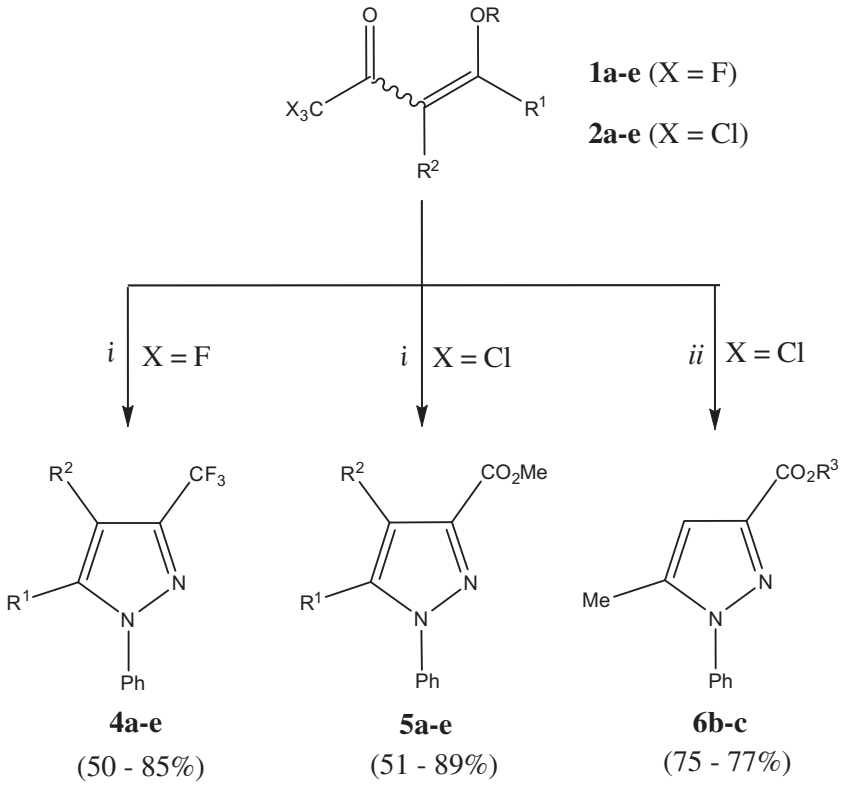
Table 1
Yield and isomer relationship for compounds **4a**–**e**

Product	Yield[a] (%)/(Lit.)[b]	Isomer 1,3:1,5[c]/(Lit.)[b]
4a	50/(16)[23], (94)[24a]	50:50/(100:0)[23,24a]
4b	77/(70)[24c], (80)[24b]	100:0/(50:50)[24b,c]
4c	54	97:3
4d	65/(–[d])[24c], (65)[25]	100:0/(82:18)[24c], (100:0)[25]
4e	85/(–[d])[24c]	100:0/(100:0)[24c]

[a] Yields of isolated products.
[b] Literature data.
[c] GC–MS data analysis.
[d] Uninformed yields from literature data.

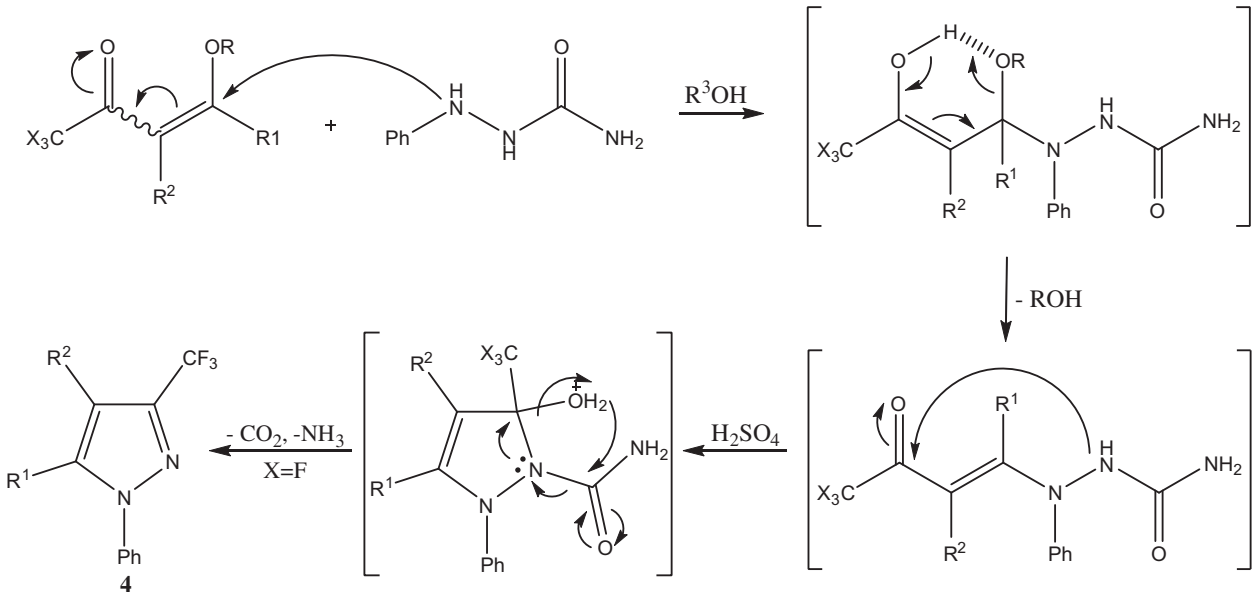
Consequently, the first attack to the β-olefinic carbon of the vinyl ketone is conducted by *N*1 with subsequent elimination of an alcohol molecule (ROH). Hereafter, a second attack promoted by *N*2 to the vinyl ketone carbonyl group closes the five membered ring with subsequent aromatization of the system by the dehydration and the elimination of the carbamoyl group in a one-step reaction (Scheme 2).

Following the successful demonstration of the regioselective trifluoromethylation at C-3 position of pyrazoles **4**, we proceeded to extend the generality of the reaction conditions to trichloromethylated precursors (**2a**–**e**). Thus, we employed the 4-alkoxy-1,1,1-trichloro-3-alken-2-ones (**2a**–**e**) aiming to obtain the 3-trichloro-

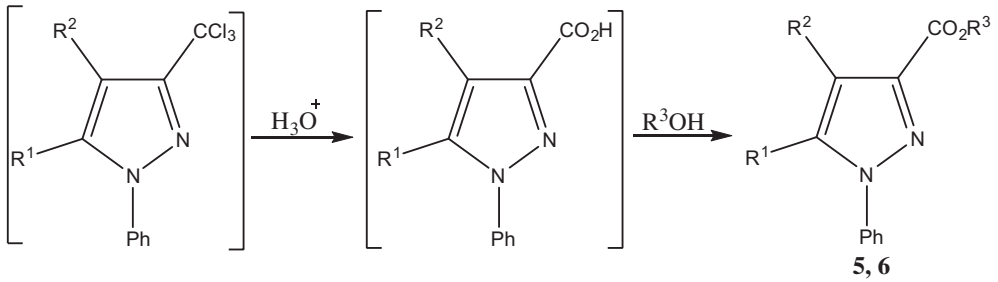


1-2, 4-6	a	b	c	d	e
R	Et	Me	Me	Me	Me
R^1	H	Me	$-C_4H_8-$	Ph	2-Furyl
R^2	H	H		H	H
R^3		Et	*i*-Pr		

Scheme 1. Reagents and conditions: (i) $Ph(NH)_2CONH_2$(**3**),MeOH, H_2SO_4conc., 60 °C, 24 h; (ii) Ph(NH) $CONH_2$(**3**), R^3OH, H_2SO_4conc., 60 °C, 24 h.



Scheme 2. Proposed mechanism for the formation of the 3-trifluoromethyl-substituted pyrazoles.



Scheme 3. Proposed convention of the trichloromethyl group to the respective ester.

Table 2
Yield and isomer relationship of compounds **5a–e** and **6b–c**

Product	Yield[a] (%)/(Lit.)[b]	Isomer 1,3:1,5[c]
5a	51/(15)[26]	74:26/(100:0)[26]
5b	88	100:0
5c	73	100:0
5d	70	100:0
5e	89	100:0
6b	75/(62)[27a], (60)[27b]	98:2/(100:0)[27a], (–[d])[27b]
6c	77	96:4

[a] Yields for isolated products.
[b] Literature data.
[c] GC–MS data analysis.
[d] Uninformed yields from literature data.

methyl-substituted pyrazoles under similar conditions. However, we observed that water present in methanol (reaction solvent) due to the dehydration reaction and the acid catalyst was responsible for converting the trichloromethyl group to ester similarly as described previously by us (Scheme 3).[20] By this synthetic procedure, a series of methyl-5-alkyl(aryl/heteroaryl)-1*H*-1-phenylpyrazole-3-carboxylates (**5a–e**) were obtained as dark yellow colored oils in 51–89% yields (Scheme 1).[14,15,21]

By taking the compound **5b** as standard to propose evaluating the solvent influence in the isomeric relationship between the products acquired and to show the versatility of the methodology, we promoted the synthesis of alkyl-5-methyl-1*H*-1-phenylpyrazole-3-carboxylates (**6b–c**) using other alcohols as the reaction solvents. As a result, we found that the larger the alcohol structure, the lower the regioselectivity for the resultant ester and consequently also lower yields. Compounds **6b–c** were obtained as dark yellow colored oils in 75–77% yields.[14,15,22]

The structures of all compounds **5a–e** and **6b–c** were compared with the literature data and confirmed by ^{1}H, $^{13}C\{^{1}H\}$ NMR, and by the mass spectrometry (GC-MS) (Table 2).[21,22]

In conclusion, we have developed a mild, convenient, and improved protocol for the regioselective synthesis of 3-trifluoromethyl- and 3-carboxyalkyl-1*H*-1-phenylpyrazoles in alcoholic reaction solvents and sulfuric acid as catalyst. The present procedure is carried out in easier work-up and good yields. The method reported here is not only simple to operate but also efficient for the achievement of regioselective products.

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 acquired on a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz) or Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz and ^{13}C at 100.61 MHz), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in $CDCl_3$, using TMS as internal reference. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split–splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and He was used as the carrier gas.

Acknowledgments

The authors thank the financial support from Conselho Nacional de Desenvolvimento Científico e Tecnológico–CNPq (Proc. nr. 303.013/2011-7 and 470.788/2010-0 - Universal). Fellowships from CAPES and CNPq are also acknowledged.

References and notes

1. (a) Martins, M. A. P.; Sauzem, P. D.; Machado, P.; Rubin, M. A.; Sant'anna, G. S.; Faber, H. B.; Souza, A. H.; Mello, C. F.; Beck, P.; Burrow, R. A.; Bonacorso, H. G.; Zanatta, N. *Eur. J. Med. Chem.* **2008**, *43*, 1237; (b) Martins, M. A. P.; Machado, P.; Rosa, F. A.; Rossatto, M.; Sauzem, P. D.; Silva, R. M. S.; Rubin, M. A.; Ferreira, J.; Bonacorso, H. G.; Zanatta, N. ARKIVOC 2007, xvi, 281.
2. Silva, P. E. A.; Ramosa, D. F.; Bonacorso, H. G.; Iglesia, A. I.; Oliveira, M. R.; Coelho, T.; Navarini, J.; Morbidoni, H. R.; Zanatta, N.; Martins, M. A. P. *Int. J. of Antimicrob. Ag.* **2008**, *32*, 139.
3. (a) Bonacorso, H. G.; Pittaluga, E. P.; Alves, S. H.; Schaffer, L. F.; Cavinatto, S.; Porte, L. M. F.; Paim, G. R.; Martins, M. A. P.; Zanatta, N. ARKIVOC 2012, viii, 62.; (b) Zanatta, N.; Alves, S. H.; Coelho, H. S.; Borchhardt, D. M.; Machado, P.; Flores, K. M.; Silva, F. M.; Spader, T. B.; Santurio, J. M.; Bonacorso, H. G.; Martins, M. A. P. *Bioorg. Med. Chem.* **2007**, *15*, 1947.
4. Milano, J.; Oliveira, S. M.; Rossato, M. F.; Sauzem, P. D.; Machado, P.; Beck, P.; Zanatta, N.; Martins, M. A. P.; Mello, C. F.; Rubin, M. A.; Ferreira, J.; Bonacorso, H. G. *Eur. J. Pharmacol.* **2008**, *581*, 86.
5. Bonacorso, H. G.; Cavinatto, S.; Campos, P. T.; Porte, L. M. F.; Navarini, J.; Paim, G. R.; Martins, M. A. P.; Zanatta, N.; Stuker, C. Z. *J. Fluorine Chem.* **2012**, *135*, 303.
6. (a) Cunico, W.; Cechinel, C. A.; Bonacorso, H. G.; Martins, M. A. P.; Zanatta, N.; de Souza, M. V. N.; Freitas, I. O.; Soares, R. P. P.; Krettli, A. U. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 649; (b) Martins, M. A. P.; Cunico, W.; Brondani, S.; Peres, R. L.; Zimmermann, N. E. K.; Rosa, A.; Fiss, G. F.; Zanatta, N.; Bonacorso, H. G. *Synthesis* **2006**, 1485; (c) Bonacorso, H. G.; Wentz, A. P.; Lourega, R. V.; Cechinel, C. A.; Moraes, T. S.; Coelho, H. S.; Zanatta, N.; Martins, M. A. P.; Höerner, M.; Alves, S. H. *J. Fluorine Chem.* **2006**, *127*, 1066; (d) Bonacorso, H. G.; Porte, L. M. F.; Cechinel, C. A.; Paim, G. R.; Deon, E. D.; Zanatta, N.; Martins, M. A. P. *Tetrahedron Lett.* **2009**, *50*, 1392.
7. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347.
8. Varnes, J. D.; Wacker, D. A.; Pinto, D. J. P.; Orwat, M. J.; Theroff, J. P.; Wells, B.; Galemo, R. A.; Luettgen, J. M.; Knabb, R. M.; Bai, S.; He, K.; Lam, P. Y. S.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 749.
9. (a) Levy, M.; Zylber-Katz, E.; Rosenkranz, B. *Clin. Pharmacokinet.* **1995**, *28*, 216; (b) Lorenzetti, B. B.; Ferreira, S. H. *Eur. J. Pharmacol.* **1985**, *114*, 375; (c) Stevens, M. M.; Helliwell, S.; Warren, G. N. *Field Crops Res.* **1998**, *57*, 195.
10. (a) Makino, K.; Kim, H. S.; Kurasawa, Y. *J. Heterocycl. Chem.* **1998**, *39*, 489; (b) Sing, S. P.; Kumar, D.; Batra, H.; Naithani, R.; Rozas, I.; Elguero, J. *Can. J. Chem.* **2000**, *78*, 1109; (c) Song, L. P.; Chu, Q. L.; Zhu, S. Z. *J. Fluorine Chem.* **2001**, *107*, 107; (d) Zhu, S. Z.; Wang, Y. L.; Peng, W. M.; Song, L. P.; Jin, G. F. *Curr. Org. Chem.* **2002**, *6*, 1057; (e) Hojo, M.; Okada, E.; Masuda, R. *Heterocycles* **1992**, *34*, 791; (f) Druzhinin, S. V.; Balenkova, E. S.; Nenajdenko, V. G. *Tetrahedron* **2007**, *63*, 7753; (g) Singh, S. P.; Kumar, V.; Aggarwal, R.; Elguero, J. *J. Heterocycl. Chem.* **2006**, *43*, 1003.
11. (a) Fustero, S.; Román, R.; Sanz-Cervera, J. F.; Simón-Fuentes, A.; Cuñat, A. C.; Villanova, S.; Murguía, M. *J. Org. Chem.* **2008**, *73*, 3523; (b) Raghupathi, R. A.; Goverdhan, G.; Sampath, A.; Thirupathi, R. A.; Yakambram, B. US Patent 2008/0234491 A1, 2008.
12. Hamper, B. C.; Kurtzweil, M. L.; Beck, J. P. *J. Org. Chem.* **1992**, *57*, 5680.
13. (a) Bonacorso, H. G.; Correa, M. S.; Porte, L. M. F.; Martins, M. A. P.; Zanatta, N. BR Patent deposited on National Institute for Industrial Property - INPI (PI1105807-2) in agreement to Federal University of Santa Maria, 2011.; (b) Correa, M. S. Master Dissertation, Federal University of Santa Maria, Brazil, 2011.
14. *Synthesis of 5-alkyl(aryl/heteroaryl)-3-carboxyalkyl/trifluoromethyl)-1H-1-phenylpyrazoles (**4a–e**, **5a–e**, **6b–c**). General procedure:* To a stirred solution of **1a–e**, **2a–e** (1 mmol) and 1-phenylsemicarbazide (3) (1.5 mmol) in (methyl, ethyl or i-propyl) alcohol (20 mL) was added four drops of concentrated sulfuric acid. After addition, the reaction mixture was stirred at 60 °C for 24 h, then water was added (10 mL) and the mixture was neutralized with NaOH 0.1 M. The resulting solution was extracted with dichloromethane (3 × 30 mL) and distilled water (2 × 20 mL). The dichloromethane layer was separated, dried over anhydrous Na_2CO_3 and filtered. The solvent was evaporated under reduced pressure, obtaining the corresponding compounds **4a–e**, **5a–e**, **6b–c** which were purified following the next procedures.
15. Compounds **4a–e**, **5a–e**, **6b–c** were obtained as oils and purified by flash chromatography on silica gel (eluent hexane/ethyl acetate 4:1). Compounds **4a–e**, **5a–e**, **6b–c** were characterized by ^{1}H and ^{13}C NMR and GC–MS.
16. *Data of 3-trifluoromethyl-1-phenyl-4,5,6,7-tetrahydro-1H- indazole (**4c**):* Yield 54%, oil. ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 7.48–7.47 (m, 5H, Ph), 2.70–2.68 (m, 4H, H-1; H-4), 1.84–1.78 (m, 4H, H-2; H-3). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 142.5 (q, $^2J_{C\text{-}F}$ = 38, C-3), 140.0 (Ph), 138.8 (Ph), 129.1 (Ph), 128.6 (Ph), 125.2 (Ph), 121.3 (q, $^1J_{C\text{-}F}$ = 268, CF_3), 104.7 (C-4), 99.9 (C-5), 12.1 (Me). GC/MS (EI, 70 eV): *m*/*z* (%) 266 (M^+, 100), 238 (98), 197 (21), 77 (37). Melting points and yields of compounds **4**. Compd. [Physical property, Yield (%)]: **4a** [oil, 50]; **4b** [oil, 77]; **4d** [oil, 65]; **4e** [oil, 85].
17. (a) Bonacorso, H. G.; Wastowski, A. D.; Zanatta, N.; Martins, M. A. P.; Naue, J. A. *J. Fluorine Chem.* **1998**, *92*, 23; (b) Bonacorso, H. G.; Wastowski, A. D.; Zanatta, N.; Martins, M. A. P. *Synth. Commun.* **2000**, *30*(8), 1457.
18. Braibante, M. E. F.; Clar, G.; Martins, M. A. P. *J. Heterocycl. Chem.* **1993**, *30*, 1159.
19. Shaban, M. E. *J. Chem. Soc. Pak.* **1988**, *10*, 235.
20. (a) Martins, M. A. P.; Freitag, R.; Flores, A. F. C.; Zanatta, N. *Synthesis* **1995**, 1491; (b) Martins, M. A. P.; Flores, A. F. C.; Bastos, G. P.; Sinhorin, A.; Bonacorso, H. G.; Zanatta, N. *Tetrahedron Lett.* **2000**, *41*, 293; (c) Martins, M. A. P.; Cunico, W.; Pereira, C. M. P.; Sinhorin, A. P.; Flores, A. F. C.; Bonacorso, H. G.; Zanatta, N. *Cur. Org. Chem.* **2004**, *1*, 391. and references cited therein.
21. *Data of methyl-5-methyl-1H-1-phenylpyrazole-3-carboxylate (**5b**):* Yield 88%, oil. ^{1}H NMR (200.13 MHz, $CDCl_3$): 7.49–7.43 (m, 5H, Ph); 6.75 (s, 1H, H-4); 3.93 (s, 3H, Me); 2.34 (s, 3H, CH_3). ^{13}C NMR (100.61 MHz, $CDCl_3$): 162.9 (CO); 143.3 (C-3); 140.5 (C-5); 139.0 (Ph); 129.0 (Ph); 128.5 (Ph); 125.3 (Ph), 109.1 (C-4); 51.8 (Me); 12.2 (CH_3). GC–MS (EI, 70 eV): *m*/*z* (%) 218 (M^+, 80), 187 (100), 159 (53), 77 (96). Melting points and yields of compounds **5**. Compd. [Physical property, Yield (%)]: **5a** [oil, 51]; **5c** [oil, 73]; **5d** [oil, 70]; **5e** [oil, 89].
22. *Data of isopropyl 5-methyl-1H-1-phenylpyrazole-3-carboxylate (**6c**):* Yield 77%, oil. ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 7.46 (s, 5H, Ph), 6.72 (s, 1H, H-4), 4.95–4.83 (m, 1H, H), 2.33 (s, 3H, Me), 1.24 (d, J = 6, 6H, Me). ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 162.0 (CO), 156.8 (C-3), 140.2 (C-5), 138.9 (Ph), 128.9 (Ph), 128.3 (Ph), 125.3 (Ph), 112.9 (C-4), 68.2 (CH), 21.8 (Me), 12.1 (Me). GC/MS (EI, 70 eV): *m*/*z* (%) 244 (M+, 24), 185 (79), 158 (100), 77 (21). Melting point and yield of compound **6b**: oil, 75%.
23. Tanaka, K.; Maeno, S.; Mitsuhashi, K. *Bull. Chem. Jpn.* **1985**, *58*, 1841.
24. (a) Cristau, H.; Cellier, P. P.; Spindler, J.; Taillefer, M. *Eur. J. Org. Chem.* **2004**, 695; (b) Martins, M. A. P.; Pereira, C. M. P.; Moura, S.; Frizzo, C. P.; Beck, P.; Zanatta, N.; Bonacorso, H. G.; Flores, A. F. C. *J. Heterocycl. Chem.* **2007**, *44*, 1195; (c) Sloop, J. C.; Bumgardner, C. L.; Loehle, W. D. *J. Fluorine Chem.* **2002**, *118*, 135.
25. Diab, J.; Laurent, A.; Le Dréan, I. *J. Fluorine Chem.* **1997**, *84*, 145.
26. Molteni, G.; Pont, A.; Orlani, M. *New J. Chem.* **2002**, *26*, 1340.
27. (a) Padwa, A.; Kulkarni, Y. S.; Zhang, Z. *J. Org. Chem.* **1990**, *55*, 13; (b) Schmidt, A.; Habeck, T.; Kindermann, M. K.; Nieger, M. *J. Org. Chem.* **2003**, *68*, 5977.