Tetrahedron 66 (2010) 9835–9839

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of dialkyl 5-(aryl)-1-phenyl-1*H*-prazole-3,4-dicarboxylates via a one-pot and four-component reaction

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ARTICLE INFO

Article history:
Received 16 July 2010
Received in revised form 6 October 2010
Accepted 25 October 2010
Available online 1 November 2010

Keywords:
Trimethyl phosphite
Acetylenic ester
Aroyl chlorides
Phenylhydrazine
Pyrazole
Four-component reaction

ABSTRACT

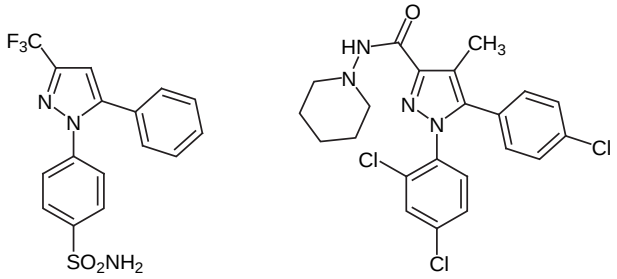
A number of new dialkyl 5-(aryl)-1-phenyl-1*H*-prazole-3,4-dicarboxylate derivatives have been prepared regiospecifically in moderate to good yield from the cyclocondensation reaction of dialkyl (*E*)-2-(dialkoxyphosphoryl)-3-(aroyl)-2-butenedioate, derived from the reaction between trimethyl phosphite, an acetylenic ester, and an aroyl chloride, with phenylhydrazine. The reaction is four-component and is carried out under reflux conditions in dry toluene.

1. Introduction

Substituted pyrazoles are an important class of five-membered heterocyclic compounds that find widespread use in the pharmaceutical and agrochemical industries.[1] These heterocycles are known to possess wide variety of biological activities including herbicidal,[2] antimicrobial,[3] antibacterial,[4] anti-inflammatory,[5] insecticidal,[6] analgesic,[7] and antipyretic[8] activities. Specifically the 1,3,5-tri- and 1,3,4,5-tetrasubstituted pyrazoles, which constitute the key structural units of blockbuster drugs, such as, Celebrex **1**[9] and Acomplia **2**[10] are of interest to medicinal chemist (Scheme 1).

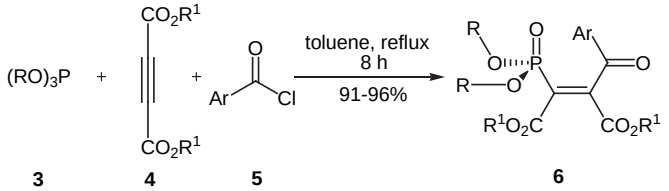
The first method of 1,3,5-trisubstituted pyrazoles synthesis goes back to 19th century when Knorr employed 1,3-diketones and hydrazines as starting materials.[11] Owing to the formation of two product isomers from the reactions of hydrazines with unsymmetrical dicarbonyl compounds and the difficulty in separation, many efforts, such as replacing the dicarbonyl compounds with olefinic or acetylenic ketones have been reported to develop the regioselective synthesis of the pyrazole rings.[12] However α,β-unsaturated ketones have been applied as building blocks for the preparation of pyrazoles, vinylphosphonates are also important synthetic intermediates[13] in heterocycle synthesis.

Recently, our research group reported the diastereoselective synthesis of a novel series of dialkyl (*E*)-2-(dialkoxyphosphoryl)-3-(aroyl)-2-butenedioate derivatives using the reaction of trialkyl phosphite and an acetylenic ester with various aroyl chlorides via one-pot MCRs (Scheme 2).[14]



Celebrex **1** Acomplia **2**

Scheme 1.



3 **4** **5** **6**

Scheme 2. Synthesis of dialkyl (*E*)-2-(dialkoxyphosphoryl)-3-(aroyl)-2-butenedioate derivatives.

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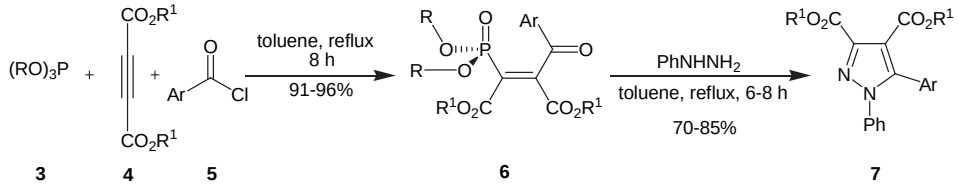
doi:10.1016/j.tet.2010.10.070

2. Results and discussion

In continuation of this research, we became interested in the application of phenylhydrazine as the fourth component in a multicomponent reaction for the synthesis of dialkyl 5-(aryl)-1-phenyl-1*H*-prazole-3,4-dicarboxylate **7**. Our strategy to reach this goal is outlined in Scheme 3. Reaction between trialkyl phosphite **3**, acetylenic ester **4**, aroyl chlorides **5**, and phenylhydrazine in toluene under thermal and one-pot conditions leads to the formation of dialkyl 5-(aryl)-1-phenyl-1*H*-prazole-3,4-dicarboxylate **7** after 14 h in 70–85% yields.



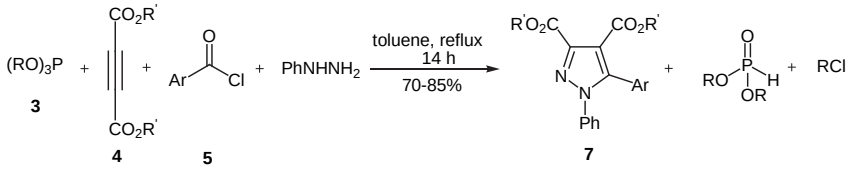
Scheme 3.

The diversity of the MCR with respect to the aroyl chloride component was investigated and indicated in Table 1.

The structures of compounds **7a**–**f** were deduced from their elemental analysis, mass, IR and high field ^{1}H and ^{13}C NMR spectra as described for **7a**. The mass spectrum of **7a** displayed molecular ion peak at *m*/*z* 381. The IR spectrum of **7a** exhibited absorption bands due to the carbonyl group of esters at 1729, Ar group at 1598 and 1521, C=N group at 1557 cm^{-1} and the absorption bands of the C–O stretching appeared at 1345, 1220, 1096, and 1074 cm^{-1}.

The ^{1}H NMR spectrum of **7a** exhibited two sharp singlets readily recognized as arising from methoxy groups (δ=3.80 and 4.00 ppm). The aryl moiety exhibited characteristic signals in the aromatic region of the spectrum and 15 distinct signals in the ^{1}H decoupled ^{13}C NMR spectrum of **7a** are in agreement with proposed structure. The ^{1}H and ^{13}C NMR spectra of compound **7b**–**f** are similar to those of **7a** except for the alkoxy of the ester groups, and the aryl moiety, which exhibit characteristic signals with appropriate chemical shifts. Finally, the structure of **7**, for example, **7c**, was further confirmed by a single crystal X-ray diffraction analysis (Fig. 1).

Table 1
Synthesis of dialkyl 5-(aryl)-1-phenyl-1*H*-prazole-3,4-dicarboxylate **7**



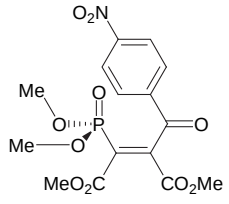
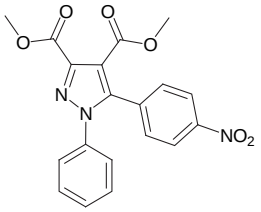
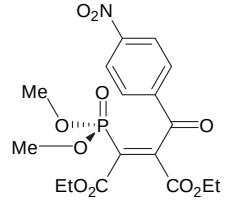
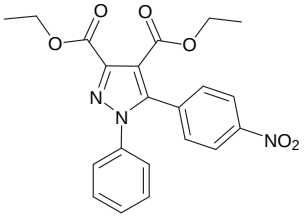
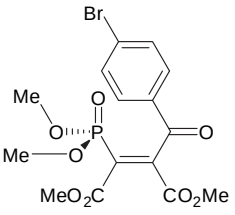
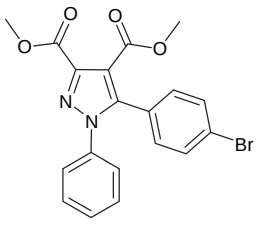
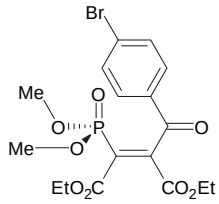
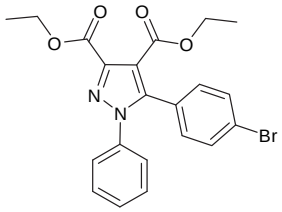
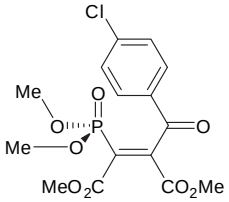
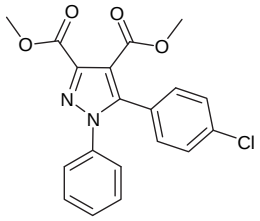
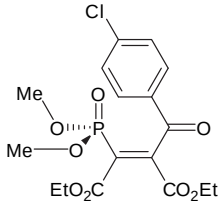
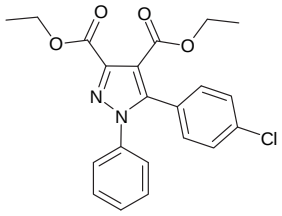
Entry	Vinylphosphonate **6** as intermediate	Product **7**	Yield %
a			85
b			83
c			75

Table 1 (*continued*)

Entry	Vinylphosphonate **6** as intermediate	Product **7**	Yield %
d			73
e			70
f			74

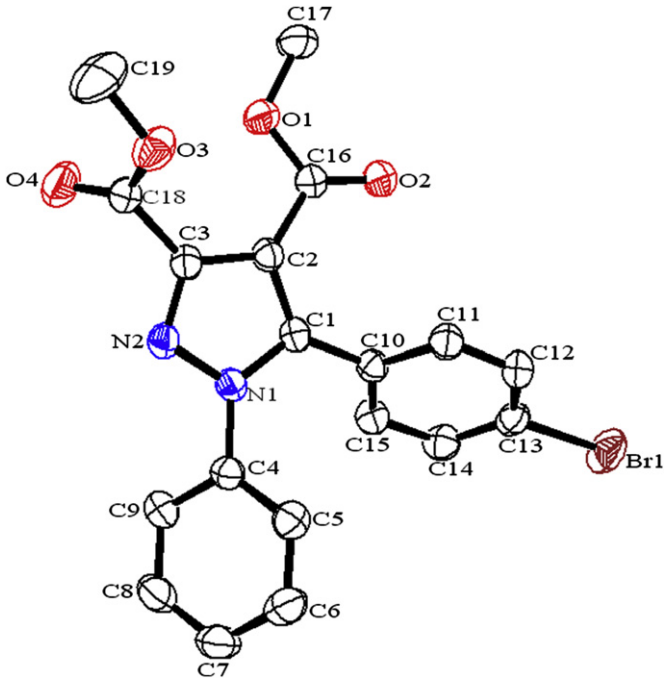
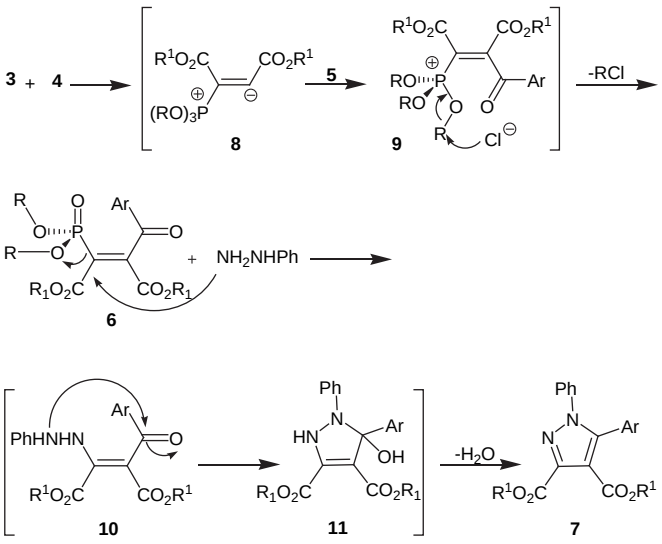


Fig. 1. The molecular structure of compound **7c**.

Although we have not established the mechanism of the reaction between phosphites **3**, acetylenic ester **4**, and aroyl chloride **5** in the presence of phenylhydrazine in an experimental manner, a possible explanation is proposed in Scheme 4. On the basis of the well-established chemistry of acetylenic esters,[15,16] it is reasonable to assume that the functionalized pyrazole derivatives **7** apparently result from initial addition of the phosphite to the acetylenic ester and subsequent attack of the resulting zwitterion **8** to the aroyl chloride **5** to yield ion pair **9**. Then, attack of the chloride ion would yield the vinylphosphonates **6** (Scheme 4). The reaction of vinylphosphonate **6** with phenylhydrazine leads to formation of intermediate **10**. Probably, the intermediate **10** undergoes cyclization followed by removal of a H_2O molecule to convert to Product **7**.



Scheme 4. Possible mechanism for the formation of products **7a**–**f**.

3. Conclusion

In summary, we have demonstrated that the one-pot four-component reaction between phosphites **3**, acetylenic esters **4**, and

aroyl chloride **5** in the presence of phenylhydrazine provides a simple method for the preparation of dialkyl 5-(aryl)-1-phenyl-1*H*-prazole-3,4-dicarboxylates **7** of potential synthetic and pharmacological interest. Fairly high yields of the products without any activation, the ready availability of the starting materials, the reaction's simplicity are the main advantages of this method.

4. Experimental

4.1. General

Phosphites, dialkyl acetylenedicarboxylates, aroyl chloride, and phenylhydrazine were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 20 eV ^{1}H and ^{13}C NMR spectra were measured (in $CDCl_3$) with a Bruker DRX-500 AVANCE spectrometer at 500 and 125 MHz, respectively. IR spectra (KBr) were recorded on a Shimadzu IR-460 spectrometer (ν in cm^{-1}).

4.2. General synthesis procedure: (for example, 7a)

To a magnetically stirred solution of dimethyl acetylenedicarboxylate (0.14 g, 1 mmol) and *p*-nitrobenzoyl chloride (0.19 g, 1 mmol) in dry toluene (2 mL) was added dropwise a solution of trimethyl phosphite (0.12 g, 1 mmol) in dry toluene (3 mL) at room temperature for 10 min. The reaction mixture was then allowed to stir for 8 h at reflux. Finally a solution of phenylhydrazine (0.11 g, 1 mmol) in dry toluene (3 mL) was added and allowed to stir for 6 h at reflux. Solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–240 mesh) column chromatography using hexane–ethyl acetate mixture as eluent.

*4.2.1. Dimethyl 5-(4-nitrophenyl)-1-phenyl-1H-prazole-3,4-dicarboxylate (**7a**).* White crystals, 0.32 g, yield 85%, mp 132–134 °C. IR (KBr): 1729 (CO_2Me), 1598 and 1521 (Ar), 1557 (C=N), 1345, 1220, 1096, and 1074 (C–O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%)=382 (M^++1, 19), 381 (M^+, 83), 364 (15), 350 (100), 304 (25), 265 (11), 139 (20), 111 (19), 84 (46), 69 (39), 43 (28). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=3.80 (3H, s, OMe), 4.00 (3H, s, OMe), 7.22 (2H, d, $^3J_{HH}$=7.1 Hz, 2CH$_{ortho}$ of Ph), 7.36 (2H, d, $^3J_{HH}$=7.4 Hz, 2CH$_{meta}$ of Ph), 7.38 (1H, t, $^3J_{HH}$=6.5 Hz, CH$_{para}$ of Ph), 7.47 (2H, d, $^3J_{HH}$=8.8 Hz, 2CH of Ar), 8.20 (2H, d, $^3J_{HH}$=8.7 Hz, 2CH of Ar). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=52.4 (MeO), 52.77 (MeO), 116.0 (C^5 of pyrazole), 123.5 (2×CH of Ar), 125.7 (2×CH$_{ortho}$ of Ph), 129.3 (CH$_{para}$ of Ph), 129.4 (2×CH of Ar), 131.3 (2×CH$_{meta}$ of Ph), 134.3 (C^4 of pyrazole), 138.0 (C$_{ipso}$–C), 142.61 (C$_{ipso}$–N), 143.9 (C$_{ipso}$–NO$_2$), 148.3 (C^3 of pyrazole), 162.0 (*C*O$_2$Me), 162.8 (*C*O$_2$Me). Anal. Calcd for $C_{19}H_{15}N_3O_6$ (381.34): C, 59.84; H, 3.96; N, 11.02. Found: C, 59.81; H, 3.93; N, 10.98.

*4.2.2. Diethyl 5-(4-nitrophenyl)-1-phenyl-1H-prazole-3,4-dicarboxylate (**7b**).* White crystals, 0.34 g, yield 83%, mp 94–96 °C. IR (KBr): 1743 (CO_2Et), 1717 (CO_2Et), 1580 and 1520 (Ar), 1547 (C=N), 1354 and 1218 (C–O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%)=410 (M^++1, 23), 409 (M^+, 100), 364 (65), 336 (94), 290 (22), 265 (70), 225 (50), 179 (61), 149 (26), 97 (22), 81 (35), 69 (65), 57 (43), 43 (49). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=1.23 (3H, t, $^3J_{HH}$=7.1 Hz, C*H*$_3$CH$_2$O), 1.43 (3H, t, $^3J_{HH}$=7.1, C*H*$_3$CH$_2$O), 4.25 (2H, q, $^3J_{HH}$=7.1 Hz, CH$_3$C*H*$_2$O), 4.47 (2H, q, $^3J_{HH}$=7.1 Hz, CH$_3$C*H*$_2$O), 7.22 (2H, d, $^3J_{HH}$=6.9 Hz, 2CH$_{ortho}$ of Ph), 7.33–7.38 (3H, m, 3CH of Ph), 7.48 (2H, d, $^3J_{HH}$=8.6 Hz, 2CH of Ar), 8.19 (2H, d, $^3J_{HH}$=8.6 Hz, 2CH of Ar). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=13.9 (*C*H$_3$CH$_2$O), 14.2 (*C*H$_3$CH$_2$O), 61.4 (CH$_3$*C*H$_2$O), 61.9 (CH$_3$*C*H$_2$O), 115.9 (C^5 of pyrazole), 123.4 (2×CH of Ar), 125.7 (2×C*H*$_{ortho}$ of Ph), 129.2 (C*H*$_{para}$ of Ph), 129.3 (2×CH of Ar), 131.4 (2×C*H*$_{meta}$ of Ph), 134.5 (C^4 of pyrazole), 138.1 (C$_{ipso}$–C), 142.4 (C$_{ipso}$–N), 144.5 (C$_{ipso}$–NO$_2$), 148.2 (C^3 of pyrazole), 161.8 (*C*O$_2$Et), 162.3 (*C*O$_2$Et). Anal. Calcd for $C_{21}H_{19}N_3O_6$ (409.40): C, 61.61; H, 4.68; N, 10.26. Found: C, 61.62; H, 4.62; N, 10.12.

*4.2.3. Dimethyl 5-(4-bromophenyl)-1-phenyl-1H-prazole-3,4-dicarboxylate (**7c**).* White crystals, 0.31 g, yield 75%, mp 151–153 °C. IR (KBr): 1748 (CO_2Me), 1725 (CO_2Me), 1597 and 1475 (Ar), 1538 (C=N), 1250 and 1225 (C–O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%)=416 (M^++1, 9), 415 (M^+, 3), 381 (31), 350 (36), 304 (10), 257 (9), 236 (18), 149 (16), 137 (16), 111 (24), 97 (43), 81 (52), 69 (100), 57 (69), 43 (74). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=3.78 (3H, s, OMe), 3.98 (3H, s, OMe), 7.14 (2H, d, $^3J_{HH}$=8.5 Hz, 2CH of Ar), 7.21–7.23 (2H, m, 2CH of Ph), 7.33 (2H, d, $^3J_{HH}$=7.2 Hz, 2CH$_{ortho}$ of Ph), 7.34 (1H, t, $^3J_{HH}$=6.1 Hz, CH$_{para}$ of Ph), 7.46 (2H, d, $^3J_{HH}$=8.5 Hz, 2CH of Ar). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=52.3 (MeO), 52.6 (MeO), 115.5 (C^5 of pyrazole), 124.2 (C$_{ipso}$–Br), 125.7 (2×CH$_{ortho}$ of Ph), 126.8 (C^4 of pyrazole), 128.9 (CH$_{para}$ of Ph), 129.2 (2CH of Ar), 131.7 (2×CH$_{meta}$ of Ph), 131.7 (2×CH of Ar), 138.4 (C$_{ipso}$–C), 143.5 (C$_{ipso}$–N), 143.8 (C^3 of pyrazole), 162.2 (*C*O$_2$Me), 163.2 (*C*O$_2$Me). Anal. Calcd for $C_{19}H_{15}BrN_2O_4$ (415.24): C, 54.96; H, 3.64; N, 6.75. Found: C, 54.58; H, 3.41; N, 6.71. Crystal data for **7c** $C_{19}H_{15}BrN_2O_4$ (CCDC 778305): M_W=415.24, triclinic, space group *P*–1, *a*=8.9430 (4) Å, *b*=10.6351 (4) Å, *c*=11.7088 (5) Å, α=63.9010 (10) β=88.2710 (10), γ=67.5250 (10), *V*=911.24 (7) Å^3, *Z*=2, D_c=1.513 mg/m^3, *F* (000)=420, crystal dimension 0.51×0.18×0.15 mm, radiation, Mo Kα (λ=0.71073 Å), $2.75 \le 2\theta \le 27.22$, intensity data were collected at 295 (2) K with a Bruker APEX area-detector diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of $-10 \le h \le 10$, $-12 \le k \le 12$, $-14 \le l \le 14$; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 2835 observed reflections with R (into)=0.0377 by a full-matrix least-squares technique converged to *R*=0.0313 and Raw=0.0902 [$I > 2\sigma(I)$].

*4.2.4. Diethyl 5-(4-bromophenyl)-1-phenyl-1H-prazole-3,4-dicarboxylate (**7d**).* White crystals, 0.32 g, yield 73%, mp 161–163 °C. IR (KBr): 1734 (CO_2Et), 1713 (CO_2Et), 1594 and 1489 (Ar), 1532 (C=N), 1312, 1251, 1203 and 1067 (C–O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%)=444 (M^++1, 61), 443 (M^+, 16), 442 (62), 397 (58), 369 (44), 325 (13), 298 (40), 258 (43), 218 (18), 190 (10), 179 (10), 77 (100), 51 (20). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=1.23 (3H, t, $^3J_{HH}$=7.1 Hz, C*H*$_3$CH$_2$O), 1.42 (3H, t, $^3J_{HH}$=7.1 Hz, C*H*$_3$CH$_2$O), 4.25 (2H, q, $^3J_{HH}$=7.1, CH$_3$C*H*$_2$O), 4.46 (2H, q, $^3J_{HH}$=7.1 Hz, CH$_3$C*H*$_2$O), 7.15 (2H, d, $^3J_{HH}$=8.4 Hz, 2CH of Ar), 7.22–7.24 (2H, m, 2CH$_{meta}$ of Ph), 7.33 (2H, d, $^3J_{HH}$=6.8 Hz, 2CH$_{ortho}$ of Ph), 7.34 (1H, t, $^3J_{HH}$=6.8 Hz, CH$_{para}$ of Ph), 7.47 (2H, d, $^3J_{HH}$=8.3 Hz, 2CH of Ar). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=13.9 (*C*H$_3$CH$_2$O), 14.2 (*C*H$_3$CH$_2$O), 61.2 (CH$_3$*C*H$_2$O), 61.8 (CH$_3$*C*H$_2$O), 115.5 (C^5 of pyrazole), 124.1 (C$_{ipso}$–Br), 125.7 (2×CH$_{ortho}$ of Ph), 127.0 (C^4 of pyrazole), 128.7 (CH$_{para}$ of Ph), 129.1 (2×CH of Ar), 131.6 (2×CH$_{meta}$ of Ph), 131.7 (2CH of Ar), 138.5 (C$_{ipso}$–C), 143.6 (C$_{ipso}$–N), 144.1 (C^3 of pyrazole), 162.0 (*C*O$_2$Et), 162.7 (*C*O$_2$Et). Anal. Calcd for $C_{21}H_{19}BrN_2O_4$ (443.29): C, 56.90; H, 4.32; N, 6.32. Found: C, 56.69; H, 4.29; N, 6.25.

*4.2.5. Dimethyl 5-(4-chlorophenyl)-1-phenyl-1H-prazole-3,4-dicarboxylate (**7e**).* White crystals, 0.26 g, yield 70%, mp 131–134 °C. IR (KBr): 1746 (CO_2Me), 1724 (CO_2Me), 1599 and 1471 (Ar), 1537 (C=N), 1258 and 1225 (C–O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%)=372 (M^++1, 20), 371 (M^+, 13), 370 (57), 339 (100), 214 (13), 77 (34). ^{1}H NMR (500.13 MHz, $CDCl_3$): δH=3.79 (3H, s, OMe), 3.99 (3H, s, OMe), 7.20 (2H, d, ^3J=8.4 Hz, 2CH of Ar), 7.31 (2H, d, ^3J=8.5 Hz, 2H, 2CH of Ar), 7.20–7.35 (m, 5H, 5CH of Ph). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=52.3 (OMe), 52.6 (OMe), 115.6 (C^5 of pyrazole), 125.7 (2×CH$_{ortho}$ of Ph), 126.3 (C^4 of pyrazole), 128.8 (2×CH of Ar), 128.9 (CH$_{para}$ of Ph), 129.2 (2×CH of Ar), 131.5 (2×CH$_{meta}$ of Ph), 135.9 (C$_{ipso}$–C),

138.4 (C_{ipso}–Br), 143.5 (C_{ipso}–N), 143.8 (C^3 of pyrazole), 162.2 (CO_2Me), 163.2 (CO_2Me). Anal. Calcd for $C_{19}H_{15}ClN_2O_4$ (370.79): C, 61.55; H, 4.08; N, 7.56. Found: C, 60.53; H, 3.93; N, 7.57.

*4.2.6. Diethyl 5-(4-chlorophenyl)-1-phenyl-1H-prazole-3,4-dicarboxylate (**7f**).* White crystals, 0.29 g, yield 74%, mp 122–125 °C. IR (KBr): 1736 (CO_2Et), 1716 (CO_2Et), 1598 and 1491 (Ar), 1535 (C=N), 1314, 1251, 1203 and 1071 (C–O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%)=400 (M^++1, 35), 399 (M^+, 24), 398 (94), 381 (16), 353 (71), 325 (68), 281 (19), 254 (56), 214 (77), 199 (15), 111 (16), 77 (100), 69 (30), 43 (25). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=1.23 (3H, t, $^3J_{HH}$=7.1, C*H*$_3$CH$_2$O), 1.43 (3H, t, $^3J_{HH}$=7.1, C*H*$_3$CH$_2$O), 4.25 (2H, q, $^3J_{HH}$=7.1 Hz, CH$_3$C*H*$_2$O), 4.47 (2H, q, $^3J_{HH}$=7.2 Hz, CH$_3$C*H*$_2$O), 7.20–7.34 (5H, m, 5CH of Ph), 7.21 (2H, d, $^3J_{HH}$=8.5 Hz, 2CH of Ar), 7.31 (2H, d, $^3J_{HH}$=8.4 Hz, 2CH of Ar). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=13.9 (*C*H$_3$CH$_2$O), 14.2 (*C*H$_3$CH$_2$O), 61.2 (CH$_3$*C*H$_2$O), 61.8 (CH$_3$*C*H$_2$O), 115.5 (C^5 of pyrazole), 125.7 (2×CH of Ar), 126.5 (C^4 of pyrazole), 128.7 (2×CH of Ar), 128.7 (CH$_{para}$ of Ph), 129.1 (2×CH$_{ortho}$ of Ph), 131.5 (2×CH$_{meta}$ of Ph), 135.8 (C_{ipso}–C), 138.5 (C_{ipso}–Br), 143.6 (C_{ipso}–N), 144.1 (C^3 of pyrazole), 162.0 (CO_2Et), 162.7 (CO_2Et). Anal. Calcd for $C_{21}H_{19}ClN_2O_4$ (398.84): C, 63.24; H, 4.80; N, 7.02. Found: C, 63.02; H, 4.56; N, 6.96.

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.10.070. These data include MOL files and InChIKeys of the most important compounds described in this article.

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