One-Pot Synthesis of Functionalized 3-Aryl-1-phenyl-1*H*-pyrazoles from Hydrazonoyl Chlorides and Acetylenic Esters in the Presence of Ph_3P

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The zwitterionic 1:1 intermediates generated by addition of Ph_3P to acetylenic esters is trapped by 1-[(aryl)chloromethylene]-2-phenylhydrazines (= *N*-phenylarenecarbohydrazonoyl chlorides) to yield functionalized 3-aryl-1-phenyl-1*H*-pyrazoles in good yields.

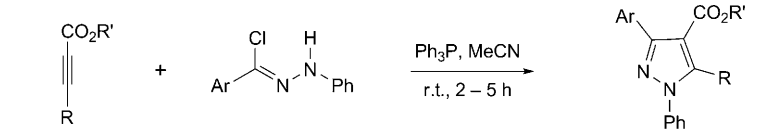
Introduction. – Pyrazoles have occupied a unique position in the design and synthesis of novel biologically active agents that exert remarkable anticancer activities. In fact, pyrazoles have been studied for over a century as an important class of heterocyclic compounds and still continue to attract considerable attention due to the broad range of biological activities they possess [1–4]. Among these, *N*-arylpyrazoles are an interesting class of heterocycles with remarkable pharmacological activities such as antibacterial-antifungal [5], tumor-necrosis inhibitor [6], antimicrobial [7], hypoglycemic [8], hypolipidemic [9], and anti-inflammatory [10][11].

Results and Discussion. – As a part of our current studies on the development of new routes in heterocyclic synthesis [12–15], we report the results of our studies involving the reaction of the zwitterionic intermediates derived from triphenylphosphine (Ph_3P) and acetylenic esters **1** with 1-[(aryl)chloromethylene]-2-phenylhydrazines (= *N*-phenylarenecarbohydrazonoyl chlorides) **2** [16–18], which constitutes a synthesis of functionalized 3-aryl-1-phenyl-1*H*-pyrazoles (**3**) in good yields (*Scheme 1*).

The structures of compounds **3a**–**3j** were deduced from their IR, ^{1}H-NMR, and ^{13}C-NMR spectra. For example, the ^{1}H-NMR spectrum of **3a** exhibited two *s*s (δ 3.87 and 3.90) for the MeO groups, along with *m*s for the Ph groups. The ^{1}H-decoupled ^{13}C-NMR spectrum of **3a** showed 15 distinct resonances that confirm the proposed structure. The IR spectrum of **3a** displayed characteristic C=O bands (1726 and 1725 cm^{-1}). The NMR spectra of **3b**–**3j** were similar to those for **3a**, except for the aryl and ester moieties, which exhibited characteristic resonances in appropriate regions of the spectra. The ^{1}H-NMR spectra of **3e**–**3j** exhibited a *s* at δ *ca.* 8.50 for the pyrazole CH group, which confirms the proposed structures.

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation. Presumably, the zwitterionic intermediate [19–21] **4**, formed from Ph_3P and **1**, adds to the hydrazonoyl chloride **2** to produce **5** (*Scheme 2*). This intermediate undergoes a cyclization reaction to afford **6**, which is converted to **3** by elimination of Ph_3P.

Scheme 1

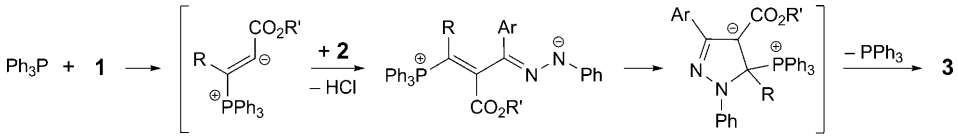


	R	R'
1a	CO_2Me	Me
1b	CO_2Et	Et
1c	H	Me
1d	H	Et

2a Ar = Ph
2b Ar = 4-MeC_6H_4
2c Ar = 4-ClC_6H_4

	R	R'	Ar	Yield [%]
3a	CO_2Me	Me	Ph	93
3b	CO_2Me	Me	4-MeC_6H_4	90
3c	CO_2Et	Et	Ph	90
3d	CO_2Et	Et	4-MeC_6H_4	89
3e	H	Me	Ph	92
3f	H	Me	4-MeC_6H_4	86
3g	H	Et	Ph	87
3h	H	Et	4-MeC_6H_4	85
3i	H	Me	4-ClC_6H_4	83
3j	H	Et	4-ClC_6H_4	86

Scheme 2



4 **5** **6**

The formation of a mixture of two regioisomers of 1,3,4-trisubstituted and 1,3,5-trisubstituted pyrazoles, in a ratio of 1:4, has been reported [22] from the reaction of 1-[(aryl)chloromethylene]-2-phenylhydrazines with alkyl prop-2-ynolates **1c** and **1d** in the presence of Et_3N. When we carried out this reaction in the presence of Ph_3P, only one regioisomer, namely the 1,3,4-trisubstituted products **3e**–**3j**, were obtained in 83–92% yields. Structures **3e**–**3j** were distinguished from the corresponding 1,3,5-trisubstituted pyrazoles by their NMR spectra. Thus, the methine H-atom of **3e**–**3j** showed a *s* at $\delta > 8.5$, whereas the methine signal of the 1,3,5-trisubstituted pyrazoles is expected at δ *ca.* 7 ppm. Similarly, the ^{13}C-NMR signal of the pyrazole CH group in compounds **3e**–**3j** appeared at $\delta > 130$, which is a deshielding by more than 10 ppm compared to the expected resonance for the 1,3,5-trisubstituted isomer.

In conclusion, the zwitterionic 1:1 intermediates generated by addition of Ph_3P to acetylenic esters is trapped by 1-[(aryl)chloromethylene]-2-phenylhydrazines to yield functionalized 3-aryl-1-phenyl-1*H*-pyrazoles in good yields. The present method may be considered as a practical route for the synthesis of pyrazole-ring systems.

Experimental Part

General. Compounds **1** and Ph_3P were obtained from *Merck* and used without further purification. Compounds **2** were prepared according to [16]. M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Shimadzu-IR-460* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-DRX-500-Avance* instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, resp.; δ in ppm, *J* in Hz. MS: *Finnigan-MAT-8430* mass spectrometer, at 70 eV; in *m*/*z* (rel. %). Elemental analyses (C, H, N): *Heraeus-CHN-O-Rapid* analyzer.

Compounds **3**: *General Procedure.* To a stirred soln. of Ph_3P (0.52 g, 2 mmol) and 1-[(aryl)chloromethylene]-2-phenylhydrazine **2** (2 mmol) in MeCN (10 ml) was added the acetylenic ester **1** (2 mmol) at −5°. The mixture was allowed to reach r.t. After completion of the reaction (2–4 h; TLC (AcOEt/hexane 2:1) monitoring), the solvent was evaporated, and the residue was purified by column chromatography (silica gel (230–240 mesh; *Merck*), hexane/AcOEt 4:1): pure product.

*Dimethyl 1,3-Diphenyl-1*H*-pyrazole-4,5-dicarboxylate* (**3a**): Yield 0.31 g (93%). Colorless crystals. M.p. 153–155°. IR (KBr): 1726 (C=O), 1725 (C=O), 1521, 1487, 1442, 1265, 1227, 1140, 1098, 1015, 786, 752, 688. ^{1}H-NMR: 3.87 (*s*, MeO); 3.90 (*s*, MeO); 7.45–7.55 (*m*, 6 CH); 7.57–7.59 (*m*, 2 CH); 7.78–7.80 (*m*, 2 CH). ^{13}C-NMR: 52.1 (MeO); 53.1 (MeO); 114.4 (C); 124.6 (2 CH); 128.2 (2 CH); 128.8 (2 CH); 129.0 (CH); 129.1 (CH); 129.2 (2 CH); 131.4 (C); 136.9 (C); 139.1 (C); 152.0 (C); 160.7 (COO); 163.4 (COO). EI-MS: 336 (75, M^+), 305 (90), 77 (100), 51 (60). Anal. calc. for $C_{19}H_{16}N_2O_4$ (336.34): C 67.85, H 4.79, N 8.33; found: C 67.72, H 4.85, N 8.20.

*Dimethyl 3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazole-4,5-dicarboxylate* (**3b**): Yield 0.31 g (90%). Colorless crystals. M.p. 65–67°. IR (KBr): 1729 (C=O), 1706 (C=O), 1585, 1527, 1490, 1432, 1292, 1261, 1230, 1179, 1110, 1003, 817, 750, 688. ^{1}H-NMR: 2.42 (*s*, Me); 3.85 (*s*, MeO); 3.88 (*s*, MeO); 7.26 (*d*, ^3J = 8.0, 2 CH); 7.43–7.49 (*m*, CH); 7.55 (*d*, ^3J = 7.8, 2 CH); 7.67 (*d*, ^3J = 8.0, 2 CH). ^{13}C-NMR: 21.3 (Me); 52.0 (MeO); 53.0 (MeO); 114.1 (C); 124.6 (2 CH); 128.5 (C); 128.7 (2 CH); 128.9 (2 CH); 129.1 (CH); 129.3 (2 CH); 136.8 (C); 138.3 (C); 139.2 (C); 152.0 (C); 160.7 (COO); 163.5 (COO). EI-MS: 350 (75, M^+), 319 (84), 77 (100), 51 (65). Anal. calc. for $C_{20}H_{18}N_2O_4$ (350.37): C 68.56, H 5.18, N 8.00; found: C 68.78, H 5.25, N 8.10.

*Diethyl 1,3-Diphenyl-1*H*-pyrazole-4,5-dicarboxylate* (**3c**): Yield 0.32 g (90%). Pale yellow crystals. M.p. 52–53°. IR (KBr): 1716 (C=O), 1702 (C=O), 1523, 1489, 1440, 1261, 1227, 1143, 1099, 1011, 756, 691. ^{1}H-NMR: 1.26 (*t*, ^3J = 6.3, Me); 1.31 (*t*, ^3J = 6.3, Me); 4.33–4.35 (*m*, 2 CH_2O); 7.44–7.48 (*m*, 4 CH); 7.55–7.57 (*m*, CH); 7.78–7.80 (*m*, CH). ^{13}C-NMR: 13.7 (Me); 14.0 (Me); 61.1 (CH_2O); 62.4 (CH_2O); 114.4 (C); 124.8 (2 CH); 128.1 (2 CH); 128.7 (CH); 128.8 (2 CH); 128.9 (CH); 129.1 (2 CH); 131.6 (C); 137.1 (C); 139.2 (C); 151.9 (C); 160.2 (COO); 162.9 (COO). EI-MS: 364 (69, M^+), 319 (85), 77 (100), 51 (55). Anal. calc. for $C_{21}H_{20}N_2O_4$ (364.40): C 69.22, H 5.33, N 7.69; found: C 69.30, H 5.40, N 7.80.

*Diethyl 3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazole-4,5-dicarboxylate* (**3d**): Yield 0.33 g (89%). Pale yellow crystals. M.p. 210–212°. IR (KBr): 1728 (C=O), 1706 (C=O), 1525, 1488, 1432, 1261, 1229, 1170, 1153, 1109, 1002, 816, 749. ^{1}H-NMR: 1.24 (*t*, ^3J = 7.1, Me); 1.30 (*t*, ^3J = 7.1, Me); 2.40 (*s*, Me); 4.28–4.33 (*m*, 2 CH_2O); 7.24 (*d*, ^3J = 7.9, 2 CH); 7.45–7.50 (*m*, CH); 7.53–7.55 (*m*, 2 CH); 7.66 (*d*, ^3J = 7.9, 2 CH). ^{13}C-NMR: 13.8 (Me); 14.0 (Me); 21.3 (Me); 61.0 (CH_2O); 62.3 (CH_2O); 114.3 (C); 124.8 (2 CH); 128.6 (C); 128.7 (2 CH); 128.8 (2 CH); 128.9 (CH); 129.0 (2 CH); 136.8 (C); 138.7 (C); 139.3 (C); 152.0 (C); 160.1 (COO); 163.0 (COO). EI-MS: 378 (75, M^+), 333 (70), 77 (100), 51 (59). Anal. calc. for $C_{22}H_{22}N_2O_4$ (378.42): C 69.83, H 5.86, N 7.40; found: C 69.68, H 5.80, N 7.31.

*Methyl 1,3-Diphenyl-1*H*-pyrazole-4-carboxylate* (**3e**): Yield 0.25 g (92%). Pale yellow crystals. M.p. 110–112°. IR (KBr): 1692 (C=O), 1589, 1525, 1433, 1360, 1274, 1221, 1133, 1053, 1007, 753, 680. ^{1}H-NMR: 3.85 (*s*, MeO); 7.39 (*t*, ^3J = 6.4, CH); 7.42–7.53 (*m*, 5 CH); 7.81 (*dd*, ^4J = 1.0, ^3J = 8.5, 2 CH); 7.91 (*dd*, ^4J = 1.4, ^3J = 8.0, 2 CH); 8.53 (*s*, CH). ^{13}C-NMR: 50.8 (MeO); 112.8 (C); 119 (2 CH); 126.9 (CH); 127.4 (2 CH); 128.2 (CH); 128.8 (2 CH); 129.0 (2 CH); 131.6 (C); 131.7 (CH); 138.7 (C); 153.5 (C); 162.8 (COO). EI-MS: 278 (70, M^+), 247 (63), 77 (100), 51 (66). Anal. calc. for $C_{17}H_{14}N_2O_2$ (278.31): C 73.37, H 5.07, N 10.07; found: C 73.50, H 5.10, N 10.15.

*Methyl 3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazole-4-carboxylate* (**3f**): Yield 0.25 g (86%). Pale yellow crystals. M.p. 103–105°. IR (KBr): 1723 (C=O), 1587, 1517, 1492, 1443, 1275, 1201, 1108, 1024, 823, 750, 687. ^{1}H-NMR: 2.44 (*s*, Me); 3.86 (*s*, MeO); 7.27 (*t*, ^3J = 7.8, 2 CH); 7.37 (*t*, ^3J = 7.5, CH); 7.48–7.51 (*m*, 2 CH); 7.78–7.80 (*m*, 4 CH); 8.51 (*s*, CH). ^{13}C-NMR: 21.4 (Me); 51.3 (MeO); 113.3 (C); 119.5 (2 CH); 127.4 (CH); 126.6 (2 CH); 128.0 (C); 129.2 (2 CH); 129.5 (2 CH); 132.2 (CH); 138.6 (C); 139.3 (C); 154.1 (C); 163.4 (COO). EI-MS: 292 (72, M^+), 261 (68), 77 (100), 51 (69). Anal. calc. for $C_{18}H_{16}N_2O_2$ (292.33): C 73.96, H 5.52, N 9.58; found: C 73.90, H 5.60, N 9.64.

*Ethyl 1,3-Diphenyl-1*H*-pyrazole-4-carboxylate* (**3g**): Yield 0.25 g (87%). Pale yellow crystals. M.p. 63–64°. IR (KBr): 1679 (C=O), 1525, 1272, 1224, 1143, 1029, 744, 681. ^{1}H-NMR: 1.34 (*t*, ^3J = 7.2, Me); 4.33 (*q*, ^3J = 7.2, CH_2O); 7.38 (*t*, ^3J = 7.4, CH); 7.42–7.53 (*m*, 5 CH); 7.81 (*d*, ^3J = 8.3, 2 CH); 7.89 (*d*, ^3J = 8.3, 2 CH); 8.53 (*s*, CH). ^{13}C-NMR: 14.2 (Me); 60.3 (CH_2O); 113.8 (C); 119.5 (2 CH); 127.4 (CH); 127.9

(2 CH); 128.6 (CH); 129.4 (2 CH); 129.6 (2 CH); 132.3 (CH); 138.5 (C); 139.3 (C); 154.0 (C); 162.9 (COO). EI-MS: 292 (74, M^+), 247 (65), 77 (100), 51 (66). Anal. calc. for $C_{18}H_{16}N_2O_2$ (292.33): C 73.96, H 5.52, N 9.58; found: C 73.90, H 5.58, N 9.71.

*Ethyl 3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazole-4-carboxylate* (**3h**): Yield 0.26 g (85%). Pale yellow crystals. M.p. 98–100°. IR (KBr): 1682 (C=O), 1522, 1272, 1220, 1133, 1052, 765, 677. ^{1}H-NMR: 1.34 (*t*, ^3J = 7.1, Me); 2.41 (*s*, Me); 4.30 (*q*, ^3J = 7.1, CH_2O); 7.26 (*t*, ^3J = 7.9, 2 CH); 7.35 (*t*, ^3J = 7.4, CH); 7.47–7.50 (*m*, 2 CH); 7.77–7.80 (*m*, 4 CH); 8.50 (*s*, CH). ^{13}C-NMR: 14.3 (Me); 21.3 (Me); 60.3 (CH_2O); 113.7 (C); 119.5 (2 CH); 127.3 (CH); 128.4 (C); 128.5 (2 CH); 129.3 (2 CH); 129.5 (2 CH); 132.3 (CH); 138.5 (C); 139.3 (C); 154.0 (C); 163.0 (COO). EI-MS: 306 (77, M^+), 261 (62), 77 (100), 51 (60). Anal. calc. for $C_{19}H_{18}N_2O_2$ (306.36): C 74.49, H 5.92, N 9.14; found: C 74.60, H 5.85, N 9.25.

*Methyl 3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carboxylate* (**3i**): Yield 0.25 g (83%). Pale yellow crystals. M.p. 149°. IR (KBr): 1692 (C=O), 1597, 1527, 1501, 1436, 1277, 1222, 1138, 1090, 1061, 1091, 959, 838, 771, 702. ^{1}H-NMR: 3.84 (*s*, MeO); 7.37 (*t*, ^3J = 7.4, CH); 7.42 (*d*, ^3J = 8.5, 2 CH); 7.50 (*t*, ^3J = 7.8, 2 CH); 7.77 (*d*, ^3J = 7.8, 2 CH); 7.87 (*d*, ^3J = 8.5, 2 CH); 8.50 (*s*, CH). ^{13}C-NMR: 51.4 (MeO); 113.3 (C); 119.5 (2 CH); 127.6 (CH); 128.1 (C); 129.5 (2 CH); 130.5 (2 CH); 130.6 (2 CH); 132.4 (CH); 134.7 (C); 139.1 (C); 152.8 (C); 163.1 (COO). EI-MS: 312 (70, M^+), 281 (72), 77 (100), 51 (56). Anal. calc. for $C_{17}H_{13}ClN_2O_2$ (312.74): C 65.28, H 4.20, N 8.95; found: C 65.13, H 4.53, N 8.71.

*Ethyl 3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carboxylate* (**3j**): Yield 0.28 g (86%). Pale yellow crystals. M.p. 146–148°. IR (KBr): 1685 (C=O), 1596, 1531, 1273, 1225, 1130, 1059, 1030, 953, 839, 770. ^{1}H-NMR: 1.34 (*t*, ^3J = 7.1, Me); 4.31 (*q*, ^3J = 7.1, CH_2O); 7.37 (*t*, ^3J = 7.3, CH); 7.42 (*d*, ^3J = 8.4, 2 CH); 7.50 (*t*, ^3J = 7.9, 2 CH); 7.77 (*d*, ^3J = 8.1, 2 CH); 7.87 (*d*, ^3J = 8.4, 2 CH); 8.50 (*s*, CH). ^{13}C-NMR: 14.2 (Me); 60.4 (CH_2O); 113.7 (C); 119.5 (2 CH); 127.5 (CH); 128.0 (C); 129.5 (2 CH); 130.6 (2 CH); 130.7 (2 CH); 132.3 (CH); 134.7 (C); 139.2 (C); 152.8 (C); 162.7 (COO). EI-MS: 326 (71, M^+), 281 (71), 77 (100), 51 (58). Anal. calc. for $C_{18}H_{15}ClN_2O_2$ (326.77): C 66.15, H 4.62, N 8.57; found: C 66.73, H 4.19, N 8.43.

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Received June 29, 2009