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Improved Protocol for Thorpe Reaction: Synthesis of 4-Amino-1-arylpyrazole using Solid–Liquid Phase-Transfer Conditions

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Abstract: Solid–liquid phase-transfer conditions were employed for the first time in the Thorpe reaction to synthesize 4-amino-1-aryl-3,5-substituted-1*H*-pyrazoles **3**. Aryl amines were diazotized and coupled with various active methylene compounds such as cyano acetamide, cyanoacetophenone, malononitrile, and ethyl cyanoacetate, resulting into α-arylhydrazononitriles **1**. Cyclization of **1** using α-bromo ketones or esters resulted in compounds **3**.

Keywords: 4-amino-1-arylpyrazole, α-arylhydrazononitriles, 18-crown-6, phase-transfer catalyst, Thorpe reaction

INTRODUCTION

The intermolecular Thorpe[1] reaction and its intramolecular version, Thorpe–Zeigler[2] reaction, are two of the most promising lines in the chemistry of five-member amino heterocycles. They are base catalyzed, and sodium or potassium alkoxide,[3a–e] sodium hydride,[3f,g] potassium hydroxide,[3h] lithium hydroxide,[3i] and potassium carbonate[1a,b] were employed frequently. Radical alternatives,[4a] solvent-free[4b] strategies, and iridium

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hydride complexes[4c] also have been applied to intramolecular as well as intermolecular Thorpe reactions. Yet, a little to our surprise, no attempt has been made to employ comprehensive strategies for the Thorpe reaction involving phase-transfer conditions.

Pyrazoles are an important class of heteroaromatic ring systems that find extensive use in the agrochemical industry and pharmaceutical industries.[5] More recently, extensive studies have focused on pyrazoles for exhibiting cyclooxygenase-2 (COX-2), nonnucleoside HIV-1 reverse transcriptase inhibitory properties[6,7] and in a novel class of synthetic Hsp90 inhibitor.[8] By far the most prevalent method of obtaining pyrazoles is by the reaction of 1,3-diketones with hydrazine, hydrazine derivatives,[9] and the nitrene insertion reaction.[10] However, if a diversity-oriented synthesis of pyrazoles[11] is desired, this method becomes cumbersome as each 1,3-diketone must be purified and is often obtained as a mixture of condensation products. Furthermore, most electrophilic functional groups such as aldehydes, nitriles, esters, and alkyl halides do not survive the transformation.

Other methods for the synthesis of pyrazoles that do not require 1,3-diketones have been reported[12] but tend to have serious drawbacks such as being step intensive. In light of this, and in continuation of our interest in the use of phase-tansfer catalysis (PTC) in heterocycles,[13] described herein are the results of a study that has culminated in the development of a process for the efficient synthesis of 4-amino-1-aryl-3,5-substituted-1*H*-pyrazoles **3**. Comparative study of the Thorpe reaction with and without phase-transfer catalyst was also carried out.

RESULTS AND DISCUSSION

Nonsubstituted and substituted aryl amines were diazotized and coupled with cyanoacetamide, cyanoacetophenone, malononitrile, and ethyl cyanoacetate according to the method prescribed in literature,[14] affording 2-arylhydrazonocyanoacetamide **1a**, ethyl 2-arylhydrazonocyanoacetophenone **1b**, 2-arylhydrazonomalononitriles **1c–e**, and ethyl 2-arylhydrazonocyanoacetates **1f–l,** respectively, in very good yields.

Thorpe reaction[1ab] of α-arylhydrazononitriles **1** with α-bromo ketone or ester in DMF/K_2CO_3/Et_3N resulted in 4-amino-1-aryl-3,5-substituted-1*H*-pyrazoles **3** (Table 1). A similar reaction by Kaja et al.[15] resulted in very poor yields, and moreover, reagents need to be used in excess to improve the yields. In view of these findings, we decided to set an improved protocol by introducing phase-transfer conditions for the Thorpe reaction. All reactions were carried out at 60–70°C or slightly warmer. Potassium hydroxide along with 18-crown-6 was our choice of catalyst, and acetonitrile was used as solvent. There was significant improvement in the reaction time and yields, and workup was clean compared to the methods reported so far.[1ab,15] However, any alteration in molar quantities of the catalyst

Table 1. Synthesis of 4-amino-1-aryl-3,5-substituted-1*H*-pyrazoles **3a–o**

				With PTC							
				Without PTC DMF/K_2CO_3/Et_3N		Liquid–liquid PTC condition[a] $TBHSO_4^b$		Solid–liquid PTC condition[c] 18-Crown-6			
									Yield (%)		
Entry	R	R^1	R^2	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Toluene	MeCN	Mp (°C) found/lit.
3a	H	$CONH_2$	COC_6H_5	6–8	80	3.5	58	2.5	74	84	192–93 (lit. 189–90)[1a]
3b	H	$CONH_2$	$COOC_2H_5$	6–8	60	3	49	2	67	80	199–200 (lit. 194–96)[1a]
3c	H	COC_6H_5	COC_6H_5	6–8	68	3.5	55	2.5	66	79	138–39 (lit. 134–36)[1a]
3d	H	COC_6H_5	$COOC_2H_5$	6–8	88	3.5	66	2.5	86	94	143–44 (lit. 140–42)[1a]
3e	H	CN	$COOC_2H_5$	6–8	86	3.5	52	2.5	64	91	123 (lit. 120–22)[1a]
3f	3-Br	CN	$COOC_2H_5$	6–8	27	3.5	35	2.5	60	67	125–26 (lit. 121–23)[15]
3g	3-Cl-4-F	CN	$COOC_2H_5$	—	—	3.5	40	2.5	58	65	132–33
3h	H	$COOC_2H_5$	COC_6H_5	6–8	80	3	65	2	79	87	173–74 (lit. 170–72)[1a]
3i	H	$COOC_2H_5$	$COOC_2H_5$	6–8	70	3.5	50	2	72	81	110–11 (lit. 91–92)[1a]
3j	3-Cl	$COOC_2H_5$	$COOC_2H_5$	—	—	3	47	2.5	70	78	100
3k	4-Cl	$COOC_2H_5$	$COOC_2H_5$	—	—	3.5	40	2	73	87	127–28
3l	4-F	$COOC_2H_5$	$COOC_2H_5$	—	—	3.5	42	2.5	53	62	109–10
3m	4-OCH_3	$COOC_2H_5$	$COOC_2H_5$	—	—	3	43	2	70	90	149–50
3n	4-CH_3	$COOC_2H_5$	$COOC_2H_5$	—	—	3.5	50	2	69	86	118
3o	3-Cl-4-F	$COOC_2H_5$	$COOC_2H_5$	—	—	3	55	2.5	78	89	155–56

Note: PTC = phase-transfer catalyst.
[a]CH_2Cl_2/KOH (aq. 40% w/v).
[b]Tetrabutylammoniumhydrogensulfate.
[c]18-Crown-6, KOH (solid), CH_3CN.

resulted in undesired by-products; a similar observation was made for the solvent.

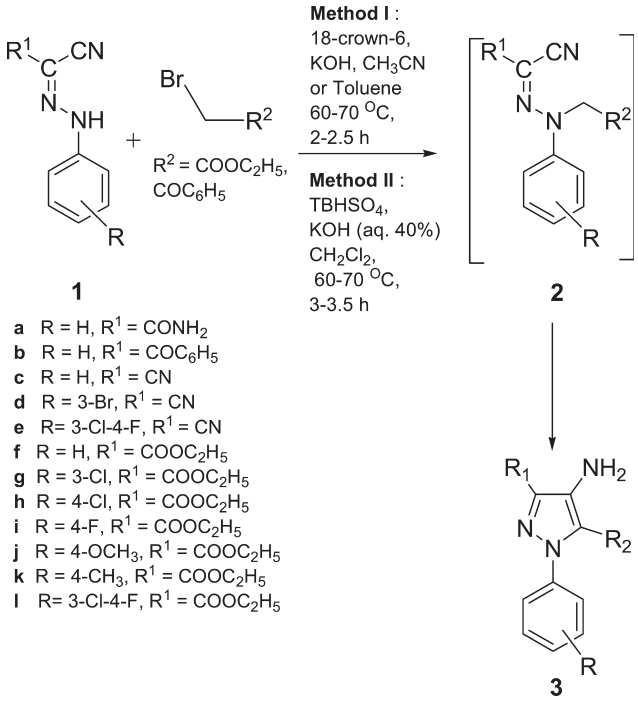
Given the frequent appearance of pyrazole fragments in pharmaceutical compounds, we sought to expand the scope of this potentially useful phase-transfer method and optimize its efficiency. To optimize the synthesis of **3**, different phase-transfer catalysts and solid–liquid and liquid–liquid phase-transfer conditions were examined (Table 1). For liquid–liquid phase-transfer conditions, CH_2Cl_2/KOH (aq. 40% w/v), lack of reactivity was observed in the presence of catalysts such as tetrabutylammonium bromide (TBAB) and triethylbenzylammonium chloride (TEBA). Results also showed concomitant decomposition of both reactants after prolonged heating (24 h, 60–70°C). Employing tricaprylmethylammonium chloride (Aliquat®) was also unsuccessful. However, under similar conditions, tetrabutylammonium hydrogen sulfate ($TBHSO_4$) proved to be a better catalyst, and compounds **3** were obtained in yields of 35–66%. Reducing the catalyst loading or changing the solvent resulted in a significant decrease in the yields. Increasing the temperature past 70°C had little effect on the yields. Finally, in solid–liquid phase-transfer conditions, the use of 18-crown-6 KOH along with acetonitrile or toluene as a solvent resulted in the formation of the product **3a–o**; however, in acetonitrile, the yields were excellent (Scheme 1).

A plausible mechanism for the Thorpe reaction is proposed in Scheme 2. The initial HBr removal from α-bromo ketone or ester and α-arylhydrazononitriles **1** resulting into the intermediate **2**, followed by intramolecular nucleophilic addition of -CH- onto the nitrile group, gave imines that could yield an enamine and also aromatic system for the formation of 4-amino-1-aryl-3,5-substituted-1*H*-pyrazoles **3**.

In conclusion, we have described a simple, clean, and convenient synthesis of 4-amino-1-aryl-3,5-substituted-1*H*-pyrazole **3**, which is an important building block for the construction of various fused heterocycles. A comparison of conventional method, liquid–liquid PTC, and solid–liquid PTC suggests that the solid–liquid PTC conditions using 18-crown-6 is the method of choice with excellent yields. The ease with which the phase-transfer catalyst reacts presents new opportunities for expanding the Thorpe reaction for the synthesis of numerous heterocycles, a use that remains almost unexplored.

EXPERIMENTAL

Melting points were determined by an electrothermal method in an open capillary tube and are uncorrected. The IR spectra were recorded in centimeters^{-1} for KBr pellets on a Buck-500 spectrophotometer. The ^{1}H NMR spectra were recorded on a Bruker 300-MHz spectrophotometer in $CDCl_3$ using TMS as internal standard, and the chemical shifts are



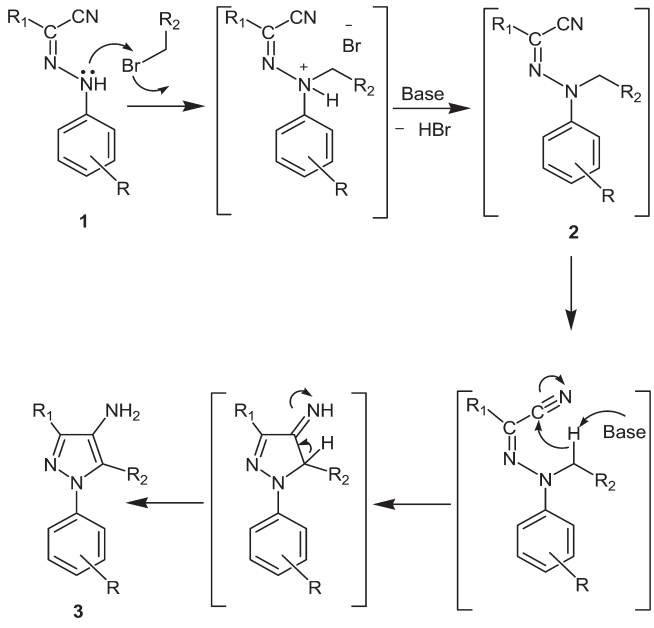
Scheme 1.

expressed in δ ppm. MS spectra were recorded on a Jeol SX-102 mass spectrophotometer under electron-impact (EI) ionization. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL III microanalyzer. The purity of the compounds was routinely checked by thin-layer chromatography (TLC) using silica gel G, and spots were exposed in iodine vapor.

Synthesis of 4-Amino-1-aryl-3,5-substituted-1*H*-pyrazole 3a–o, General Procedures

Method 1: Solid–Liquid Phase-Transfer Catalysis Conditions

α-Arylhydrazononitrile **1** (5 mmol) was added to the well-stirred solution of toluene or MeCN (20 mL), powdered KOH (0.700 g, 12.5 mmol), and 18-crown-6 (0.132 g, 0.5 mmol) and stirred for 30 m. To this α-bromo ketone or ester (8 mmol) were added portionwise. The reaction mixture was further stirred at 70–80°C for 1.5–2 h (TLC). The solvent was distilled under reduced pressure, and the reaction mixture was poured onto crushed ice



Scheme 2.

(20 g) and neutralized with acetic acid (50% v/v). The products thus obtained were filtered, washed with water, dried, and crystallized from absolute ethyl alcohol.

Method 2: Liquid–Liquid Phase-Transfer Catalysis Conditions

α-arylhydrazononitrile **1** (5 mmol) was added to the stirred mixture of CH_2Cl_2 (15 mL), KOH solution (5 mL, 40% w/v), and $TBHSO_4$ (1.69 g, 5 mmol) at room temperature. To this, α-bromo ketone or ester (8 mmol) was added portionwise in 30 m. The reaction mixture was stirred further at room temperature for 2.5–3 h (TLC). The organic phase was separated and washed with water, acetic acid (10% v/v), and water. The solvent was distilled under reduced pressure and cooled to 5–10°C; the solid thus obtained was filtered, washed with chilled methanol, and crystallized from absolute ethyl alcohol.

Data

4-Amino-5-benzoyl-1-phenyl-1*H*-pyrazole-3-carboxamide (**3a**)[1a]

IR (KBr): $\nu = 3590, 3450, 3370, 3200$ (NH), 1696, 1640 (C=O), 1616, 1504 (C=C, C=N ring) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 1.35 (t, $J = 7.2$ Hz

3H, $OCH_2\underline{CH_3}$), 4.29 (q, 2H, $O\underline{CH_2}CH_3$), 5.60 (br S, 2H, NH_2 at C4), 7.30–7.90 (m, 5H, Ar-H + NH_2 exchangeable with D_2O). MS (EI): $m/z = 306$ (M^+). Anal. calcd. for $C_{17}H_{14}N_4O_2$ (306.32): C, 66.66; H, 4.61; N, 18.29. Found: C, 66.84; H, 4.44; N, 18.10.

Ethyl 4-Amino-3-carbamoyl-1-phenyl-1*H*-pyrazole-5-carboxylate (**3b**)[1a]

IR (KBr): $\nu = 3490, 3450, 3360, 3190$ (NH), 1712, 1686 (C=O), 1604, 1500 (C=C, C=N ring) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 1.30 (t, $J = 7.2$ Hz 3H, $OCH_2\underline{CH_3}$), 4.25 (q, 2H, $O\underline{CH_2}CH_3$), 5.65 (br S, 2H, NH_2 at C4), 7.32–7.88 (m, 5H, Ar-H + NH_2 exchangeable with D_2O). MS (EI): $m/z = 274$ (M^+). Anal. calcd. for $C_{13}H_{14}N_4O_3$ (274.28): C, 56.93; H, 5.14; N, 20.43. Found: C, 56.95; H, 5.34; N, 20.32.

4-Amino-3,5-dibenzoyl-1-phenyl-1*H*-pyrazole (**3c**)[1a]

IR (KBr): $\nu = 3500, 3400$ (NH), 1652, 1624 (C=O), 1616, 1500 (C=C, C=N ring) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 5.55 (br S, 2H, NH_2), 7.30–7.90 (m, 15H, Ar-H). MS (EI): $m/z = 367$ (M^+). Anal. calcd. for $C_{23}H_{17}N_3O_2$ (367.4): C, 75.19; H, 4.66; N, 11.44. Found: C, 75.35; H, 4.86; N, 11.30.

Ethyl 4-Amino-3-benzoyl-1-phenyl-1*H*-pyrazole-5-carboxylate (**3d**)[1a]

IR (KBr): $\nu = 3490, 3370$ (NH), 1732, 1684 (C=O), 1604, 1516 (C=C, C=N ring) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 1.30 (t, $J = 7.2$ Hz 3H, $OCH_2\underline{CH_3}$), 4.27 (q, 2H, $O\underline{CH_2}CH_3$), 5.52 (br S, 2H, NH_2), 7.33–7.89 (m, 10H, Ar-H). MS (EI): $m/z = 335$ (M^+). Anal. calcd. for $C_{19}H_{17}N_3O_3$ (335.36): C, 68.05; H, 5.11; N, 12.53. Found: C, 68.15; H, 5.01; N, 12.65.

Ethyl 4-Amino-3-cyano-1-phenyl-1*H*-pyrazole-5-carboxylate (**3e**)[1a]

IR (KBr): $\nu = 3460, 3350$ (NH), 2220 (CN), 1708 (C=O), 1616, 1500 (C=C, C=N ring) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 1.35 (t, $J = 7.2$ Hz 3H, $OCH_2\underline{CH_3}$), 4.29 (q, 2H, $O\underline{CH_2}CH_3$), 5.48 (br S, 2H, NH_2), 7.30–7.85 (m, 5H, Ar-H). MS (EI): $m/z = 256$ (M^+). Anal. calcd. for $C_{13}H_{12}N_4O_2$ (256.26): C, 60.93; H, 4.72; N, 21.86. Found: C, 61.05; H, 4.88; N, 21.92.

Ethyl 4-Amino-3-cyano-1-(3-bromophenyl)-1*H*-pyrazole-5-carboxylate (**3f**)[15]

IR (KBr): $\nu = 3440, 3320$ (NH), 2210 (CN), 1712 (C=O), 1616, 1500 (C=C, C=N ring) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 1.33 (t, $J = 7.2$ Hz 3H, $OCH_2\underline{CH_3}$), 4.31 (q, 2H, $O\underline{CH_2}CH_3$), 5.50 (br S, 2H, NH_2), 7.22–7.78

(m, 4H, Ar-H). MS (EI): $m/z = 335$ (M^+). Anal. calcd. for $C_{13}H_{11}BrN_4O_2$ (335.16): C, 46.59; H, 3.31; N, 16.72. Found: C, 46.45; H, 3.41; N, 16.82.

Ethyl 4-Amino-3-cyano-1-(3-chloro-4-fluorophenyl)-1*H*-pyrazole-5-carboxylate (**3g**)

IR (KBr): $\nu = 3460, 3310$ (NH), 2210 (CN), 1716 (C═O), 1612, 1508 (C═C, C═N ring) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 1.32 (t, $J = 7.2$ Hz 3H, $OCH_2\underline{CH_3}$), 4.34 (q, 2H, $O\underline{CH_2}CH_3$), 5.45 (br S, 2H, NH_2), 7.32–7.88 (m, 3H, Ar-H). MS (EI): $m/z = 308$ (M^+). Anal. calcd. for $C_{13}H_{10}ClFN_4O_2$ (308.7): C, 50.58; H, 3.27; N, 18.15. Found: C, 50.45; H, 3.41; N, 18.12.

Ethyl 4-Amino-5-benzoyl-1-phenyl-1*H*-pyrazole-3-carboxylate (**3h**)[1a]

IR (KBr): $\nu = 3520, 3380$ (NH), 1732, 1684 (C═O), 1604, 1516 (C═C, C═N ring) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 1.35 (t, $J = 7.2$ Hz 3H, $OCH_2\underline{CH_3}$), 4.29 (q, 2H, $O\underline{CH_2}CH_3$), 5.75 (br S, 2H, NH_2), 7.30–7.90 (m, 10H, Ar-H). MS (EI): $m/z = 335$ (M^+). Anal. calcd. for $C_{19}H_{17}N_3O_3$ (335.36): C, 68.05; H, 5.11; N, 12.53. Found: C, 68.12; H, 5.27; N, 12.45.

Diethyl 4-Amino-1-phenyl-1*H*-pyrazole-3,5-dicarboxylate (**3i**)[1a]

IR (KBr): $\nu = 3520, 3410$ (NH), 1730, 1712 (C═O), 1612, 1504 (C═C, C═N ring) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 1.14–1.42 (t × 2, 6H, $OCH_2\underline{CH_3}$), 4.17–4.48 (q × 2, 4H, $O\underline{CH_2}CH_3$), 5.47 (br S, 2H, NH_2), 7.12–7.21 (m, 5H, Ar-H). MS (EI): $m/z = 303$ (M^+). Anal. calcd. for $C_{15}H_{17}N_3O_4$ (303.31): C, 59.40; H, 5.65; N, 13.85. Found: C, 59.55; H, 5.58; N, 13.93.

Diethyl 4-Amino-1-(3-chlorophenyl)-1*H*-pyrazole-3,5-dicarboxylate (**3j**)

IR (KBr): $\nu = 3510, 3380$ (NH), 1732, 1696 (C═O), 1604, 1516 (C═C, C═N ring) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 1.14–1.41 (t × 2, 6H, $OCH_2\underline{CH_3}$), 4.17–4.47 (q × 2, 4H, $O\underline{CH_2}CH_3$), 5.50 (br S, 2H, NH_2), 7.21–7.28 (m, 4H, Ar-H). MS (EI): $m/z = 337$ (M^+). Anal. calcd. for $C_{15}H_{16}ClN_3O_4$ (337.76): C, 53.34; H, 4.77; N, 12.44. Found: C, 53.29; H, 4.70; N, 12.35.

Diethyl 4-Amino-1-(4-chlorophenyl)-1*H*-pyrazole-3,5-dicarboxylate (**3k**)

IR (KBr): $\nu = 3520, 3400$ (NH), 1712, 1696 (C═O), 1604, 1516 (C═C, C═N ring) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 1.12–1.40 (t × 2, 6H, $OCH_2\underline{CH_3}$), 4.14–4.45 (q × 2, 4H, $O\underline{CH_2}CH_3$), 5.47 (br S, 2H, NH_2), 7.16–7.27 (m, 4H, Ar-H). MS (EI): $m/z = 337$ (M^+). Anal. calcd. for

$C_{15}H_{16}ClN_3O_4$ (337.76): C, 53.34; H, 4.77; N, 12.44. Found: C, 53.44; H, 4.98; N, 12.51.

Diethyl 4-Amino-1-(4-fluorophenyl)-1*H*-pyrazole-3,5-dicarboxylate (**3l**)

IR (KBr): $\nu = 3510$, 3380 (NH), 1732, 1696 (C═O), 1604, 1516 (C═C, C═N ring) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 1.15–1.43 (t × 2, 6H, $OCH_2\underline{CH_3}$), 4.18–4.49 (q × 2, 4H, $O\underline{CH_2}CH_3$), 5.53 (br S, 2H, NH_2), 7.18–7.25 (m, 4H, Ar-H). MS (EI): $m/z = 321$ (M^+). Anal. calcd. for $C_{15}H_{16}FN_3O_4$ (321.3): C, 56.07; H, 5.02; N, 13.08. Found: C, 56.19; H, 4.92; N, 12.95.

Diethyl 4-Amino-1-(4-methoxyphenyl)-1*H*-pyrazole-3,5-dicarboxylate (**3m**)

IR (KBr): $\nu = 3490$, 3390 (NH), 1724, 1704 (C═O), 1604, 1516 (C═C, C═N ring) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 1.16–1.49 (t × 2, 6H, $OCH_2\underline{CH_3}$), 3.78 (s, 3H, OCH_3), 4.20–4.52 (q × 2, 4H, $O\underline{CH_2}CH_3$), 5.51 (br S, 2H, NH_2), 7.20–7.31 (m, 4H, Ar-H). MS (EI): $m/z = 333$ (M^+). Anal. calcd. for $C_{16}H_{19}N_3O_5$ (333.34): C, 57.65; H, 5.75; N, 12.61. Found: C, 57.50; H, 5.74; N, 12.69.

Diethyl 4-Amino-1-(4-methylphenyl)-1*H*-pyrazole-3,5-dicarboxylate (**3n**)

IR (KBr): $\nu = 3510$, 3410 (NH), 1732, 1712 (C═O), 1604, 1516 (C═C, C═N ring) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 1.14–1.43 (t × 2, 6H, $OCH_2\underline{CH_3}$), 2.40 (s, 3H, CH_3), 4.17–4.47 (q × 2, 4H, $O\underline{CH_2}CH_3$), 5.47 (br S, 2H, NH_2), 7.19–7.27 (m, 4H, Ar-H). MS (EI): $m/z = 317$ (M^+). Anal. calcd. for $C_{16}H_{19}N_3O_4$ (317.34): C, 60.56; H, 6.03; N, 13.24. Found: C, 60.72; H, 5.93; N, 13.44.

Diethyl 4-Amino-1-(3-chloro-4-fluorophenyl)-1*H*-pyrazole-3,5-dicarboxylate (**3o**)

IR (KBr): $\nu = 3500$, 3400 (NH), 1716, 1696 (C═O), 1604, 1516 (C═C, C═N ring) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 1.12–1.41 (t × 2, 6H, $OCH_2\underline{CH_3}$), 4.16–4.48 (q × 2, 4H, $O\underline{CH_2}CH_3$), 5.41 (br S, 2H, NH_2), 7.16–7.27 (m, 3H, Ar-H). MS (EI): $m/z = 355$ (M^+). Anal. calcd. for $C_{15}H_{15}ClFN_3O_4$ (355.75): C, 50.64; H, 4.25; N, 11.81. Found: C, 50.44; H, 4.08; N, 12.01.

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