Palladium-catalyzed Dehalogenation of 5-Halopyrazoles

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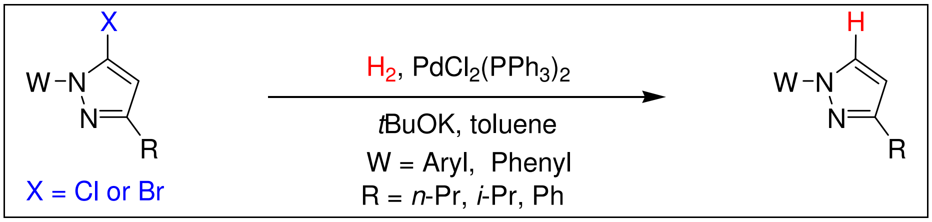

Abstract – A new and efficient method for the dehalogenation of 5-halopyrazoles was developed by using the catalytic amount of palladium (II) chloride and triphenylphosphine as a ligand at reflux under constant flow of hydrogen gas. The reaction gave the corresponding pyrazole products in good to excellent yields (≥83%).

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INTRODUCTION

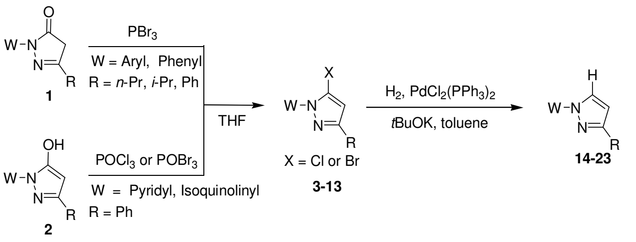
Pyrazoles [1] and pyrazolones [2] are an important family of heterocyclic compounds due to their wide range of pharmacological properties [3–11]. In particular, modified pyrazoles [12–18], pyrazolones [19–21], and polypyrroles [22–27] are the component of various active materials. They are also key starting materials for the synthesis of commercial aryl/hetarylpyrazolone dye [28–30] and acting as the efficient ligand [31] for the construction of various organometallic catalysts especially with early transition metals and lanthanides.

A halogen atom is often introduced to a given position of an arene or a heterocyclic compound to make them as the blocking group [32–36]. Occasionally, it is introduced from the side reactions [37]. Since a great number of halogenated organic compounds are hazardous pollutants widely distributed in the environment, especially polychlorinated biphenyls (PCBs) [38–41]. However, the dehalogenation is an important chemical transformation in organic synthesis and environmental remediation [42–45].

Many dehalogenation methods have been developed over years [46]. Recently, several new methods were provided by employing palladium [39,47–56], rhodium [53], iron [54], and nickel [55,56] as the catalysts. In particular, palladium catalyst is a very stable, readily commercially available, inexpensive, and comparatively nonhazardous source of hydrogen donor. However, a large number of methodologies are developed and utilized toward aryl halides, especially aryl chlorides [47–59]. To the best of our knowledge, a few dehalogenation methods were performed in the heterocyclicor pyrazole systems according to the stronger bond energy of carbon–halogen [60–62]. Whatever, the withdrawing groups (ex. carbonyl group) was introduced toward the heterocyclic or pyrazole systems to promote the dehalogenation [61]. In this paper, we report the first use of palladium chloride in the presence of triphenylphosphine and potassium *tert*-butoxide to remove the halogen atom in pyrazoles.

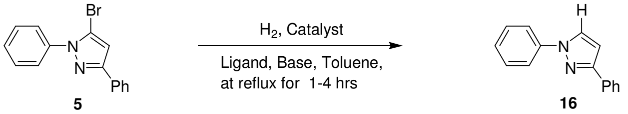
RESULTS AND DISCUSSION

As shown in Scheme 1, 5-halopyrazoles **3–13** were served as the substrates for the study of the newly developed dehalogenation method. Pyrazolones **1** and 5-hydroxypyrazoles **2,** served as the starting material**,** were obtained by reacting α-keto esters with equal equivalent of arylhydrazines through tandem condensation and thermal cyclization reaction [21,63]. 5-Bromopyrazoles **3–10** were prepared from **1** with PBr_3 in refluxing acetonitrile [63], and 5-bromopyrazoles **11–12** with 5-chloropyrazole **13** were prepared from the reaction of **2** with pure $POCl_3$ or $POBr_3$ at 60 °C [64,65].



Scheme 1

To search for the best palladium catalyst and phosphine ligand, we chose 1,3-diphenyl-5-bromopyrazole **5** as the model for the dehalogenation reaction (see Scheme 2 and Table 1). When compound **5** was reacted with various palladium catalysts including palladium chloride ($PdCl_2$), palladium acetylacetonate ($Pd(OAc)_2$), and $Pd(PPh_3)_4$, the poor yields of the product were obtained (<46%, see entry 1 and 4 of Table 1). Using $PdCl_2$ or $Pd(OAc)_2$ as the catalyst in presence of various of bulky phosphine ligands, including 1,4-bis(diphenylphosphino)butane, 1,1-bis(diphenylphosphino)ferrocene (dppf), triphenylphosphine (PPh_3), tri-*o*-tolylphosphine (P(*o*-tolyl)$_3$), tri-2,4,6-tri-methoxyphenylphosphine P(2,4,6-tri-OMePh)$_3$ provided the model product **16** in good to excellent yields (≥93%, see entry 2–7 of Table 1). Considering the reactivity and the law material cost, we envisioned that the commercially available palladium chloride and triphenylphosphine PPh_3 were the best dehalogenated catalyst and ligand for this reaction.



Scheme 2

Table 1. The Optimization study of dehalogenation of 5-bromopyrazole **5**.

Entry	Catalyst[a]	Ligand	Base	Yields of Product **16** (%)
1	$PdCl_2$	-	*t*-BuOK	4
2	$PdCl_2$	PPh_3	*t*-BuOK	98
3	$PdCl_2$	dppf	*t*-BuOK	96
4	$Pd(OAc)_2$	-	*t*-BuOK	46
5	$Pd(OAc)_2$	P(tolyl)$_3$	*t*-BuOK	97
6	$Pd(OAc)_2$	P(2,4,6-tri-OMePh)$_3$	*t*-BuOK	93
7	$Pd(OAc)_2$	1,4-bis(diphenylphosphino) butane	*t*-BuOK	95
8	$Pd(PPh)_4$	PPh_3	*t*-BuOK	51
9	$PdCl_2$	PPh_3	K_2CO_3	76
10	$PdCl_2$	PPh_3	$CsCO_3$	54
11	$PdCl_2$	PPh_3	NaOMe	not detectable
12	$PdCl_2$	PPh_3	$NaHCO_3$	trace
13	$PdCl_2$	PPh_3	Pyridine	not detectable

[a] The amount of catalysts was used 0.03 equivalent

To investigate the effect of alkali-metal base, we applied the standard procedure to 1,3-diphenyl-5-bromopyrazole **5** in presence of palladium chloride and triphenylphosphine with 2.0 equivalents of the different bases including cesium and potassium carbonate, sodium hydrogencarbonate, and sodium methoxide. However, only the poor result was obtained and most of starting material was recovered (see entry 9–12 of Table 1). When pyridine was used as a base under the same condition for 1,3-diphenyl-5-bromopyrazole **5**, we did not detect the dehalogenated product **16** (see entry 13 of Table 1). The study showed the reactivity of bases was *t*-BuOK > K_2CO_3 > $CsCO_3$ > $NaHCO_3$ > NaOMe > pyridine for the reaction.

In the newly developed dehalogenation method, we first generated $PdCl_2(PPh_3)_2$ by reacting $PdCl_2$ with triphenylphosphine (PPh_3) in EtOH at 60 ^oC [66,67]. 5-Halopyrazoles **3–13** were then treated with catalyst amount (3.0 mol%) of the resulting catalyst in toluene at reflux for 1–4 h under hydrogen atmosphere. The reaction provided the corresponding dehalogenated products **14–23** in good to excellent yields (see Table 2). For simple 5-bromo-1-phenylpyrazoles **3–5** bearing *n*-propyl, *i*-propyl, or phenyl group at the C-3 position of the pyrazole ring, the desired dehalogenation products **14–16** were obtained in good to excellent yields (92–98%, see Table 2).

Table 2. The results of dehalogenation of 5-halopyrazoles **3–13**.

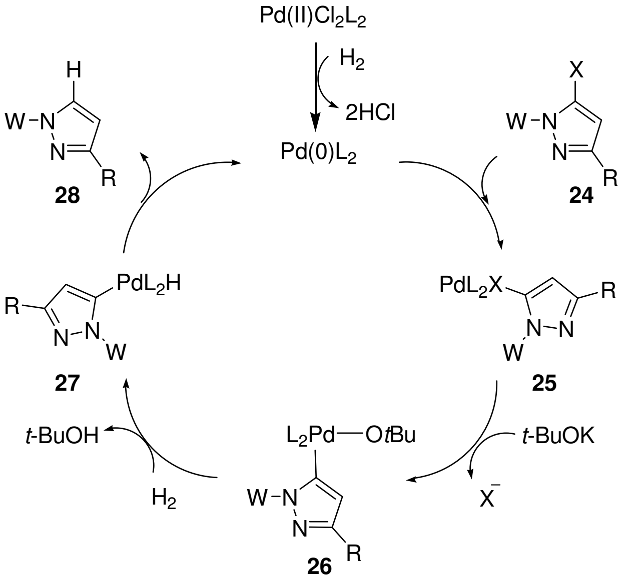
5-Halopyrazoles (**3**–**13**)				Pyrazoles (**14**–**23**)		
S.M.	X	W	R	Products	X	Yields (%)
3	Br	Ph	*n*-Pr	**14**	H	94
4	Br	Ph	*i*-Pr	**15**	H	92
5	Br	Ph	Ph	**16**	H	98
6	Br	*o*-Me-Ph	Ph	**17**	H	95
7	Br	*p*-OMe-Ph	Ph	**18**	H	92
8	Br	*p*-Cl-Ph	Ph	**19**	H	83
9	Br	*p*-Br-Ph	Ph	**16** (W = Ph)	H	96
10	Br	2,4,6-tri-Cl-Ph	Ph	**20** (W = 2,6-di-Cl-Ph) **21** (W = 2,4,6-tri-Cl-Ph)	H H	52 44
11	Br	2-quinolinyl	Ph	**22**	H	85
12	Br	Pyridyl	Ph	**23**	H	88
13	Cl	Pyridyl	Ph	**23**	H	84

[a] Compounds **14**, **16**, **18**–**19** and **21** were reported previously, our spectroscopic data (**14** [68], **16** [69], **18**–**19** and **21** [70]) are consistent with those of an authentic sample or published data in the literature. [b] Catalyst $PdCl_2(PPh_3)_2$ was prepared by followed the previous reported procedure [66,67].

To search for the effect of the substitution on the pyrazole ring, the newly dehalogenation method was applied to substrates **6**–**12**, which were attached with *o*-Me-Ph, *p*-OMe-Ph, *p*-Cl-Ph, *p*-Br-Ph, 2,4,6-tri-Cl-Ph, 2-quinolinyl or pyridyl groups at the *N*-1 position of the pyrazole. For compound **6** and **7** with *o*-Me-Ph, *p*-OMe-Ph, the reaction provided the corresponding debromination products **17**–**18** in 92–95% yields (see Table 2). The bromo atom on the pyrazole ring of compounds **8** and **9** with *p*-Cl-Ph or *p*-Br-Ph at the C-5 position was also debrominated. However, the debromination also took place on the phenyl ring in compound **9** to give the corresponding di-debrominated product **16** in 96% yield (see Table 2). As a result, the reaction was applicable to the aromatic and pyrazolic halide compounds. When we extended the same condition to 5-bromo-1-(2,4,6-tri-chlorophenyl)pyrazole **10**, the corresponding debromination product **20** and di-dehalogenation product **21** were obtained in 52% and 44% yields, respectively (see Table 2).

The dehalogenation also proceeded smoothly in compounds **11**–**13** bearing *N*-1 2-quinolinyl or pyridyl group. The expected corresponding products **22** and **23** were obtained 85% and 88% yields, respectively (see Table 2). Comparing the reaction conditions for **12** and **13**, we found that the dechlorination is more difficult than debromination (see Table 2). For example, the reaction time for the dechlorination reaction for **13** should be prolonged to 8 hours to provide the **23** in good yield [71]. The structure of dehalogenated products **14**–**23** were fully characterized by spectroscopic methods. Served as an example, compound **16** possessed pyrazole ring characteristic peaks: a doublet resonance at δ 6.78 ppm for the C-4 proton, a doublet resonance at δ 7.96 ppm for the C-5 proton, and at δ 105.02 and 126.32 ppm, which represented the ^{13}C in tertiary carbon in C-4 and C-5 on the pyrazole ring.

A general catalytic cycle for dehalogenation of 5-halopyrazoles **24** to pyrazoles **28** in the presence of palladium, phosphine, and *t*-BuOK base was depicted in Scheme 3 [72]. In the first step of this catalytic cycle, it involves the oxidation-addition process for the formation of the active catalyst Pd(0)L$_2$ to active the pyrazole–halogen bond **25** by coordination of PPh$_3$ ligand. The second step is *t*-BuOK base attacking the palladium atom and replacing halide to form the pyrazole-palladium complex **26** and potassium halide (KX) [73]. In the next step, palladium complex **26** was rapidly converted to generate palladium hydride complex **27** with bubble H$_2$. Consequently, the reduction-elimination step was followed to give the dehalogenated pyrazole product **28** and regenerate the Pd (0) species under hydrogen atmosphere.



Scheme 3

In conclusion, we have successfully developed a new palladium-catalyzed dehalogenation reaction for 5-halopyrazoles by using palladium chloride as a catalyst and triphenylphosphine as a ligand at reflux with bubble H$_2$. The reaction gave the corresponding dehalogenated products in excellent yields.

EXPERIMENTAL

General Procedure: Pyrazolones **1** or 5-hydroxypyrazoles **2** were synthesized according to literature procedure [21,63]. All chemicals were reagent grade and used as purchased unless otherwise noted. All reactions were monitored by TLC. Flash column chromatography was carried out on silica gel (70–230 mesh). Dichloromethane, ethyl acetate, hexanes, and toluene were purchased from Mallinckrodt Chemical Co. The following compounds were purchased from Acros Chemical Co: *o*-tolyhydrazine hydrochorolide, *n*-propyl acetoacetate, 4-bromophenylhydrazine hydrochloride, 4-chlorophenylhydrazine hydrochloride, ethyl isopropylacetate, 4-methoxyphenylhydrazine hydrochloride, palladium acetylacetonate, palladium chloride, phenylhydrazine, and tetrakis(triphenylphosphine)palladium. 2,4,6-Trichlorophenyl hydrazine, 2-hydrazinopyridine, and isonicotinic acid hydrazide, 1,1-bis(diphenylphosphino)ferrocene were purchased from TCI Chemical Co. 1,4-Bis(diphenylphosphino)butane, ethyl benzoylacetate, triphenylphosphine, tri-*o*-tolylphosphine, tri-2,4,6-tri-methoxyphenylphosphine were purchased from Alfa Chemical Co. Purification by gravity column chromatography was carried out by use of Merck Reagents Silica Gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wavenumbers reported are referenced to the polystyrene 1601 cm^{-1} absorption. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker (200 MHz) spectrometer by use of CDCl$_3$, CH$_3$OD, and *d6*-DMSO as solvent. Carbon-13 NMR spectra were obtained on a Bruker (50

MHz) spectrometer by used of $CDCl_3$, CH_3OD, and *d6*-DMSO as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (Hz). Elemental analyses were carried out on a Heraeus CHN–O RAPID element analyzer.

Standard Procedure for Bromination to Prepare 5-Halopyrazoles (3–13) [63–65]**.** To a solution of pyrazolones **1** or 5-hydroxypyrazoles **2** (1.0 equiv) in acetonitrile (5 mL) was added $POBr_3$, $POCl_3$ or $POBr_3$ (4.0 equiv). The reaction mixture was heated to reflux for 24–72 h. stirred at room temperature for ~1 h. After the reaction was completed, the reaction mixture was cooled to 0 °C and slowly quehched with ice/water and extracted with a 5:1 mixture of hexane and EtOAc. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20% EtOAc in hexanes as eluant) to give 5-halopyrazoles **3**–**13**.

5-Bromo-1-phenyl-3-propyl-1*H*-pyrazole (3): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (t, 3 H, *J* = 7.2 Hz, CH_3), 1.58–1.73 (m, 2 H, CH_2), 2.62 (t, 2 H, *J* = 7.4 Hz, CH_2), 6.24 (s, 1 H, Py), 7.32–7.42 (m, 3 H, ArH), 7.48–7.53 (m, 2 H, ArH) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.94, 22.65, 30.57, 109.23, 112.40, 125.48, 128.03, 128.81, 139.09, 155.17; IR (diffuse reflectance) 3053 (m), 1593 (m), 1494 (s), 1453 (s), 1407 (m), 1358 (m), 1167 (m), 1064 (w), 1018 (w), 981 (m) cm^{-1}; MS (ESI) *m/z*: 267 (M^++ 3), 265 (M^+ + H). HRMS (ESI) calcd for $C_{12}H_{14}{}^{81}BrN_2$ (M^+ + 3) 267.0320, found 267.0318; calcd for $C_{12}H_{14}{}^{79}BrN_2$ (M^+ + H) 265.0340, found 265.0339; Anal. calcd for $C_{12}H_{13}BrN_2$: C, 54.36; H, 4.94; N, 10.57. Found: C, 54.38; H, 4.92; N, 10.59.

5-Bromo-3-isopropyl-1-phenyl-1*H*-pyrazole (4): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (d, 6 H, 2 × CH_3), 2.98–3.02 (m, 1 H, CH), 6.29 (s, 1 H, Py), 7.34–7.46 (m, 3 H, ArH), 7.50–7.55 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.59, 28.26, 107.43, 112.30, 125.58, 128.05, 128.83, 139.15, 160.89; IR (diffuse reflectance) 3050 (m), 2963 (s), 2926 (s), 2870 (m), 2854 (m), 1598 (s), 1498 (s), 1458 (m), 1432 (m), 1399 (m), 1375 (m), 1297 (m), 1235 (w), 1088 (m), 988 (m), 976 (m), 909 (m) cm^{-1}; MS (ESI) *m/z*: 267 (M^++ 3), 265 (M^+ + H). HRMS (ESI) calcd for $C_{12}H_{14}{}^{81}BrN_2$ (M^+ + 3) 267.0320, found 267.0321; calcd for $C_{12}H_{14}{}^{79}BrN_2$ (M^+ + H) 265.0340, found 265.0338; Anal. calcd for $C_{12}H_{13}BrN_2$: C, 54.36; H, 4.94; N, 10.57. Found: C, 54.33; H, 4.90; N, 10.54.

5-Bromo-1,3-diphenyl-1*H*-pyrazole (5): Yellow solid in 81% yield; mp 74–75 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.78 (s, 1 H, Py), 7.37–7.62 (m, 8 H, ArH), 7.82 (d, 2 H, *J* = 6.4 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 107.71, 113.64, 125.65, 125.72, 128.41, 128.46, 128.71, 128.94, 132.35, 139.06, 153.00; IR (diffuse reflectance) 3053 (m), 1593 (m), 1494 (s), 1453 (s), 1407 (w), 1358 (m), 1168 (m), 1064 (m), 1018 (m), 981 (m) cm^{-1}; MS (ESI) *m/z*: 301 (M^++ 3), 299 (M^+ + H). HRMS (ESI) calcd for $C_{15}H_{12}{}^{81}BrN_2$ (M^+ + 3) 301.0163, found 301.0164; calcd for $C_{15}H_{12}{}^{79}BrN_2$ (M^+ + H) 299.0184, found 299.0186; Anal. calcd for $C_{15}H_{11}BrN_2$: C, 60.22; H, 3.71; N, 9.36. Found: C, 60.19; H, 3.74; N, 9.35.

5-Bromo-3-phenyl-1-*o*-tolyl-1*H*-pyrazole (6): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3 H, CH_3), 6.78 (s, 1 H, Py), 7.29–7.42 (m, 7 H, ArH), 7.82–7.86 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.47, 106.08, 115.35, 125.62, 126.57, 128.26, 128.34, 128.73, 129.85, 130.99, 132.53, 136.51, 138.13, 152.89; IR (diffuse reflectance) 3049 (m), 2924 (s), 2854 (m), 1497 (s), 1457 (m), 1357 (m), 980 (m) cm^{-1}; MS (ESI) *m/z*: 315 (M^++ 3), 313 (M^+ + H). HRMS (ESI) calcd for $C_{16}H_{14}{}^{81}BrN_2$ (M^+ + 3) 315.0320, found 315.0316; calcd for $C_{16}H_{14}{}^{79}BrN_2$ (M^+ + H) 313.0340, found 313.0338; Anal. calcd for $C_{16}H_{13}BrN_2$: C, 61.36; H, 4.18; N, 8.94. Found: C, 61.40; H, 4.21; N, 8.92.

5-Bromo-1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazole (7): White solid in 81% yield; mp 80–81 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.85 (s, 3 H, OCH_3), 6.76 (s, 1 H, Py), 6.98 (d, 2 H, *J* = 8.8 Hz, ArH), 7.33–7.43 (m, 3 H, ArH), 7.50 (d, 2 H, *J* = 8.8 Hz, ArH), 7.82 (d, 2 H, *J* = 7.4 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.54, 107.12, 114.05, 125.57, 127.20, 128.29, 128.66, 132.13, 132.41, 152.64, 159.59; IR (diffuse reflectance) 2926 (m), 2846 (m), 1606 (m), 1516 (s), 1455 (m), 1362 (m), 1300 (w), 1250 (s), 1175 (m), 1030 (m), 979 (m), 833 (m) cm^{-1}; MS (ESI) *m/z*: 331 (M^++ 3), 329 (M^+ + H); HRMS (ESI) calcd for $C_{16}H_{14}{}^{81}BrN_2O$ (M^+ + 3) 331.0269, found 331.0273; calcd for $C_{16}H_{14}{}^{79}BrN_2O$ (M^+ + H) 329.0290, found 329.0291; Anal. calcd for $C_{16}H_{13}BrN_2O$: C, 58.38; H, 3.98; N, 8.51. Found: C, 58.40; H, 3.95; N, 8.54.

5-Bromo-1-(4-chlorophenyl)-3-phenyl-1*H*-pyrazole (8): White solid; mp 94–95 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.79 (s, 1 H, Py), 7.34–7.49 (m, 5 H, ArH), 7.57 (d, 2 H, *J* = 8.7 Hz, ArH), 7.81 (d, 2 H, *J* = 6.9 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 108.02, 113.58, 125.59, 126.80, 128.53, 128.71, 129.10, 132.06, 134.24, 137.48, 153.25; IR (diffuse reflectance) 3136 (w), 3059 (w), 2922 (w), 1593 (m), 1526 (m), 1494 (s), 1454 (s), 1392 (w), 1360 (s), 1303 (w), 1237 (m), 1094 (m), 1075 (m), 1028 (m), 978 (m), 830 (m), 763 (m), 691 (m), 572 (m), 508 (w) cm^{-1}; Anal. calcd for $C_{15}H_{10}ClBrN_2$: C, 54.00; H, 3.02; N, 8.40; Cl, 10.63. Found: C, 53.90; H, 2.92; N, 8.38; Cl, 10.79.

5-Bromo-1-(4-bromophenyl)-3-phenyl-1*H*-pyrazole (9): Yellow solid in 75% yield; mp 97–98 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.79 (s, 1 H, Py), 7.34–7.43 (m, 3 H, ArH), 7.51 (d, 2 H, *J* = 8.7 Hz, ArH), 7.62 (d, 2 H, *J* = 8.7 Hz, ArH), 7.80 (d, 2 H, *J* = 7.3 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 108.09, 113.51, 122.22, 125.59, 127.05, 128.54, 128.71, 132.04, 132.07, 137.98, 153.28; IR (diffuse reflectance) 3131 (w), 3059 (m), 2923 (w), 1892 (w), 1589 (m), 1525 (m), 1493 (s), 1455 (s), 1391 (m), 1360 (m), 1302 (m), 1239 (m), 1068 (s), 978 (s), 949 (m), 827 (m), 763 (m), 691 (m), 571 (m), 507 (m) cm^{-1}; MS (ESI) *m/z*: 381 (M^++ 5), 379 (M^+ + 3), 377 (M^+ + 1); Anal. calcd for $C_{15}H_{11}Br_2N_2$: C, 47.53; H, 2.92; N, 7.39. Found: C, 47.26; H, 3.22; N, 7.21.

5-Bromo-3-phenyl-1-(2,4,6-trichlorophenyl)-1*H*-pyrazole (10): White solid in 79% yield; mp 98–99 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.83 (s, 1 H, Py), 7.35–7.44 (m, 3 H, ArH), 7.50 (s, 2 H, ArH), 7.81 (d, 2 H, *J* = 7.2 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 106.75, 116.15, 125.77, 128.65, 128.68, 128.72, 131.96, 133.50, 136.36, 136.80, 154.51; IR (diffuse reflectance) 3079 (m), 2924 (m), 1742 (m), 1555 (s), 1527 (m), 1496 (s), 1454 (s), 1385 (m), 1357 (m), 1067 (m), 977 (m), 857 (m), 824 (s) cm^{-1}; MS (ESI) *m/z*: 405 (M^+ + 5), 403 (M^+ + 3), 401 (M^+ + H); Anal. Calcd for $C_{15}H_8BrCl_3N_2$: C: 44.76; H: 2.00; N: 6.96, Found: C: 44.79; H: 1.98; N: 6.98.

5-Bromo-3-phenyl-1-(2-quinolinyl)-1*H*-pyrazole (11): White solid in 74% yield; mp 121-122 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.88 (s, 1 H, Py), 7.39–7.57 (m, 3 H, ArH), 7.60–7.73 (m, 1 H, ArH), 7.74–7.78 (m, 1 H, ArH), 7.86–7.89 (m, 3 H, ArH), 8.04 (d, 1 H, *J* = 8.8 Hz, ArH), 8.13 (d, 1 H, *J* = 8.5 Hz, ArH), 8.29–8.32 (m, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 110.03, 113.17, 116.34, 125.82, 126.87, 127.32, 127.54, 128.69, 128.71, 129.07, 130.28, 132.05, 138.69, 146.18, 150.57, 153.59; IR (diffuse reflectance) 3049 (w), 2921 (m), 1620 (m), 1600 (s), 1503 (s), 1433 (s), 1360 (s), 1229 (w), 1018 (m), 999 (s), 826 (s) cm^{-1}; MS (ESI) *m/z*: 352 (M$^+$ + 3), 350 (M$^+$ + H); HRMS (ESI) calcd for $C_{18}H_{13}{}^{81}BrN_3$ (M + 3) 352.0272, found 352.0270; calcd for $C_{18}H_{13}{}^{79}BrN_3$ (M$^+$ + H) 350.0293, found 350.0290; Anal. calcd for $C_{18}H_{12}BrN_3$: C, 61.73; H, 3.45; N, 12.00. Found: C, 61.69; H, 3.42; N, 11.98.

5-Bromo-3-phenyl-1-(2-pyridinyl)-1*H*-pyrazole (12): White solid in 82% yield; mp 55–56 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.83 (s, 1 H, Py), 7.30–7.46 (m, 4 H, ArH), 7.78–7.96 (m, 4 H, ArH), 8.58 (d, 1 H, *J* = 4.9 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 109.37, 112.87, 118.52, 122.87, 125.75, 128.61, 128.67, 132.02, 138.41, 148.15, 151.80, 153.45; IR (diffuse reflectance) 3062 (w), 1587 (m), 1469 (s), 1444 (s), 1360 (m), 1308 (w), 1236 (w), 1076 (w), 999 (w) cm^{-1}; MS (ESI) *m/z*: 302 (M$^+$ + 3), 300 (M$^+$ + H); HRMS (ESI) calcd for $C_{14}H_{11}{}^{81}BrN_3$ (M + 3) 302.0116, found 302.0115; calcd for $C_{14}H_{11}{}^{79}BrN_3$ (M$^+$ + H) 300.0136, found 300.0134; Anal. calcd for $C_{14}H_{10}BrN_3$: C, 56.02; H, 3.36; N14.00. Found: C, 56.05; H, 3.39; N, 14.03.

5-Chloro-3-phenyl-1-(2-pyridinyl)-1*H*-pyrazole (13): White solid in 71% yield; mp 56–57 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.81 (s, 1 H, Py), 7.30–7.46 (m, 4 H, ArH), 7.79–7.90 (m, 4 H, ArH), 8.58 (d, 1 H, *J* = 4.1 Hz); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 109.42, 112.90, 118.55, 122.90, 125.79, 128.70, 132.05, 138.46, 148.16, 151.81, 153.50; IR (diffuse reflectance) 3045 (w), 2924 (m), 2856 (m), 1587 (m), 1456 (s), 1365 (m), 1003 (m) cm^{-1}; MS (ESI) *m/z*: 258 (M$^+$ + 3), 256 (M$^+$ + H); HRMS (ESI) calcd for $C_{14}H_{11}{}^{37}ClN_3$ (M + 3) 258.0612, found 258.0616; calcd for $C_{14}H_{11}{}^{35}ClN_3$ (M$^+$ + H) 256.0642, found 256.0641; Anal. calcd for $C_{14}H_{10}ClN_3$: C, 65.76; H, 3.94; N, 16.43. Found: C, 65.73; H, 3.92; N, 16.46.

Standard Procedure for the Palladium-catalyzed Dehalogenation of 5-Halopyrazoles (14–23). A solution of 5-halopyrazoles (1.0 mmol, 1.0 equiv) and PdCl$_2$(PPh$_3$)$_2$ catalyst (0.03 mmol, 0.03 equiv, 3% w/w) in toluene (20 mL) was added with *t*-BuOK (2.0 mmol, 2.0 equiv) and heated at reflux for 1–4 h with bubble H$_2$ (flow rate 10 mL min^{-1}). After the reaction was completed, the reaction mixture was filtrated through Celite and the Celite bed was washed with toluene (10 mL × 2). The fitrate was washed with water (10 mL × 2), brine (10 mL × 2), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20% EtOAc in Hexanes as eluant) to give the corresponding dehalogenation products **14**–**23** in 83–98% yields.

3-Isopropyl-1-phenyl-1*H*-pyrazole (15): ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.32 (d, 6 H, *J* = 6.9 Hz, 2×CH$_3$), 3.07–3.12 (m, 1 H, CH), 6.28 (d, 1 H, *J* = 2.4 Hz, Py), 7.21–7.24 (m, 1 H, ArH), 7.38–7.43 (m, 2 H, ArH), 7.65 (d, 2 H, *J* = 8.1 Hz, ArH), 7.80 (d, 1 H, *J* = 2.4 Hz, Py); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 22.82, 28.00, 104.42, 118.88, 125.80, 127.04, 129.28, 140.32, 161.00; IR (diffuse reflectance) 3049 (w), 2963 (s), 2927 (m), 2870 (m), 1601 (s), 1531 (s), 1504 (s), 1462 (m), 1385 (m), 1302 (m), 1225 (w), 1088 (m), 1042 (s), 986 (m), 946 (s), 902 (m), 753 (s), 689 (m), 501 (w) cm^{-1}; MS (ESI) *m/z*: 187 (M$^+$ + H); HRMS (ESI) calcd for $C_{12}H_{15}N_2$ (M$^+$ + H) 187.1235, found 187.1236.

3-Phenyl-1-O-tolyl-1*H*-pyrazole (17): ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.33 (s, 3 H, CH$_3$), 6.76 (d, 1 H, *J* = 1.4 Hz, Py), 7.27–7.45 (m, 7 H, ArH), 7.63 (d, 1 H, *J* = 1.4 Hz, Py), 7.91 (d, 2 H, *J* = 7.5 Hz, ArH); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 18.20, 103.53, 125.74, 126.09, 126.60, 127.81, 128.38, 128.60, 131.35, 131.90, 133.25, 133.72, 139.98, 152.25; IR (diffuse reflectance) 3062 (m), 2925 (m), 2852 (m), 1604 (m), 1583 (m), 1529 (m), 1504 (s), 1454 (s), 1386 (m), 1359 (m), 1264 (m), 1099 (w), 1046 (m), 957 (m), 942 (m), 752 (s), 718 (m), 692 (s), 452 (w) cm^{-1}; MS (ESI) *m/z*: 235 (M$^+$ + H); HRMS (ESI) calcd for $C_{16}H_{15}N_2$ (M$^+$ + H) 235.1235, found 235.1234; Anal. calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.98; H, 6.04; N, 11.94.

1-(2,6-dichlorophenyl)-3-phenyl-1*H*-pyrazole (20): Yellow solid; mp 109–110 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.82 (d, 1 H, *J* = 2.2 Hz, Py), 7.32–7.48 (m, 6 H, ArH), 7.56 (d, 1 H, *J* = 2.2 Hz, Py), 7.86–7.92 (m, 2 H, ArH); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 104.07, 125.99, 128.06, 128.60, 128.70, 130.61, 132.88, 132.95, 134.72, 136.54, 153.15; IR (diffuse reflectance) 3060 (w), 2920 (m), 1567 (m), 1530 (m), 1503 (s), 1478 (m), 1439 (m), 1454 (m), 1358 (m), 1261 (m), 1199 (m), 1073 (m), 1036 (m), 955 (m), 941 (m), 794 (s), 750 (s), 693 (m), 636 (w) cm^{-1}; Anal. calcd for $C_{15}H_{10}Cl_2N_2$: C, 62.30; H, 3.49; N, 9.69. Found: C, 61.96; H, 3.22; N, 9.80.

3-Phenyl-1-(2-quinolinyl)-1*H*-pyrazole (22): White solid; mp 127–128 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.86 (d, 1 H, *J* = 2.5 Hz, Py), 7.33–7.54 (m, 4 H, ArH), 7.71–7.76 (m, 1 H, ArH), 7.84 (d, 1 H, *J* = 8.1 Hz, ArH), 7.96–8.06 (m, 3 H, ArH), 8.07 – 8.37 (m, 2 H, ArH), 8.86 (d, 1 H, *J* = 2.5 Hz, Py); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 105.85, 112.45, 125.81, 125.96, 126.97, 127.67, 128.28, 128.35, 128.67, 130.26, 132.82, 138.98, 146.43, 150.16, 153.99; IR (diffuse reflectance) 2916 (s), 2848 (m), 1598 (m), 1442 (m), 1359 (m), 1045 (w), 831 (m), 783 (m), 764 (m), 752 (m), 691 (m) cm^{-1}; MS (ESI) *m/z*: 272 (M$^+$ + H). HRMS (ESI) calcd for $C_{18}H_{14}N_3$ (M$^+$ + H) 272.1188, found 272.1186; Anal. calcd for $C_{18}H_{13}N_3$: C, 79.68; H, 4.83; N, 15.49. Found: C, 79.71; H, 4.86; N, 15.52.

3-Phenyl-1-(2-pyridinyl)-1*H*-pyrazole (23): Yellow solid; mp 70–71 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.80 (d, 1 H, *J* = 2.5 Hz, Py), 7.13–7.17 (m, 1 H, ArH), 7.38–7.49 (m, 3 H, ArH), 7.80 (td, 1 H, *J* = 7.7, 1.4 Hz, ArH), 7.97 (d, 2 H, *J* = 7.20 Hz, ArH), 8.12 (d, 1 H, *J* = 8.2 Hz, ArH), 8.42 (d, 1 H, *J* = 4.2 Hz, ArH), 8.62 (d, 1 H, *J* = 2.5 Hz, Py); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 105.22, 112.36, 121.11, 125.86, 128.15, 128.19, 128.59, 132.87, 138.52, 147.86, 151.46, 153.63; IR (diffuse reflectance) 3132 (w), 3059 (m), 1593 (s), 1530 (m), 1503 (m), 1469 (m), 1454 (s), 1360 (m), 1322 (w), 1304 (w), 1265 (m), 1144 (w), 1067 (m), 992 (m), 955 (m), 761 (s), 722 (m), 692 (m), 620 (w), 408 (m) cm^{-1}; MS (ESI) *m/z*: 222 (M$^+$ + H). HRMS (ESI) calcd for $C_{14}H_{12}N_3$ (M$^+$ + H) 222.1031, found 222.1030; Anal. calcd for $C_{14}H_{11}N_3$: C, 76.00; H, 5.01; N, 18.99. Found: C, 76.03; H, 4.98; N, 18.96.

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