Palladium-Catalyzed Cross-Coupling Reaction of Haloazoles with Phenylsulfonylacetonitrile

Takao Sakamoto, Yoshinori Kondo, Takashi Suginome, Setsuya Ohba, Hiroshi Yamanaka*
Pharmaceutical Institute, Tohoku University, Aobayama, Aoba-ku, Sendai 980, Japan

Received 1 July 1991; revised 9 September 1991

Condensation of halo-substituted 1,3-azoles (1,3-oxazoles, 1,3-thiazoles and imidazoles) with phenylsulfonylacetonitrile under basic conditions was promoted by catalytic action of tetrakis(triphenylphosphine)palladium(0) to give α-phenylsulfonyl-1,3-azoleacetonitriles. The adaptability of halogen atoms for the cross-coupling reaction was investigated. The reaction of 4-halo-1,2-azoles was also examined.

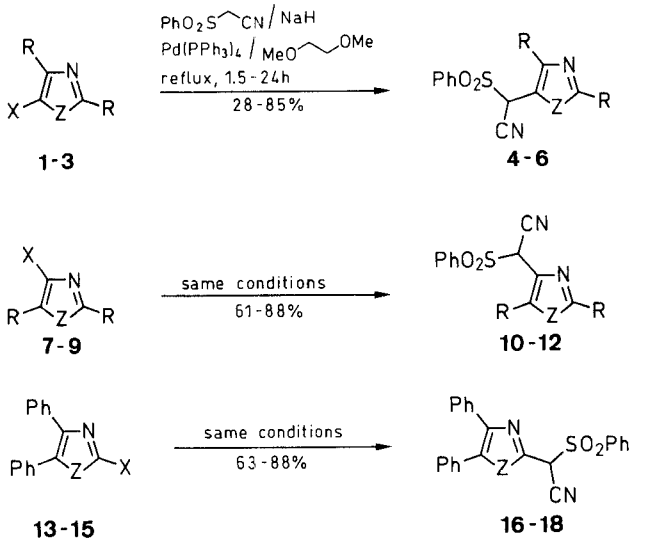
In the previous papers,[1,2] we have reported that the condensation of aryl bromides or iodides with various active methylene compounds is nicely promoted by catalytic action of tetrakis(triphenylphosphine)palladium(0)[3] to give the corresponding arene derivatives containing a functionalized methyl group. One of the products, α-phenylsulfonyl-3-pyridineacetonitrile obtained by the condensation of 3-bromopyridine with phenylsulfonylacetonitrile can be transformed into α-alkyl-3-pyridineacetonitrile by the alkylation with alkyl halides and subsequent desulfurization with zinc dust in acetic acid.[2]

In the present paper, we describe the palladium-catalyzed cross-coupling reaction of various haloazoles with phenylsulfonylacetonitrile as a representative of active methylene compounds, because the reaction was proved to have considerable scope for the synthesis of azole derivatives containing a functionalized side-chain.

When 5-bromo-2,4-diphenyloxazole (**1**) was heated with phenylsulfonylacetonitrile and sodium hydride in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) in 1,2-dimethoxyethane for 19 hours, 2,4-diphenyl-α-phenylsulfonyl-5-oxazoloacetonitrile (**4**) was obtained in 85% yield. Similarly, 5-bromo-2,4-diphenylthiazole (**2a**) reacted smoothly with phenylsulfonylacetonitrile to give 2,4-diphenyl-α-phenylsulfonyl-5-thiazoleacetonitrile (**5a**) in 78% yield. As well as **1** and **2a**, 4-bromo-2,5-diphenyloxazole (**7**)[4] and -thiazole (**8a**)[5] reacted with the same reagent, and the corresponding heteroarylacetonitriles, **10** and **11a**, were obtained in 85 and 88% yield, respectively.

In the cases of 5-bromothiazole (**2b**)[6] and 4-bromothiazole (**8b**),[7] the reaction gave rise to unsatisfactory results. For example, the reaction of **2b** under similar conditions gave α-phenylsulfonyl-5-thiazoleacetonitrile (**5b**) in 28% yield with the formation of considerable amount of resinous products. No starting material, **2b** in this case, was detected by thin-layer chromatography inspection of the reaction mixture at 14 hours reaction time. Accordingly, stability of the starting materials **2a,b** under these conditions may be a factor for the difference in the product yields.

In contrast to the cases of 5-halo- and 4-halothiazoles, the reaction of 5-halo- and 4-haloimidazole derivatives seems to be complicated. 5-Iodo-1-methylimidazole (**3b**)[8] was reduced to 1-methylimidazole during the reaction, whereas the 5-bromo-1-methylimidazole (**3a**)[9] was transformed to desired 1-methyl-α-phenylsulfonyl-5-imidazoleacetonitrile (**6**) by the reaction with phenylsulfonylacetonitrile in 42% yield. On the other hand, at the 4-position, the iodo substituent was more favorable, and 1-methyl-α-phenylsulfonyl-4-imidazoleacetonitrile (**12**) was obtained from 4-iodo-1-methylimidazole (**9**)[8] in 75% yield.



No	Z	R	X	No	Z	R
1, 7	O	Ph	Br	**4, 10**	O	Ph
2a, 8a	S	Ph	Br	**5a, 11a**	S	Ph
2b, 8b	S	H	Br	**5b, 11b**	S	H
3a	NMe	H	Br	**6, 12**	NMe	H
3b, 9	NMe	H	I			

No	Z	X	No	Z
13	O	Cl	**16**	O
14	S	Cl	**17**	S
15a	NMe	Cl	**18**	NMe
15b	NMe	Br		

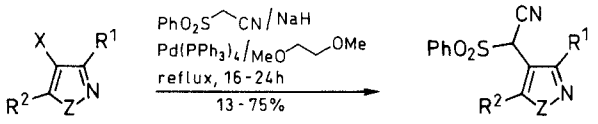
Scheme 1

At the 2-position of oxazole and thiazole, the chloro substituent has enough reactivity for the cross-coupling reaction. As shown in Scheme 1, 4,5-diphenyl-α-phenylsulfonyl-2-oxazoloacetonitrile (**16**) and -2-thiazoleacetonitrile (**17**) were formed from the corresponding chloro derivatives **13** and **14**[10,11] in 63 and 88% yield, respectively. On the other hand, at the 2-position of *N*-methylimidazole the chloro substituent was unsuitable. 2-Chloro-1-methyl-4,5-diphenylimidazole (**15a**)[12] remained unchanged under these conditions, but the 2-bromo compound **15b** was changed to 4,5-diphenyl-α-phenylsulfonyl-2-imidazoleacetonitrile (**18**) in 70% yield.

On the basis of these results described above, it can be mentioned that the palladium-catalyzed cross-coupling reaction of halo-1,3-azole derivatives with phenylsulfonylacetonitrile is a versatile method for the introduction of a functionalized carbon side-chain into these heteroaromatics, although the selection of leaving groups is a key point to obtain fruitful results.

Additionally, the palladium-catalyzed cross-coupling reaction of 4-halo-1,2-azoles with phenylsulfonylacetonitrile was examined, because the condensation reaction of these substrates with active methylene compounds is known to be difficult by means of addition–elimination under conventional conditions.[5] The palladium-catalyzed cross-coupling reaction of 4-iodo-3-methyl-5-phenylisoxazole **(19a)**[13] and 4-iodo-1-phenylpyrazole **(20a)**[14] gave the desired isoxazole **21** and pyrazole **22a** in 54 and 75% yield as expected, but the bromides **19b**[13] and **20b**,[15] corresponding to **19a** and **20a**, remained unchanged under these conditions.

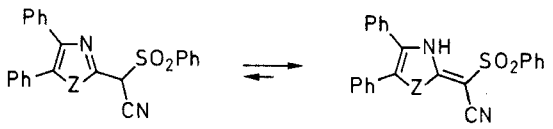
Further, 3,5-dimethyl-1-phenyl-α-phenylsulfonyl- **(22b)** and 1,3,5-triphenyl-α-phenylsulfonyl-4-pyrazoleacetonitrile **(22c)** were obtained from the corresponding bromides **20c,d** in unsatisfactory yields (13 and 32%). Based on these data, at the 4-position of isoxazole and pyrazole, iodides appear to be favorable rather than bromides for the palladium-catalyzed reaction.



No	Z	R^1	R^2	X	No	Z	R^1	R^2
19a	O	Me	Ph	I	**21**	O	Me	Ph
19b	O	Me	Ph	Br	**22a**	NPh	H	H
20a	NPh	H	H	I	**22b**	NPh	Me	Me
20b	NPh	H	H	Br	**22c**	NPh	Ph	Ph
20c	NPh	Me	Me	Br				
20d	NPh	Ph	Ph	Br				

Scheme 2

Spectral data and physical constants of all the products are listed in Table 1. The existence of imine–enamine tautomerism was observed on **16, 17,** and **18** by ^{1}H NMR spectroscopy showing the predominant enamine structure.



No	Z
16, 16'	O
17, 17'	S
18, 18'	NMe

Scheme 3

Table 1. Palladium-Catalyzed Cross-Coupling Reaction of Haloazoles with Phenylsulfonylacetonitrile

Substrate	Product	Time (h)	Yield (%)	mp (°C)[a] (solvent)	Molecular Formula[b]
1	**4**	19	85	165–166 (dec) (MeOH)	$C_{23}H_{16}N_2O_3S$ (400.4)
2a	**5a**	24	78	161–163 (MeOH)	$C_{23}H_{16}N_2O_2S_2$ (416.4)
2b	**5b**	14	28	97–99 (Et_2O-hexane)	$C_{11}H_8N_2O_2S_2$ (264.2)
3a	**6**	24	42	178–180 (dec) (AcOEt-hexane)	$C_{12}H_{11}N_3O_2S$ (261.2)
7	**10**	15	85	195–197 (MeOH)	$C_{23}H_{16}N_2O_3S$ (400.4)
8a	**11a**	8	88	174–176 (MeOH)	$C_{23}H_{16}N_2O_2S_2$ (416.4)
8b	**11b**	24	61	147–149 (MeOH)	$C_{11}H_8N_2O_2S_2$ (264.2)
9	**12**	7	75	157–158 (dec) (AcOEt-hexane)	$C_{12}H_{11}N_3O_2S$ (261.2)
13	**16**	6	63	175–177 (MeOH)	$C_{23}H_{16}N_2O_3S$ (400.4)
14	**17**	1.5	88	200–202 (dec) (MeOH)	$C_{23}H_{16}N_2O_2S_2$ (416.4)
15b	**18**	5	70	199–201 (dec) (MeOH)	$C_{24}H_{19}N_3O_2S$ (413.4)
19a	**21**	24	54	142–144 (MeOH)	$C_{18}H_{14}N_2O_3S$ (338.3)
20a	**22a**	16	75	162–164 (MeOH)	$C_{17}H_{13}N_3O_2S$ (323.3)
20c	**22b**	24	13	124–126 (MeOH)	$C_{19}H_{17}N_3O_2S$ (351.3)
20d	**22c**	24	32	108–110 (MeOH)	$C_{29}H_{21}N_3O_2S$ (475.5)

[a] Uncorrected, measured by capillary method.
[b] Satisfactory microanalyses obtained: C ±0.33, H ±0.23, S ±0.25.

2,4-Diphenyloxazole:
A mixture of benzamide (3.0 g, 25 mmol) and phenacyl bromide (1.6 g, 8 mmol) was heated at 150°C for 3 h. The hot mixture was poured onto ice, and partitioned between Et_2O (50 mL) and H_2O (50 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined ethereal solution was washed with 3N NaOH (20 mL), 3N HCl (20 mL), and sat. aq NaCl (20 mL), then dried ($MgSO_4$). The residue obtained from the ethereal solution was recrystallized from hexane/Et_2O to give colorless needles, mp 102–103°C (Lit.[16] mp 102–103°C). Yield: 1.2 g (68%).

^{1}H NMR ($CDCl_3$/TMS): δ = 7.20–7.60 (5H), m), 7.70–7.90 (2H, m), 7.95 (1H, s), 8.00–8.30 (3H, m).

5-Bromo-2,4-diphenyloxazole (1):
Br_2 (0.8 g, 5 mmol) was added dropwise to a solution of 2,4-diphenyloxazole (1.0 g, 4.5 mmol) in CCl_4 (20 mL), and the mixture was stirred at r.t. for 30 min. The solvent was decanted, and the residue was partitioned between Et_2O (20 mL) and 1N aq $NaHCO_3$ (20 mL). The ethereal solution was washed with aq $NaHSO_3$ (10 mL) and dried (Na_2SO_4). The crude product obtained from the ethereal solution was recrystallized from hexane to give colorless needles, mp 80–82°C (Lit.[17] mp 80°C). Yield: 1.1 g (81%).

^{1}H NMR ($CDCl_3$/TMS): δ = 7.3–7.7 (6H, m), 7.9–8.2 (4H, m).

5-Bromo-2,4-diphenylthiazole (2a):
2,4-Diphenylthiazole (1.0 g, 4.2 mmol) was allowed to react with Br_2 (0.8 g, 5 mmol) in CCl_4 (20 mL) for 1 h as describd above. Recrystallization from hexane gave colorless needles, mp 87–88°C (Lit.[18] mp 85°C). Yield: 1.1 g (83%).

^{1}H NMR ($CDCl_3$/TMS): δ = 7.3–7.6 (6H, m), 7.8–8.2 (4H, m).

Table 2. Spectral Data for α-Phenylsulfonylazoleacetonitriles

Product	IR (KBr)[a] ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS)[b] δ
4	2250, 1340, 1155	5.60 (1H, s), 7.10–8.20 (15H, m)
5a	2240, 1330, 1155	5.63 (1H, s), 7.20–7.70 (10H, m), 7.70–8.20 (5H, m)
5b	2250, 1340, 1160	5.53 (1H, s), 7.30–8.00 (6H, m), 8.93 (1H, s)
6	2250, 1325, 1155	3.80 (3H, m), 4.20–5.70 (1H, br), 6.80 (1H, s), 7.20–7.70 (2H, m), 7.70–8.00 (4H, m)
10	2250, 1330, 1150	5.43 (1H, s), 7.30–8.20 (15H, m)
11a	2250, 1335, 1140	5.43 (1H, s), 7.20–8.20 (15H, m)
11b	2250, 1325, 1155	5.65 (1H, s), 7.30–8.20 (6H, m), 8.32 (1H, s)
12	2250, 1355, 1155	3.70 (3H, s), 5.35 (1H, s), 7.23 (1H, s), 7.47 (1H, s), 7.50–8.20 (5H, m)
16	3200, 2200, 1360, 1150	5.60 (0.3H, s), 7.20–7.90 (13H, m), 7.90–8.20 (2H, m), 9.90–10.50 (0.7H, br)
17	3200–3100, 2200, 1325, 1320, 1145	7.30–7.50 (11H, m), 7.50–7.90 (3H, m), 7.90–8.10 (2H, m)[c]
18	3360, 2170, 1320, 1140	3.50 (3H, s), 6.90–7.70 (13H, m), 7.70–8.20 (2H, m), 10.7–11.10 (1H, br)
21	2250, 1330, 1160	2.38 (3H, s), 5.23 (1H, s), 7.30–7.80 (8H, m), 7.80–8.10 (2H, m)
22a	2250, 1330, 1150	5.23 (1H, s), 7.20–7.70 (10H, m), 7.70–8.10 (2H, m)
22b	2250, 1330, 1150	2.10 (3H, s), 2.17 (3H, s), 5.23 (1H, s), 7.20–7.60 (5H, m), 7.60–8.20 (5H, m)
22c	2250, 1335, 1160	5.30 (1H, s), 7.30–7.90 (20H, m)

[a] Recorded on a JASCO IRA-810 infrared spectrophotometer.
[b] Obtained on a JEOL JNM-PMX 60 spectrometer.
[c] Measured in DMSO-d_6/DSS [$Me_3Si(CH_2)_3SO_3Na$].

2-Bromo-1-methyl-4,5-diphenylimidazole (15b):
A mixture of 1-methyl-4,5-diphenylimidazol-2(3*H*)-one (3.0 g, 13 mmol) and $POBr_3$ (11.2 g, 39 mmol) was heated at 120–130 °C for 8 h. The mixture was poured into H_2O (50 mL) and extracted with $CHCl_3$ (3 × 20 mL). The $CHCl_3$ extract was washed with aq NH_3 (20 mL) and aq NaCl (20 mL), and dried (Na_2SO_4). The residue obtained from the $CHCl_3$ extract was passed through an alumina short column with $CHCl_3$, and the crude product was recrystallized from EtOH to give colorless needles, mp 145–147 °C. Yield: 1.9 g (47%).

$C_{16}H_{13}BrN_2$	calc.	C 61.36	H 4.18	Br 25.51	N 8.95
(313.2)	found	61.08	4.07	25.73	8.98

^1H NMR ($CDCl_3$/TMS): δ = 3.40 (3H, s), 7.10–7.70 (10H, m).

4-Bromo-3,5-dimethyl-1-phenylpyrazole (20c):
To a $CHCl_3$ (84 mL) solution of 3,5-dimethyl-1-phenylpyrazole (5 g, 29 mmol), Br_2 (1.7 mL, 32 mmol) was added at r.t. The mixture was stirred for 10 min, washed with aq $NaHSO_3$ (20 mL) and H_2O (20 mL), and dried ($MgSO_4$). The residue obtained from the $CHCl_3$ solution was distilled under reduced pressure to give a colorless liquid, bp 130 °C/4 Torr (bath temperature). Yield: 5.7 g (78%).

$C_{11}H_{11}BrN_2$	calc.	C 52.61	H 4.42	Br 31.82	N 11.16
(251.1)	found	52.37	4.46	32.04	11.25

^1H NMR (CCl_4/TMS): δ = 2.25 (3H, s), 2.30 (3H, s), 7.35 (5H, s).

4-Bromo-1,3,5-triphenylpyrazole (20d):
1,3,5-Triphenylpyrazole (3.1 g, 10.5 mmol) in $CHCl_3$ (30 mL) was brominated as described above. The crude product was recrystallized from hexane to give colorless needles mp 140–141 °C. Yield: 3.3 g (84%).

$C_{21}H_{15}BrN_2$	calc.	C 67.21	H 4.03	Br 21.29	N 7.47
(375.3)	found	67.09	4.09	21.30	7.50

^1H NMR ($CDCl_3$/TMS): δ = 7.4–7.6 (13H, m), 8.0–8.2 (2H, m).

Preparation of Tetrakis(triphenylphosphine)palladium(0) in 1,2-Dimethoxyethane:
$NaBH_4$ (7 mg, 0.2 mmol) was added to a solution of $Pd(PPh_3)_2Cl_2$ (140 mg, 0.2 mmol) and PPh_3 (104 mg, 0.4 mmol) in dry 1,2-dimethoxyethane (5 mL) under N_2 atmosphere, and the mixture was stirred for 1 min.

General Procedure for the Palladium-Catalyzed Cross-Coupling Reaction of Haloazoles with Phenylsulfonylacetonitrile
Anhydrous 1,2-dimethoxyethane (20 mL), NaH (10.5 mmol), and phenylsulfonylacetonitrile (1.0 g, 5.5 mmol) were added to a solution of $Pd(PPh_3)_4$ (0.2 mmol) in dry 1,2-dimethoxyethane prepared in situ as described above under N_2 atmosphere, and the mixture was stirred for ca. 10 min at r.t. After addition of a haloazole (5 mmol), the mixture was refluxed for an appropriate time as shown in Table 1. After removal of the solvent, the residue was diluted with H_2O (20 mL), neutralized with conc. HCl, and extracted with $CHCl_3$ (3 × 20 mL). The residue obtained from the $CHCl_3$ extract was purified by silica gel column chromatography. The product was recrystallized from an appropriate solvent, as shown in Table 1.

(1) Sakamoto, T.; Katoh, E.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1988**, *27*, 1353.
(2) Sakamoto, T.; Katoh, E.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1990**, *38*, 1513.
(3) Uno et al. reported[19] that the cross-coupling reaction of halobenzenes with active methylene compounds was catalyzed by dichlorobis(triphenylphosphine)palladium(II). But the authors proved that in the field of monoazines and diazines, tetrakis(triphenylphosphine)palladium(0) was a much better catalyst than dichlorobis(triphenylphosphine)palladium(II) for the cross-coupling reaction of haloaromatics with active methylene compounds.[20]
(4) Gilchrist, T.L.; Pearson, D.P.J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 989.
(5) Yamanaka, H.; Ohba, S.; Sakamoto, T. *Heterocycles* **1990**, *31*, 1115.
(6) Roussel, P.; Metzger, J. *Bull. Chem. Soc. Fr.* **1962**, 2075.
(7) Robba, M.; Moreau, R.C. *Ann. Pharm. Fr.* **1964**, *22*, 201; *Chem. Abstr.* **1964**, *61*, 3087.
(8) Iddon, B.; Lim, B.L. *J. Chem. Soc., Perkin. Trans. 1* **1983**, 735.
(9) Caló, V.; Ciminale, F.C.; Lopez, L.; Naso, F.; Todesco, P.E. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2567.
(10) Gompper, R.; Effenberger, F. *Chem. Ber.* **1959**, *92*, 1928.
(11) Dahlbom, R. *Acta Chem. Scand.* **1953**, *7*, 374.
(12) Whittle, C.P. *Aust. J. Chem.* **1980**, *33*, 1545.
(13) Kochetkov, N.K.; Sokolov, S.D.; Vagurtova, N.M. *Zh. Obshch. Khim.* **1961**, *31*, *2326*; *Chem. Abstr.* **1962**, *56*, 3465.
(14) Brooklyn, R.J.; Finar, I.L. *J. Chem. Soc. C* **1969**, 1515.
(15) Khan, M.A.; Lynch, B.M.; Hung, Y.-Y. *Can. J. Chem.* **1963**, *41*, 1540.
(16) Blümlein, F.O., *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2578.
(17) Shvika, O.P.; Kilimisha, G.P. *Khim. Geterotsikl. Soedin* **1966**, 677; *Chem. Abstr.* **1967**, *66*, 46356.
(18) Gusinskaya, S.L.; Telly, V.Yu.; Ovchinnikova, N.L. *Uzb. Khim. Zh.* **1971**, *15*, 47; *Chem. Abstr.* **1972**, *76*, 72617.
(19) Uno, M.; Seto, K.; Ueda, W.; Masuda, M.; Takahashi, S. *Synthesis* **1985**, 506.
Uno, M.; Seto, K.; Ueda, M.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1984**, 932.
(20) Sakamoto, T.; Katoh, E.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1644.