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Cross-Coupling of N-Heteroaryl Halides with Active Methylene Compounds in the Presence of Tetrakis(triphenylphosphine)palladium

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The cross-coupling of 3-iodo- and 3-bromopyridine with the carbanions derived from ethyl cyanoacetate and malononitrile in the presence of tetrakis(triphenylphosphine)palladium in 1,2-dimethoxyethane gave ethyl α-cyanopyridine-3-acetate and 3-pyridinemalononitrile in moderate yields. This palladium-catalyzed cross-coupling proceeded smoothly with halopyrimidines, haloquinolines, haloisoquinolines, and also bromobenzene.

Keywords——tetrakis(triphenylphosphine)palladium; aryl halide; N-heteroaryl halide; ethyl cyanoacetate; malononitrile; ethyl α-cyanoareneacetate; arenemalononitrile

It is well known that the reaction of iodobenzene (**1a**) or bromobenzene (**1b**) with active methylene compounds such as ethyl cyanoacetate or malononitrile under basic conditions gives no condensation product. Recently, Uno *et al.* reported that the dichlorobis(triphenylphosphine)palladium-catalyzed reaction of **1a** with ethyl cyanoacetate in the presence of potassium *tert*-butoxide in 1,2-dimethoxyethane (DME)[1] and with malononitrile in the presence of sodium hydride in tetrahydrofuran (THF)[2] gave the phenylated products of

1a : X=I
1b : X=Br

2a : X=COOEt
2b : X=CN

3a : X=I
3b : X=Br

4a : X=COOEt
4b : X=CN

Chart 1

TABLE I. Palladium-Catalyzed Cross-Coupling of 3-Halopyridines with Active Methylene Compounds

Run	Substrate	Catalyst	Base	Reaction time (h)	Product	Yield (%)
1	**3a** (X=I)	$Pd(PPh_3)_2Cl_2$	*tert*-BuOK	6	**4a** (Y=COOEt)	0
2	**3a** (X=I)	$Pd(PPh_3)_2Cl_2$	NaH	6	**4a** (Y=COOEt)	0
3	**3a** (X=I)	$Pd(PPh_3)_4$	*tert*-BuOK	6	**4a** (Y=COOEt)	55
4	**3a** (X=I)	$Pd(PPh_3)_4$	NaH	6	**4a** (Y=COOEt)	54
5	**3b** (X=Br)	$Pd(PPh_3)_4$	*tert*-BuOK	8	**4a** (Y=COOEt)	30
6	**3b** (X=Br)	$Pd(PPh_3)_4$	NaH	8	**4a** (Y=COOEt)	32
7	**3a** (X=I)	$Pd(PPh_3)_4$	*tert*-BuOK	1.5	**4b** (Y=CN)	87
8	**3a** (X=I)	$Pd(PPh_3)_4$	NaH	1.5	**4b** (Y=CN)	91
9	**3b** (X=Br)	$Pd(PPh_3)_4$	*tert*-BuOK	2	**4b** (Y=CN)	75
10	**3b** (X=Br)	$Pd(PPh_3)_4$	NaH	2	**4b** (Y=CN)	71

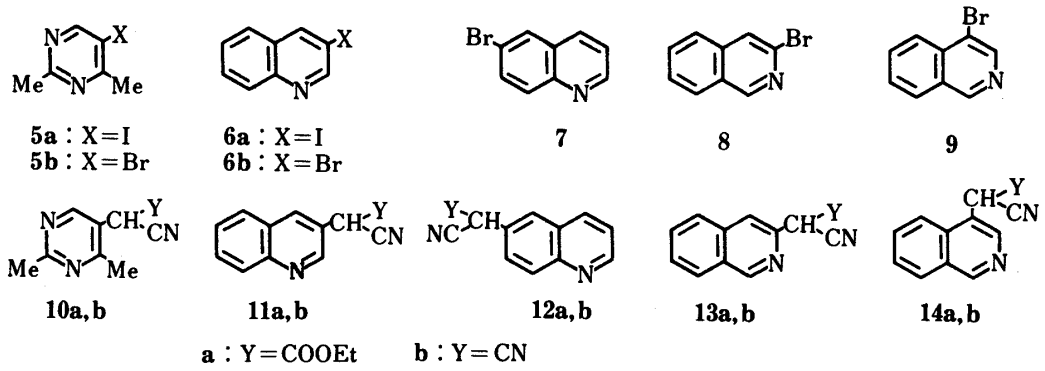

Chart 2

TABLE II. Palladium-Catalyzed Cross-Coupling of N-Heteroaryl Halides and Aryl Halides with Active Methylene Compounds

Substrate	Base	Reaction time (h)	Product	Yield (%)
5a (X=I)	*tert*-BuOK	6	**10a** (Y=COOEt)	17
5a (X=I)	NaH	6	**10a** (Y=COOEt)	47
5b (X=Br)	NaH	20	**10a** (Y=COOEt)	22
5a (X=I)	*tert*-BuOK	1	**10b** (Y=CN)	62
5a (X=I)	NaH	2	**10b** (Y=CN)	77
5b (X=Br)	NaH	6	**10b** (Y=CN)	67
6a (X=I)	NaH	3	**11a** (Y=COOEt)	67
6b (X=Br)	*tert*-BuOK	4	**11a** (Y=COOEt)	45
6b (X=Br)	NaH	6	**11a** (Y=COOEt)	60
6a (X=I)	NaH	1	**11b** (Y=CN)	73
6b (X=Br)	*tert*-BuOK	1.5	**11b** (Y=CN)	90
6b (X=Br)	NaH	2	**11b** (Y=CN)	67
7 (X=Br)	*tert*-BuOK	10	**12a** (Y=COOEt)	71
7 (X=Br)	NaH	9	**12a** (Y=COOEt)	30
7 (X=Br)	*tert*-BuOK	1	**12b** (Y=CN)	82
7 (X=Br)	NaH	3	**12b** (Y=CN)	55
8 (X=Br)	*tert*-BuOK	9	**13a** (Y=COOEt)	0
8 (X=Br)	NaH	17	**13a** (Y=COOEt)	6
8 (X=Br)	NaH	3	**13b** (Y=CN)	61
9 (X=Br)	NaH	6	**14a** (Y=COOEt)	64
9 (X=Br)	NaH	2	**14b** (Y=CN)	61
1b (X=Br)	*tert*-BuOK	20	**2a** (Y=COOEt)	48
1b (X=Br)	NaH	20	**2a** (Y=COOEt)	24
1b (X=Br)	*tert*-BuOK	20	**2b** (Y=CN)	60
1b (X=Br)	NaH	20	**2b** (Y=CN)	76

such active methylene compounds, but ethyl α-cyanophenylacetate was obtained in poor yield from **1b**.

Meanwhile, the introduction of an active methylene moiety into the so-called inactive position[3] of π-deficient N-heteroaromatic rings is always a source of difficulty to investigators, whereas such introduction at the active position[3] can mostly be done by means of the condensation of active methylene compounds with N-heteroarenes containing an appropriate leaving group. From this point of view, we investigated the condensation of inactive N-heteroaryl halides with ethyl cyanoacetate and malononitrile in the presence of a palladium catalyst.

Firstly, in order to estimate optimum reaction conditions, the reactions of 3-iodopyridine

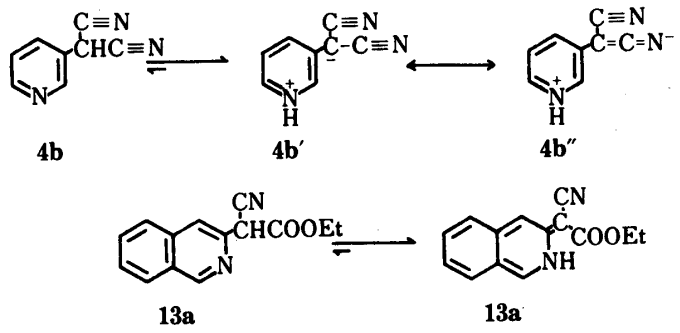

Chart 3

TABLE III. Spectral Data for Ethyl α-Cyanoareneacetates and Arenemalononitriles

No.	IR cm^{-1}			^{1}H-NMR δ (ppm)
2a	($CHCl_3$)	1740, 2250	(CCl_4)	1.20 (3H, t, J=7), 4.20 (2H, q, J=7), 4.74 (1H, s), 7.2—7.6 (5H, m)
2b	($CHCl_3$)	2250	($CDCl_3$)	4.97 (1H, s), 7.48 (5H, s)
4a	($CHCl_3$)	1750, 2250	($CDCl_3$)	1.17 (3H, t, J=7), 4.25 (2H, q, J=7), 4.89 (1H, br s), 7.2—7.5 (1H, m), 7.7—8.0 (1H, m), 8.5—8.8 (2H, m)
4b	(KBr)	2140, 2160	(DMSO-d_6)	7.5—7.8 (2H, m), 7.8—8.1 (2H, m), 11.7—13.2 (1H, br)
10a	($CHCl_3$)	1750, 2250	(CCl_4)	1.27 (3H, t, J=7), 2.46 (3H, s), 2.56 (3H, s), 4.24 (2H, q, J=7), 4.98 (1H, s), 8.44 (1H, s)
10b	(KBr)	2110, 2170	(DMSO-d_6)	2.61 (3H, s), 2.64 (3H, s), 8.31 (1H, s), 9.0—10.2 (1H, br)
11a	($CHCl_3$)	1750, 2250	($CDCl_3$)	1.30 (3H, t, J=7), 4.18 (2H, q, J=7), 4.81 (1H, s), 7.2—7.8 (3H, m), 7.8—8.0 (1H, m), 8.08 (1H, d, J=2), 8.69 (1H, d, J=2)
11b	(KBr)	2140, 2180	(DMSO-d_6)	7.5—7.8 (2H, m), 7.8—8.2 (3H, m), 8.57 (1H, d, J=2), 10.0—14.0 (1H, br)
12a	($CHCl_3$)	1740, 2250	($CDCl_3$)	1.24 (3H, t, J=7), 4.24 (2H, q, J=7), 5.25 (1H, br s), 7.2—7.6 (1H, m), 7.6—8.3 (4H, m), 8.91 (1H, dd, J=2, 4)
12b	(KBr)	2140, 2180	(DMSO-d_6)	7.25 (1H, d, J=2), 7.5—8.1 (3H, m), 8.6—8.9 (2H, m), 12.0—17.0 (1H, br)
13a	($CHCl_3$)	1650, 2200	($CDCl_3$)	1.29 (3H, t, J=7), 4.28 (2H, q, J=7), 7.1—7.4 (1H, m), 7.5—8.0 (4H, m), 8.50 (1H, d, J=8), 15.0—16.5 (1H, br)
13b	(KBr)	2160, 2190	(DMSO-d_6)	7.1—7.2 (2H, m), 7.2—7.9 (2H, m), 8.00 (1H, d, J=8), 8.96 (1H, s), 11.5—16.5 (1H, br)
14a	($CHCl_3$)	1750, 2250	($CDCl_3$)	1.26 (3H, t, J=7), 4.29 (2H, q, J=7), 5.25 (1H, s), 7.6—8.3 (4H, m), 8.70 (1H, s), 9.35 (1H, s)
14b	(KBr)	2140, 2170	(DMSO-d_6)	7.7—8.5 (4H, m), 8.1—9.3 (2H, m), 13.1—16.0 (1H, br)

DMSO-d_6: dimethyl sulfoxide-d_6.

(**3a**) and 3-bromopyridine (**3b**) with ethyl cyanoacetate and malononitrile were tested; the results are listed in Table I.

The reaction of **3a** with ethyl cyanoacetate under the reported conditions[1,2] (runs 1 and 2) gave no condensation product, but the use of tetrakis(triphenylphosphine)palladium[4] instead of dichlorobis(triphenylphosphine)palladium in DME promoted the reaction to give ethyl α-cyanopyridine-3-acetate (**4a**) (runs 3 and 4) in considerable yields. The use of tetrakis(triphenylphosphine)palladium was so effective that the condensation of **3a** with malononitrile gave pyridine-3-malononitrile (**4b**) in high yields (runs 7 and 8). Although the reaction of 3-bromopyridine (**3b**) with ethyl cyanoacetate provided the product (**4a**) in relatively low yields (runs 5 and 6), the reaction with malononitrile afforded **4b** in good yields (runs 9 and 10). In the above reactions, no significant difference in the yields of **4a**, **b** depending on the use of potassium *tert*-butoxide or sodium hydride was observed.

On the basis of these results, the standard reaction conditions were fixed for the next

investigation. Namely, a mixture of an N-heteroaryl halide (5 mmol) with an active methylene compound (10 mmol) in the presence of tetrakis(triphenylphosphine)palladium (0.2 mmol) and a base (sodium hydride or potassium *tert*-butoxide, 15 mmol) in DME was refluxed for an appropriate time.

As shown in Chart 2 and Table II, most of the N-heteroaryl halides except for 3-bromoisoquinoline (**8**) reacted with ethyl cyanoacetate under these conditions to give the cross-coupling products. Similarly to the reaction of 3-halopyridines, the reactions with malononitrile were generally observed to give better yields than the reaction with ethyl cyanoacetate.

Finally, the reactions of bromobenzene (**1b**) with ethyl cyanoacetate and malononitrile were re-investigated using tetrakis(triphenylphosphine)palladium as a catalyst. As shown in Table II, tetrakis(triphenylphosphine)palladium is a better catalyst than dichlorobis(triphenylphosphine)palladium for the condensation.

Additionally, it should be mentioned that N-heteroarenemalonitriles have a betaine structure on the basis of the spectral data, *e.g.*, **4b''** for pyridine-3-malononitrile (**4b**). For example, the infrared (IR) spectrum of **4b** shows an absorption band due to an ammonium structure at 3100—3200 cm^{-1}, and two bands at 2140 and 2180 cm^{-1} were assigned to absorptions of the cyano group and the ketenimine group. The proton nuclear magnetic (^1H-

TABLE IV. Physical Constants and Analytical Data for Ethyl α-Cyanoareneacetates and Arenemalononitriles

No.	mp or bp/mmHg (°C)	Appearance (Recryst. solvent)	Formulae	Analysis (%) Calcd (Found)		
				C	H	N
2a	105—110/10	Colorless liquid	$C_{11}H_{11}NO_2$	lit.[1] bp 115 °C/11 mmHg		
2b	67—68	Colorless needles (Hexane)	$C_9H_6N_2$	lit.[5] mp 68—69 °C		
4a	100—101	Yellow needles (C_6H_6)	$C_{10}H_{10}N_2O_2$	63.15 (62.92	5.30 5.30	14.73 14.50)
4b	242—244	Yellow needles (EtOH)	$C_8H_5N_3$	lit.[6] mp 246—248 °C		
10a	100—105/4	Yellow liquid	$C_{11}H_{13}N_3O_2$	60.26 (60.46	5.98 5.85	19.17 19.39)
10b	196—198	Yellow scales (EtOH)	$C_9H_8N_4$	62.78 (63.01	4.68 4.69	32.54 32.41)
11a	75—76	Colorless needles (Hexane)	$C_{14}H_{12}N_2O_2$	69.99 (69.97	5.03 4.97	11.66 11.58)
11b	246—247	Reddish-purple needles (EtOH)	$C_{12}H_7N_3$	74.60 (74.35	3.65 3.49	21.75 21.81)
12a		Bluish-purple viscous oil	$C_{12}H_{15}N_5O_9$[a]	51.18 (50.97	3.22 2.94	14.92 14.85)
12b	240 (dec.)	Reddish-purple needles (EtOH)	$C_{12}H_7N_3$	74.60 (74.62	3.65 3.44	21.75 21.54)
13a	159—161	Orange needles (AcOEt–hexane)	$C_{14}H_{12}N_2O_2$	69.99 (69.72	5.03 4.96	11.66 11.45)
13b	245—247 (dec.)	Red needles (EtOH)	$C_{12}H_7N_3$	74.60 (74.83	3.65 3.47	21.75 21.49)
14a	133—134	Colorless needles (Hexane)	$C_{14}H_{12}N_2O_2$	69.99 (70.22	5.03 4.90	11.66 11.39)
14b	158—159	Yellow needles (EtOH)	$C_{12}H_7N_3$	74.60 (74.80	3.65 3.54	21.75 21.45)

a) Picrate: mp 157—159 °C (yellow needles from MeOH).

NMR) spectrum of **4b** shows no signal of a methine group and a broad signal attributed to an NH moiety at 11.7—13.2 ppm. On the other hand, the ^{1}H-NMR spectra of ethyl α-cyano-N-heteroareneacetates except for ethyl α-cyanoisoquinoline-3-acetate (**13a**) show a signal of a methine group. Compound **13a** was concluded to exist as an exomethylene structure (**13a'**) on the basis of the spectral data.

Experimental

All melting points and boiling points are uncorrected. IR spectra were measured with JASCO IRA-1 and IR-810 spectrometers. ^{1}H-NMR spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer and at 99.55 MHz with a JEOL JNM-FX100 spectrometer. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet, and br = broad.

General Procedure for the Cross-Coupling of Aryl Halides with Active Methylene Compounds——A mixture of ethyl cyanoacetate or malononitrile (10 mmol) and *tert*-BuOK or NaH (15 mmol) in dry DME (20 ml) was added under an N_2 atmosphere to a dry DME solution of $Pd(PPh_3)_4$ prepared as described below, and the mixture was stirred at room temperature for 10 min. After addition of an aryl halide (5 mmol), the mixture was refluxed for an appropriate time (shown in Tables I and II). After removal of the solvent *in vacuo*, the residue was diluted with H_2O, neutralized with concentrated HCl, and extracted with $CHCl_3$. The residue obtained from the $CHCl_3$ extract was purified by silica gel column chromatography, and the product was distilled or recrystallized.

Preparation of $Pd(PPh_3)_4$ in DME——Sodium borohydride (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 DME (5 ml) under an N_2 atmosphere, and the mixture was stirred for 1 min.

References and Notes

1) M. Uno, K. Seto, W. Ueda, M. Masuda, and S. Takahashi, *Synthesis*, **1985**, 506.
2) M. Uno, K. Seto, and S. Takahashi, *J. Chem. Soc., Chem. Commun.*, **1984**, 932.
3) In the present paper, inactive positions mean the β-positions of π deficient N-heteroaromatic rings such as position 3 of the pyridine ring, position 5 of the pyrimidine ring, and positions 3 and 4 of the isoquinoline ring. On the other hand, examples of active positions are positions 2 and 4 of the pyridine ring.
4) Uno *et al.*[1,2] reported that the cross-coupling of aryl halides with active methylene compounds was catalyzed by tetrakis(triphenylphosphine)palladium, but no data were given.
5) J. C. Hessler, *Am. Chem. J.*, **32**, 123 (1904).
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