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Studies on Pyrimidine Derivatives. XXXVIII.[1] Cross-Coupling Reaction of *N*-Heteroaryl Iodides with Ethoxycarbonylmethylzinc Bromide in the Presence of Palladium Catalyst

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In the presence of tetrakis(triphenylphosphine)palladium, 2-iodo-4,6-dimethylpyrimidine and 4-iodo-2,6-dimethylpyrimidine reacted with ethoxycarbonylmethylzinc bromide (Reformatsky reagent) to give ethyl 4,6-dimethyl-2-pyrimidineacetate and ethyl 2,6-dimethyl-4-pyrimidineacetate, respectively. In contrast, the reaction of 5-iodo-2,4-dimethylpyrimidine with the same reagent resulted in recovery of the starting iodide. Similar results were observed in the reactions of various *N*-heteroaryl iodides.

Keywords——Reformatsky reagent; cross-coupling reaction; *N*-heteroaryl halide; *N*-heteroarylacetic acid; palladium catalyst; ethyl bromoacetate

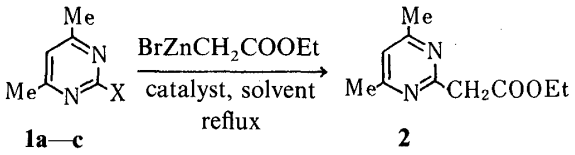
Grignard reagents are known to react with *N*-heteroaromatics such as quinoline,[2] isoquinoline,[3] acridine,[4] pyrimidine,[5] and quinazoline,[6] but there is no report dealing with the Reformatsky reaction of these *N*-heteroaromatics with α-halocarboxylic esters. Furthermore, we found that the reaction of quinoline 1-oxide with ethoxycarbonylmethylzinc bromide (Reformatsky reagent) did not proceed to any significant extent.[7] On the other hand, it has been reported that the cross-coupling reaction of *N*-heteroaryl halides with Grignard reagent is remarkably facilitated by the addition of transition metal–phosphine complex as a catalyst.[8]

From these points of view, we investigated the transition metal-catalyzed cross-coupling reaction of *N*-heteroaryl halides with ethoxycarbonylmethylzinc bromide derived from ethyl bromoacetate and zinc, and obtained promising results, which are described in the present paper.

The Reformatsky reagent employed in the present investigation was prepared by the metalation of ethyl bromoacetate with fresh zinc metal formed from zinc dichloride and potassium metal in dry tetrahydrofuran (THF). When 2-iodo-4,6-dimethylpyrimidine (**1c**) was heated with the reagent in dimethoxyethane (DME) in the presence of bis(triphenylphosphine)palladium for 20 min, ethyl 4,6-dimethyl-2-pyrimidineacetate (**2**) was obtained in 45% yield, as expected. The product (**2**) was identical with an authentic specimen synthesized by a known method.[9] In contrast, the reaction of 2-bromo-4,6-dimethylpyrimidine (**1b**) under the same conditions resulted in a poor yield (18%) of **2**, and 2-chloro-4,6-dimethylpyrimidine (**1a**) did not react with the reagent even under forcing conditions. Based on these results, *N*-heteroaryl iodides are concluded to be the best substrates among the three kinds of halides for a reaction of this type.

Next, in order to find a more favorable catalyst, **1c** was treated with the reagent in the presence of other phosphine-complexes of palladium and nickel. Prior to the above experiment, THF was confirmed to be as effective as DME for the reaction. As shown in

TABLE I.

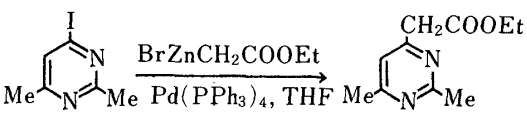


1a—c **2**

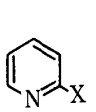
a: X=Cl
b: X=Br
c: X=I

Starting halide	Catalyst	Solvent	Reaction time (h)	Yield (**2**) (%)	Recovery (**1**) (%)
1a	$Pd(PPh_3)_2$	DME	6	0	62
1b	$Pd(PPh_3)_2$	DME	0.3	18	56
1c	$Pd(PPh_3)_2$	DME	0.3	45	0
1c	$Pd(PPh_3)_2$	THF	1.5	45	0
1c	$Pd(PPh_3)_4$	THF	1.5	65	0
1c	$Pd(PPh_3)_2Cl_2$	THF	6	27	1
1c	$Ni(PPh_3)_4$	THF	3	13	0
1c	—	THF	8	0	55

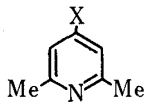
Table I, the yield of **2** depended on the kind of catalyst employed; tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] was satisfactory for the formation of **2**.



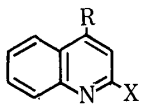
3 **4**



5: X=I
6: X=CH_2COOEt



7: X=I
8: X=CH_2COOEt

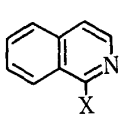


9a: R=H, X=I
9b: R=Me, X=I
10a: R=H, X=CH_2COOEt
10b: R=Me, X=CH_2COOEt

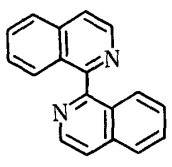
Chart 1

As shown in Chart 1, *N*-heteroaryl iodides having an iodine substituent at an active position, such as 4-iodo-2,6-dimethylpyrimidine (**3**), 2-iodopyridine (**5**), 4-iodo-2,6-dimethylpyridine (**7**), 2-iodoquinoline (**9a**), and 2-iodo-4-methylquinoline (**9b**) reacted with the Reformatsky reagent in THF in the presence of $Pd(PPh_3)_4$ to give the corresponding ethyl *N*-heteroarylacetates (**4**, **6**, **8**, and **10a**, **b**) as sole products. The structures of these products were easily determined on the basis of the spectral data.

In some cases, the concomitant formation of the bis-*N*-heteroaryl compound as well as the desired *N*-heteroarylacetates was observed. For example, in the reaction of 1-iodoisoquinoline (**11**) with the same reagent under similar conditions ethyl 1-isoquinolineacetate (**12**), and 1,1′-biisoquinoline (**13**) were isolated in nearly equal yields. As shown in Chart 2, the



11: X=I
12: X=CH_2COOEt
14: X=H



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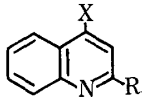
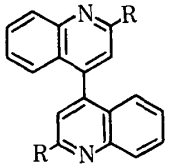


15a: R=H, X=I
15b: R=Me, X=I
16a: R=H, X=CH_2COOEt
16b: R=Me, X=CH_2COOEt
18a: R=H, X=H
18b: R=Me, X=H

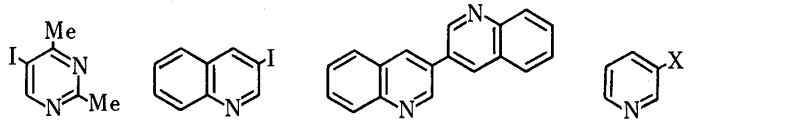


17a: R=H
17b: R=Me

Chart 2

reaction of 4-iodoquinoline (**15a**) and its 2-methyl homolog (**15b**) afforded similar results.

When the iodine substituent is located at the β-position with respect to the ring-nitrogen atom of the substrates, the reaction resulted in the exclusive formation of the corresponding bis-*N*-heteroaryl compound or in the recovery of the starting iodide. Namely, in the reaction of 3-iodoquinoline (**20**), 3,3′-biquinoline (**21**) was isolated as a sole product, and in the reaction of 5-iodo-2,6-dimethylpyrimidine (**19**), the starting pyrimidine was recovered. Although 3-iodopyridine (**22**) appeared to be exceptional giving ethyl 3-pyridineacetate (**23**), the reactivity of **22** with the reagent is rather low, and the yield of **23** was only 13% after a relatively long reaction time.



19 **20** **21** **22**: X=I **23**: X=CH_2COOEt

Chart 3

The results of our present investigation may be briefly summarized as follows.

(1) When the iodine atom is located at the α- or γ-position with respect to ring-nitrogen atom of an *N*-heteroaryl iodide, the cross-coupling reaction with the Reformatsky reagent proceeds to give the ethyl *N*-heteroarylacetate.

(2) When the iodide atom is located at the β-position with respect to ring-nitrogen atom of an *N*-heteroaryl iodide, the homo-coupling reaction of the substrate proceeds to give the bis-*N*-heteroaryl compound, or the starting iodide is recovered.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 60 MHz with a JEOL JMN-PMX 60 spectrometer. Chemical shifts are expressed in δ (ppm) values. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet.

Preparation of the Catalyst——Tetrakis(triphenylphosphine)palladium: Sodium borohydride (20 mg, 0.48 mmol) was added to a dry DME solution (10 ml) of $Pd(PPh_3)_2Cl_2$ (330 mg, 0.48 mmol) and PPh_3 (250 mg, 0.96 mmol) under an N_2 atmosphere and the mixture was stirred for 1 min. The DME solution was used in the cross-coupling reaction.

Tetrakis(triphenylphosphine)nickel was similarly prepared from $Ni(PPh_3)_2Cl_2$.

Bis(triphenylphosphine)palladium was similarly prepared from $Pd(PPh_3)_2Cl_2$ without the addition of PPh_3.

General Procedure for the Cross-Coupling Reaction of *N*-Heteroaryl Halides with Ethoxycarbonylmethylzinc Bromide——Potassium (35 mmol) was added under an N_2 atmosphere to a dry THF (20 ml) solution of $ZnCl_2$ (35 mmol) which had been dried at 180 °C under 3 mmHg pressure for 4 h, and the mixture was refluxed for 0.5 h. When DME was used as a solvent, the THF was evaporated off and dry DME (20 ml) was added. After the mixture had cooled, ethyl bromoacetate (20 mmol), which had been washed with 1 N $NaHCO_3$, dried over K_2CO_3, and distilled, was added, and then an *N*-heteroaryl halide (10 mmol) in dry THF (10 ml) and a transition metal catalyst (0.48 mmol) in DME (10 ml) were added with stirring at room temperature. The whole was refluxed for an appropriate time, then the solvent was evaporated off. The residue was triturated with $CHCl_3$ and 3 N HCl, and made alkaline with K_2CO_3. The mixture was filtered in the presence of a filter aid and the filtrate was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over K_2CO_3 and the $CHCl_3$ was evaporated off. The residue was purified by SiO_2 column chromatography and the product was distilled under reduced pressure.

Ethyl 4,6-Dimethyl-2-pyrimidineacetate (2)——The crude extract obtained by the general procedure (reaction time, 1.5 h) from 2-iodo-4,6-dimethylpyrimidine (**1c**) (2.34 g, 10 mmol) in the presence of $Pd(PPh_3)_4$ was purified by SiO_2 column chromatography with $CHCl_3$ as an eluent. The eluate was distilled to afford a pale yellow solid, bp 130 °C (3 mmHg), which was recrystallized from hexane to give pale yellow needles, mp 64—66 °C. Lit.[9] mp 62—66 °C. Yield 1.26 g (65%).

Ethyl 2,6-Dimethyl-4-pyrimidineacetate (4)——The crude extract obtained by the general procedure (reaction

time, 1 h) from 4-iodo-2,6-dimethylpyrimidine (**3**) (2.34 g, 10 mmol) was purified by SiO_2 column chromatography with hexane–AcOEt (1 : 1, v/v) as an eluent. The eluate gave a colorless liquid, bp 110 °C (3 mmHg). Yield 0.74 g (38%). *Anal.* Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 62.13; H, 7.41; N, 14.40.

Ethyl 2-Pyridineacetate (6)——The crude extract obtained by the general procedure (reaction time, 1.5 h) from 2-iodopyridine (**5**) (2.05 g, 10 mmol) was purified by SiO_2 column chromatography with hexane–AcOEt (7 : 3, v/v) as an eluent. The eluate gave a colorless liquid, bp 110 °C (3 mmHg). Yield 0.9 g (55%). Lit.[10] bp 110—113 °C (6 mmHg).

Ethyl 2,6-Dimethyl-4-pyridineacetate (8)——The crude extract obtained by the general procedure (reaction time, 1.5 h) from 4-iodo-2,6-dimethylpyridine (**7**) (2.33 g, 10 mmol) was purified by SiO_2 column chromatography with hexane–AcOEt (7 : 3, v/v) as an eluent. The eluate gave a colorless liquid, bp 120 °C (3 mmHg). Yield 0.92 g (48%). *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.18; H, 7.58; N, 7.02.

Ethyl 2-Quinolineacetate (10a)——The crude extract obtained by the general procedure (reaction time, 1.5 h) from 2-iodo-quinoline (**9a**) (2.55 g, 10 mmol) was purified by SiO_2 column chromatography with hexane–AcOEt (7 : 3, v/v) as an eluent. The eluate gave a pale yellow liquid, bp 160 °C (3 mmHg). Yield 0.79 g (37%). Lit.[11] bp 156 °C (3 mmHg).

Ethyl 4-Methyl-2-quinolineacetate (10b)——The crude extract obtained by the general procedure (reaction time, 1.5 h) from 2-iodo-4-methylquinoline (**9b**) (2.69 g, 10 mmol) was purified by SiO_2 column chromatography with hexane–AcOEt (7 : 3, v/v) as an eluent. The eluate gave a pale yellow liquid, bp 170 °C (3 mmHg). Yield 1.43 g (64%). *Anal.* Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 72.92; H, 6.80; N, 5.90.

Ethyl 1-Isoquinolineacetate (12)——The crude extract obtained by the general procedure (reaction time, 2 h) from 1-iodoisoquinoline (**11**) (2.55 g, 10 mmol) was purified by SiO_2 column chromatography with hexane–AcOEt (7 : 3, v/v) as an eluent. The first fraction gave a pale yellow liquid (**12**), bp 135—140 °C (3 mmHg). Yield 0.66 g (31%). Lit.[12] bp 135—140 °C (3 mmHg).

The second fraction gave isoquinoline (**14**) as a colorless liquid, bp 105 °C (3 mmHg). Yield 60 mg (5%).

The third fraction gave 1,1′-biisoquinoline (**13**) as pale yellow needles, mp 163—164 °C, which were recrystallized from hexane–ether. Yield 0.34 g (27%). Lit.[13] mp 162—163 °C. ^{1}H-NMR ($CDCl_3$): 7.5—8.0 (10H, m), 8.70 (2H, d, J=6.0 Hz).

Ethyl 4-Quinolineacetate (16a)——The crude extract obtained by the general procedure (reaction time, 2 h) from 4-iodoquinoline (**15a**) (2.55 g, 10 mmol) was purified by SiO_2 column chromatography with hexane–AcOEt (7 : 3, v/v) and hexane–AcOEt (1 : 1, v/v) as eluents. The first fraction of the hexane–AcOEt (7 : 3, v/v) eluate gave quinoline (**18a**) as a colorless liquid, bp 85—90 °C (4 mmHg). Yield 0.2 g (16%).

The second fraction of the hexane–AcOEt (7 : 3, v/v) eluate gave a pale yellow liquid (**16a**), bp 155—160 °C (3 mmHg). Yield 0.2 g (10%). Lit.[14] bp 147—150 °C (5 mmHg).

The hexane–AcOEt (1 : 1, v/v) eluate gave 4,4′-biquinoline (**17a**) as pale yellow needles, mp 168—169 °C, which were recrystallized from hexane–acetone. Yield 0.13 g (10%). Lit.[15] mp 171 °C. ^{1}H-NMR ($CDCl_3$): 7.1—8.3 (10H, m), 8.83 (2H, d, J=4.0 Hz).

Ethyl 2-Methyl-4-quinolineacetate (16b)——The crude extract obtained by the general procedure (reaction time, 1.5 h) from 4-iodo-2-methylquinoline (**15b**) (2.69 g, 10 mmol) was purified by SiO_2 column chromatography with $CHCl_3$ and hexane–AcOEt (7 : 3, v/v) as eluents. The $CHCl_3$ eluate gave 2-methylquinoline (**18b**) as a colorless liquid, bp 105—110 °C (4 mmHg). Yield 40 mg (2.8%).

The first fraction of the hexane–AcOEt (7 : 3, v/v) eluate gave 2,2′-dimethyl-4,4′-biquinoline (**17b**) as yellow

Table II. Spectral Data for Ethyl *N*-Heteroarylacetates

Compd. No.	IR cm^{-1} ($CHCl_3$) >C=O	^{1}H-NMR ($CDCl_3$) δ (ppm) CH_3CH_2O– (3H, t, J=7.0 Hz)	CH_3CH_2O– (2H, q, J=7.0 Hz)	–CH_2CO– (2H, s)	Other protons
2	1730	1.25	4.16	3.80	2.40 (6H, s), 6.83 (1H, s)
4	1730	1.25	4.13	3.57	2.41 (3H, s), 2.57 (3H, s), 6.89 (1H, s)
6	1730	1.23	4.10	3.72	7.0—8.6 (4H, m)
8	1730	1.23	4.07	3.40	2.42 (6H, s), 6.75 (2H, s)
10a	1730	1.13	4.17	4.00	7.2—8.2 (6H, m)
10b	1730	1.20	4.10	3.80	2.53 (3H, s), 7.10 (1H, s), 7.2—8.0 (4H, m)
12	1730	1.15	4.10	4.20	7.4—8.1 (5H, m), 8.37 (1H, d, J=6.0 Hz)
16a	1730	1.20	4.20	4.04	7.32 (1H, d, J=4.0 Hz), 7.4—8.3 (4H, m), 8.85 (1H, d, J=4.0 Hz)
16b	1730	1.21	4.17	4.01	2.73 (3H, s), 7.25 (1H, s), 7.4—8.2 (4H, m)
23	1720	1.24	4.13	3.52	7.1—8.2 (4H, m)

needles, mp 242—244 °C, which were recrystallized from hexane–acetone. Yield 0.46 g (32%). ^{1}H-NMR ($CDCl_3$): 2.85 (6H, s), 7.3—8.2 (10H, m). *Anal.* Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.53; H, 5.77; N, 9.56.

The second fraction of the hexane–AcOEt (7 : 3, v/v) eluate gave a pale yellow liquid (**16b**), bp 170—175 °C (3 mmHg). Yield 0.23 g (11%). *Anal.* Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.76; H, 6.59; N, 5.83.

Reaction of 5-Iodo-2,4-dimethylpyrimidine (19) with Ethoxycarbonylmethylzinc Bromide——The crude extract obtained by the general procedure (reaction time, 17 h) from **19** (1.17 g, 5 mmol) was purified by SiO_2 column chromatography with $CHCl_3$ as an eluent. The $CHCl_3$ eluate gave the pyrimidine (**19**), 0.44 g (38%).

Reaction of 3-Iodoquinoline (20) with Ethoxycarbonylmethylzinc Bromide——The crude extract obtained by the general procedure (reaction time, 5 h) from **21** (1.28 g, 5 mmol) was purified by SiO_2 column chromatography with CH_2Cl_2–AcOEt (4 : 1, v/v) as an eluent. The first fraction gave the quinoline (**20**), 70 mg, and the second fraction gave 3,3′-biquinoline (**21**) as pale yellow needles, mp 265—266 °C, which were recrystallized from hexane–acetone. Yield 0.2 g (47%). Lit.[16] mp 271 °C. ^{1}H-NMR ($CDCl_3$): 7.5—8.4 (10H, m), 9.27 (2H, d, J = 3.0 Hz).

Ethyl 3-Pyridineacetate (23)——The crude extract obtained by the general procedure (reaction time, 6 h) from 3-iodopyridine (**22**) (2.05 g, 10 mmol) was purified by SiO_2 column chromatography with AcOEt as an eluent. The AcOEt eluate gave a pale yellow liquid, bp 115—120 °C (3 mmHg). Yield 0.21 g (13%). Lit.[17] bp 121—122 °C (10 mmHg).

References and Notes

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