Studies on Pyrazines. 31 [1]. Alkylation of Chloropyrazine *N*-Oxides by Nickel-Catalyzed Cross-Coupling Reaction with Dialkylzincs

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3-Chloro-2,5-dimethylpyrazine 1-oxide underwent cross-coupling with dialkylzinc reagents forming 3-alkyl-2,5-dimethylpyrazine 1-oxides. The reaction was realized by catalytic 1,3-bis(diphenylphosphino)-propane nickel(II) chloride and the optimum results were examined.

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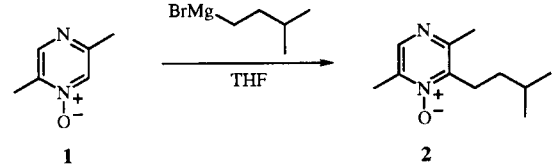
Alkylpyrazines are well known naturally occurring flavors in food and alarm pheromones in various species of ants [2]. This class of compounds was conventionally obtained by primary synthesis from aliphatic fragments [3] and more recently by palladium(0)-catalyzed cross-coupling of pyrazinyl halides with alkylborans [4,5], alkylaluminums [4,6], aryltins [7,8] and alkylzinc derivatives [4]. The transition metal mediated reactions can be also adapted to synthesis of alkyl- or arylpyrazine *N*-oxides. Compared with tetrakis(triphenylphosphine)palladium(0) used in the above reactions, 1,3-bis(diphenylphosphino)-propane nickel(II) chloride is an easier-handled catalyst since it is stable in air, besides the coupling reaction with organometallics including Grignard reagents [9] proceeds more smoothly under very mild conditions. For example, the catalytic nickel complex enabled spontaneous reaction of 2,6-dichloropyrazine with diethylzinc in toluene at room temperature to form 2,6-diethylpyrazine [10]. In this paper we wish to report nickel-catalyzed reaction of 3-chloro-2,5-dimethylpyrazine 1-oxide with Grignard reagents and dialkylzinc compounds because the product, trialkylpyrazine *N*-oxides, are needed for a future project directed towards synthesis of ant pheromones.

First, we approached the synthesis of alkylpyrazine *N*-oxides by reaction of 2,5-dimethylpyrazine 1-oxide (**1**) with isopentylmagnesium bromide as shown in Scheme 1. The starting *N*-oxide was completely consumed after stirring at room temperature for 15 hours but the desired product of 2-isopentyl-3,6-dimethylpyrazine 1-oxide (**2**) was obtained in 37% yield. Probably, the low yield is caused by pyrazine-ring opening of the Meisenheimer intermediate, such a behavior is rather usual in reaction of pyridine *N*-oxides with Grignard reagents or alkynyl carbanions [11]. For this reason, our strategy was turned to cross-coupling of halogenopyrazine *N*-oxides with Grignard reagents. However, reaction of 3-chloro-2,5-dimethylpyrazine 1-oxide (**3**) with isopentylmagnesium bromide in THF caused decomposition of the majority of starting material **3**, which provided only a 16% yield of 3-chloro-2,5-dimethyl-6-isopentylpyrazine 1-oxide (**4**) as the preceding reaction of the *N*-oxide (**1**). An addition of 1,3-bis(diphenylphosphino)propane nickel(II) chloride to the reaction had no effect on the cross-coupling to form 2,5-dimethyl-3-isopentylpyrazine 1-oxide, where the *N*-oxide **4** was also formed in an almost equal yield to that obtained without nickel-catalyst (Scheme 2 and Table 1).

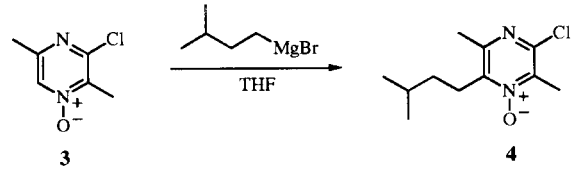
When diethylzinc was used in place of the Grignard reagents, the cross-coupling proceeded in the presence of the nickel complex in THF at room temperature to afford 2,5-dimethyl-3-ethylpyrazine 1-oxide (**5**) (Scheme 3 and Table 2) whereas the reaction did not occur without the catalyst (entry 1). A slightly excess equivalent of diethylzinc is the optimum, and doubling the amount of organozinc strikingly reduced the yield of coupling product **5** (entries 2, 3, 4). In refluxing THF, the yield was similarly decreased perhaps because of decomposing the *N*-oxide **5** or its precursors (entries 3,5). The most important factor to govern the yield is the amount of the nickel catalyst,

Scheme 1



1 **2**

Scheme 2



3 **4**

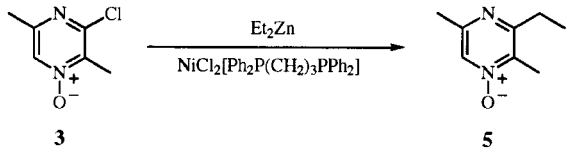
Table 1

Reaction of 3-Chloro-2,5-dimethylpyrazine 1-Oxide (**3**) with Isopentylmagnesium Bromide to Form 3-Chloro-2,5-dimethyl-6-isopentylpyrazine (**4**)

NiCl2(dppp) [1] (mole %)	Temperature	Time (hours)	Yield (%)	Starting material recovered (%)
0	r.t.	45	16	4
1	r.t.	45	17	13
1	reflux	19	14	25

[1] Dppp: $Ph_2P(CH_2)_3PPh_2$.

Scheme 3



3 5

Table 2

Reaction of 3-Chloro-2,5-dimethylpyrazine (**3**) with Diethylzinc to Produce 2,5-Dimethyl-3-ethylpyrazine 1-oxide (**5**)

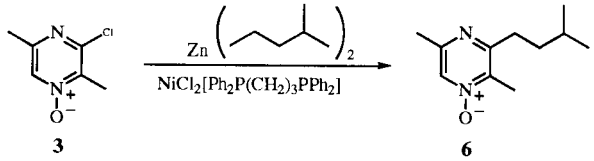
Entry	$NiCl_2$(dppp) [a] (mole %)	Et_2Zn (eq.)	Solvent	Temperature	Time (hours)	Yield (%)	Starting material recovered (%)
1	0	1.2	THF	r.t.	48	0	75
2	1	0.6	THF	r.t.	48	7	66
3	1	1.2	THF	r.t.	48	32	48
4	1	2.4	THF	r.t.	48	13	35
5	1	1.2	THF	reflux	17	17	13
6	5	1.2	THF	r.t.	5	39	0
7	10	1.2	THF	r.t.	2	46	0
8	10	1.2	Toluene	r.t.	21	33	3
9	10	1.2	DMF	r.t.	1	0	90
10	15	1.2	THF	r.t.	3	49	0

[a] Dppp: $Ph_2P(CH_2)_3PPh_2$.

and its increase improved the yield of *N*-oxide **5** and reduced the reaction period (entries 3, 6, 7). Instead of THF, toluene can be used as the solvent but there is no advantage in terms of both yield and reaction time (entry 8). In DMF, the reaction did not proceed entirely (entry 9). As a result, although the best yield (49%) was obtained when using 15 mole % of nickel catalyst (entry 10), the reaction conditions with 10 mole % for 2 hours (entry 7) is acceptable.

Diisopentylzinc which generated *in situ* from isopentylmagnesium bromide with zinc bromide also underwent cross-coupling with the *N*-oxide **3** forming 2,5-dimethyl-3-isopentylpyrazine 1-oxide (**6**) (Scheme 4 and Table 3). In contrast with reactions using diethylzinc, the present conversion proceeds more easily even with 5 mole % of the nickel catalyst. In a typical case, cross-coupling product was obtained in 76% yield (entry 3), which contained a 19% yield of the deoxygenated pyrazine **7** together with the normal *N*-oxide **6** (57%).

Scheme 4



3 6

Table 3

Formation of 2,5-Dimethyl-3-isopentylpyrazine 1-Oxide (**6**) from Reaction of 3-Chloro-2,5-dimethylpyrazine 1-Oxide (**3**) with Diisopentylzinc in THF [a,b]

Entry	$NiCl_2$(dppp) [c] (mole %)	Time (hours)	Yield (%)	Starting material recovered (%)
1	0	24	0	94
2	1	2	46	0
3	5	2.5	57 [d]	0

[a] Diisopentylzinc (1.2 equivalents) was used. [b] At room temperature. [c] Dppp: $Ph_2P(CH_2)_3PPh_2$. [d] By-product: 2,5-dimethyl-3-isopentylpyrazine (**7**) (19%).

Recently, Jordan and Guram [12] effected an elegant synthesis of highly substituted alkylpyrazines, which consisted of zirconium-mediated alkenylation of dimethylpyrazines with alkynes followed by hydrogenation. However, the required catalyst of cationic zirconocene complex is not easy to deal because of its extreme instability. Therefore, our proposed current method is considered more practical and convenient to introduce an alkyl group into pyrazine ring.

EXPERIMENTAL

All melting points were determined using a Büchi 535 apparatus and are uncorrected. Boiling points were oven temperatures at Kugelrohr-distillation and are uncorrected. The ir spectra were recorded on a JASCO IR-810 spectrometer. The nmr spectra were obtained with JEOL JNM EX270 instrument with solutions in deuteriochloroform containing tetramethylsilane as the internal standard.

3-Chloro-2,5-dimethylpyrazine 1-Oxide (**3**).

A mixture of 2-chloro-3,6-dimethylpyrazine (5.0 g, 35 mmoles) and 89% *m*-chloroperbenzoic acid (7.5 g, 35 mmoles) in 1,2-dichloroethane (90 ml) was stirred and heated at 75° for

30 minutes. After cooling to room temperature, aqueous sodium hydrogen carbonate was added until the aqueous layer tested at *p*H 8, and then the organic phase was separated. The aqueous layer was extracted with chloroform (3 x 50 ml). The combined organic extracts were washed with water, dried over magnesium sulfate, evaporated *in vacuo*. The residue was recrystallized from hexane-ethyl acetate (5:1) to provide *N*-oxide **3** as colorless needles (4.05 g, 73%). The second crop was obtained from the mother-liquor (0.55 g, total yield 83%), mp 114-116° (lit [13] mp 117-117.5°); ir (potassium bromide): 3090, 1585, 1460, 1340, 1215, 1050 cm^{-1}; ^1H nmr: 2.46 (3H, s), 2.57 (3H, s), 7.98 (1H, s).

3-Chloro-2,5-dimethyl-6-isopentylpyrazine 1-Oxide (**4**).

Isopentylmagnesium bromide was prepared by adding isopentyl bromide (0.80 ml, 6.7 mmoles) to a stirred suspension of magnesium (0.194 g, 8.0 mmoles) in dry THF (4 ml) below 50° under argon and successive refluxing for 30 minutes. The Grignard reagent (0.45 ml, 0.60 mmole) was added over 2 minutes to a stirred and ice-cooled solution of *N*-oxide **3** (0.079 g, 0.50 mmole) in dry THF (3 ml) under argon. The mixture was additionally stirred for 45 hours at room temperature, then ice-cooled, and diluted with 2*N* hydrochloric acid (1.0 ml) containing a few pieces of ice. The resulting mixture was adjusted at *p*H 7 with aqueous sodium hydrogen carbonate and extracted with ethyl acetate (2 x 20 ml). The extract was washed with water, dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel (15 g), eluted with hexane-ethyl acetate (3:1) to afford trialkyl product **4** (0.018 g, 16%) as a pale yellow oil, bp 95-100° (4 mm Hg); ir (neat): 2960, 1580, 1455, 1335, 1310, 1030 cm^{-1}; ^1H nmr: 0.99 (6H, d, J = 6.6 Hz), 1.40-1.48 (2H, m), 1.65-1.75 (1H, m), 2.53 (3H, s), 2.57 (3H, s), 2.85-2.91 (2H, m).

Anal. Calcd. for $C_{11}H_{17}N_2OCl$: C, 57.77; H, 7.49; N, 12.25. Found: C, 57.88; H, 7.57; N, 12.18.

Further elution gave the starting material **3** (3 mg, 4%).

2,5-Dimethyl-3-ethylpyrazine 1-Oxide (**5**).

Diethylzinc (1.0 *M* solution in hexane, 2.4 ml, 2.4 mmoles) was added dropwise with stirring over 5 minutes under argon to a mixture of *N*-oxide **3** (0.318 g, 2.0 mmoles) and 1,3-bis(diphenylphosphino)propane nickel(II) chloride (0.120 g, 0.2 mmole, 10 mole %) in dry THF (16 ml). The resulting mixture was stirred at room temperature for 2 hours, then diluted with ice-water and extracted with ethyl acetate (2 x 20 ml). The extract was washed with water, dried over magnesium sulfate and evaporated *in vacuo*. Chromatograph of the residue on silica gel (20 g) eluted with hexane-ethyl acetate (1:4) gave the *N*-oxide **5** (0.140 g, 46%). The analytical sample was prepared by recrystallization from hexane as colorless plates, mp 42-44°; ir (potassium bromide): 1585, 1470, 1450, 1340, 1315, 1220, 1110 cm^{-1}; ^1H nmr: 1.28 (3H, t, J = 7.6 Hz), 2.44 (3H, s), 2.47 (3H, s), 2.84 (2H, q, J = 7.6 Hz), 7.93 (1H, s).

Anal. Calcd. for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 62.83; H, 7.72; N, 18.82.

2,5-Dimethyl-3-isopentylpyrazine 1-Oxide (**6**).

Isopentylmagnesium bromide was prepared similar to the above using magnesium (1.2 g, 48 mmoles), isopentyl bromide (4.8 ml, 40 mmoles) and dry THF (24 ml), a portion of which (26 ml, 36 mmoles) was added dropwise to a suspension of zinc bromide (4.1 g, 18 mmoles) in THF (30 ml) under argon while maintaining the temperature below 10°, and then the mixture was stirred at room temperature for 1 hour. The diisopentylzinc solution (37 ml, 12 mmoles) was added dropwise with stirring over a 20-minute period under argon to a suspension of *N*-oxide **3** (1.59 g, 10.0 mmoles) and nickel catalyst (0.300 g, 0.50 mmoles, 5 mole %) in dry THF (80 ml). The resulting mixture was stirred at room temperature for 2.5 hours, then diluted with ice-water and adjusted at *p*H 7 with aqueous sodium carbonate. The precipitates which formed were removed by filtration and the filtrate was extracted with ethyl acetate (2 x 50 ml). The extract was washed with water, dried over magnesium sulfate and evaporated *in vacuo*. The crude product was subjected to chromatograph on silica gel (40 g) eluted with hexane-ethyl acetate (1:1) affording 2,5-dimethyl-3-isopenthylpyrazine **7** (0.337 g, 19%), which was distilled to give a colorless oil, bp 90-96° (7 mm Hg); ir (neat): 2950, 2925, 2870, 1450, 1375, 1170 cm^{-1}; ^1H nmr: 0.97 (6H, d, J = 6.6 Hz), 1.50-1.58 (2H, m), 1.63-1.73 (1H, m), 2.48 (3H, s), 2.52 (3H, s), 2.73-2.80 (2H, m), 8.14 (1H, s).

Anal. Calcd. for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 74.08; H, 10.43; N, 15.46.

Further eluting with hexane-ethyl acetate (1:2) provided *N*-oxide **6** (1.11 g, 57%), which was distilled giving a pale yellow oil, bp 146-150° (3 mm Hg); ir (neat): 2960, 1590, 1470, 1340, 1210, 1070 cm^{-1}; ^1H nmr: 0.97 (6H, d, J = 6.3 Hz), 1.49-1.58 (2H, m), 1.62-1.69 (1H, s), 2.43 (3H, s), 2.46 (3H, s), 2.77-2.83 (2H, m), 7.92 (1H, s).

Anal. Calcd. for $C_{11}H_{18}N_2O \cdot 1/4H_2O$: C, 66.47; H, 9.38; N, 14.09. Found: C, 66.35; H, 9.27; N, 14.19.

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