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THE STUDIES OF THE ACTIVATED COMPOUND (I)

A METAL INDUCED ACYLATION

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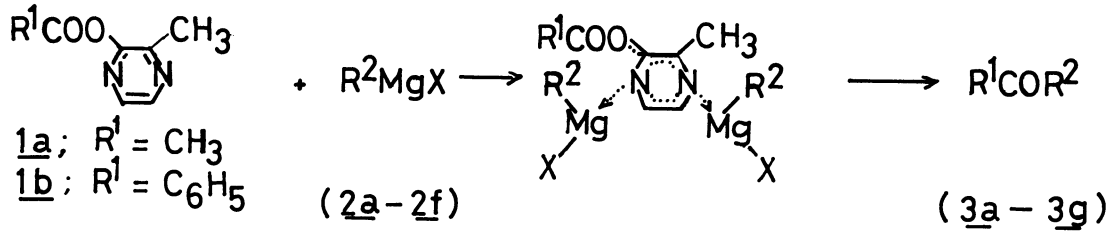
The new activated compound, 2-acyloxy-3-methylpyrazine was treated with the Grignard reagent to give ketone in high yield.
The comparison of reactivity of the activated compounds (8-acyloxyquinoline and 2-acyloxy-3-methylpyrazine) was described.

The metal induced reaction have been developed by using such activating agents as imidazole,[1] 8-quinolinol,[2),3)] and 2-pyridinthiol.[4] We wish to report that 3-methylpyrazin-2-ol also was suitable for an activating agent. In choosing 3-methylpyrazin-2-ol as an activating agent, we promoted to suppose that if two hetero atoms are contained in a ring, the power of withdrawing electrons the ring by metal cation is increased, so that the alkyl anion (R^2) in the Grignard reagent (R^2MgX) attacks predominantly on the activated point (ester group).



In the first study, 2-acyloxy-3-methylpyrazine (1) was examined as an activated compound. 3-Methylpyrazin-2-ol was conveniently synthesized from commercial alaninamide and glyoxal in methanol.[5] Its acetate (1a) and benzoate (1b) were given by the ordinary method. The typical procedure of the metal induced acylation was carried out as follows; the solution of 2-acyloxy-3-methylpyrazine (1) (3 mmol) in methylene chloride (5 ml) was added to a stirred ethereal solution of the Grignard (2) (6 mmol) at -60° under the nitrogen passed through the Fieser's solution. The reaction mixture was allowed to warm up to room temperature and stand overnight. After the resulted yellow prepicitate was filtered off, the filtrate was poured into a saturated aqueous ammonium chloride solution (10 ml), extracted with ether (10 ml × 3), and washed with saturated brine. After the evaporation of the solvent, the residue was distilled by using a short column (3 cm) to give ketones (3a - 3g) as a sole product, of which purity was cheched by means of glc and nmr. The yield of ketones was summarized on table I.

Table I
The reaction of 2-acyloxy-3-methylpyrazine with the Grignard reagent

R^1		R^2		yield of ketone R^1COR^2 (%)
C_6H_5	(1b)	CH_3	(2a)	(3a) 80
		C_2H_5	(2b)	(3b) 87.9
		n-C_4H_9	(2c)	(3c) 90
		n-C_6H_{13}	(2d)	(3d) 93
		C_6H_5	(2e)	(3e) 91.5
		$C_6H_5CH_2CH_2$	(2f)	(3f) 97
CH_3	(1a)	C_6H_5	(2e)	(3a) 79
		$C_6H_5CH_2CH_2$	(2f)	(3g) 44.1

A comparison of reactivity of the activated compounds, 8-acyloxyquinoline and 2-acyloxy-3-methylpyrazine (1), was carried out by the mixed method as follows; to a mixture of 8-acetyloxyquinoline (2 mmol; 347 mg) and 2-benzoyloxy-3-methylpyrazine (1b) (2 mmol; 428 mg) in methylene chloride (20 ml) was added the ethereal solution of β-phenethyl magnesium bromide (2 mmol equivalent) at -60° under an oxygen free nitrogen stream. The mixture was stirred at -60° for 1 hr and allowed to stand at room temperature overnight. After it was worked up as described, the crude product consisted of only 1,3-diphenylpropan-1-one (3f) on basis of its nmr spectrum (none of 4-phenylbutan-2-one was recognized). Although this result seems to indicate that 2-acyloxy-3-methylpyrazine (1) would be more reactive in the metal induced acylation than 8-acyloxyquinoline, there still remains a little doubt that the difference of reactivity depends on the difference of reactivity coming from the acyl function itself.

So the experiment was carried out that the mixture of 2-acetyloxy-3-methylpyrazine (1a) (2 mmol; 304 mg) and 8-benzoyloxyquinoline (2 mmol; 498 mg) in methylene chloride (20 ml) was treated with β-phenethyl magnesium bromide (2 mmol equivalent) in the same reaction condition as mentioned above. The crude product consisted of only 4-phenylbutan-2-one (3g) on basis of its nmr spectrum (none of 1,3-diphenylpropan-1-one was recognized.

These results led to the conclusion that 2-acyloxy-3-methylpyrazine was more reactive than 8-acyloxyquinoline in the metal induced acylation.

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