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Carbon-Carbon Bond Formation by the Use of Chloroiodomethane as a C_1 Unit. IV.[1] The Mannich Reaction of Ketones by Means of Dihalomethane and Secondary Amine[2]

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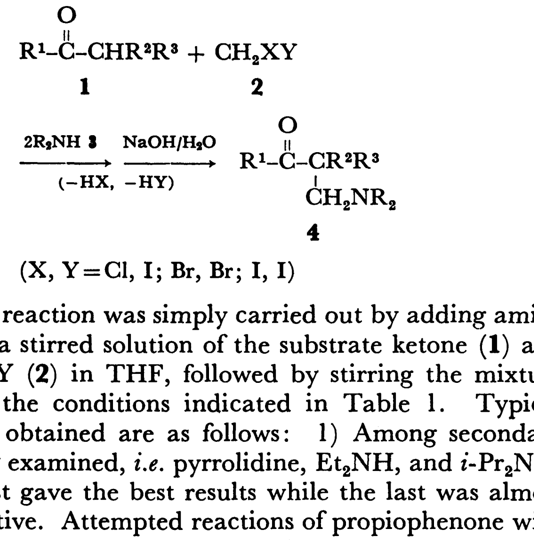
Synopsis. Treatment of ketones with dihalomethane (CH_2Br_2, CH_2ClI, and CH_2I_2) in the presence of secondary amine, preferably pyrrolidine, gave the corresponding Mannich base in varing yields depending on the substrate and/or combination of the reagents.

In previous papers[3] we have reported that chloroiodomethane reacts in the sense of I–CH_2Cl, in either homolytic or heterolytic fashion, enabling the introduction of chloromethyl moiety into various substrates. In a study to extend the scope and utility of the transformation by the use of CH_2ClI as a C_1 unit, we have for some time been trying to chloromethylate active methylene compounds with the aid of various base catalysts.

Although such attempts have not yet been realized,[4] it has been found that α-methylene protons of ketones (**1**) can be replaced with (dialkylamino)methyl moiety by a combination of dihalomethane (**2**) and secondary amine (**3**) (Eq. 1). The important features of the amino ketone products, the Mannich base, have been well documented for a long time,[5] and here we wish to report the results of the aminomethylation reaction.



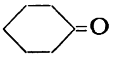
$$R^1\text{–}\overset{\overset{\displaystyle O}{\|}}{C}\text{–}CHR^2R^3 + CH_2XY \xrightarrow[(-HX,\ -HY)]{2R_2NH\ \mathbf{3}} \xrightarrow{NaOH/H_2O} R^1\text{–}\overset{\overset{\displaystyle O}{\|}}{C}\text{–}\underset{\underset{\displaystyle CH_2NR_2}{|}}{C}R^2R^3 \qquad (1)$$

1 **2** **4**

(X, Y = Cl, I; Br, Br; I, I)

The reaction was simply carried out by adding amine (**3**) to a stirred solution of the substrate ketone (**1**) and CH_2XY (**2**) in THF, followed by stirring the mixture under the conditions indicated in Table 1. Typical results obtained are as follows: 1) Among secondary amines examined, *i.e.* pyrrolidine, Et_2NH, and *i*-Pr_2NH, the first gave the best results while the last was almost ineffective. Attempted reactions of propiophenone with **2** in the presence of tertiary amine such as Et_3N or 1,4-diazabicyclo[2.2.2]octane resulted in the quaternization of the amine by the halide leaving the ketone almost intact. 2) The choice of the dihalide (**2**) should depend on the substrate **1**. For reactive ketones such as cyclohexanone and acetophenone, CH_2ClI gave better results than CH_2I_2; the latter yielded larger amounts of intractable tarry materials with the expense of **4**. On the other hand, CH_2I_2 was preferred for the less reactive ketones such as propiophenone and diethyl ketone. Dibromomethane showed intermediate character, and could be applicable to both types of ketones. 3) Heptanal was also aminomethylated in a low yield, while esters (ethyl butyrate, methyl phenylacetate, *etc.*) were recovered unchanged.

TABLE 1. AMINOMETHYLATION OF KETONES WITH CH_2XY/R_2NH[a)]

Substrate (**1**)	CH_2XY(**2**) X,Y	R_2NH[b)] (**3**)	Time / h^{-1}	Mannich base (**4**)	Yield / %[c)]
Ph–CO–Et	I, I	A	4	**4a**	60 (73)
	Br,Br	A	3		54 (61)
	Cl,I	A	5		32 (40)
	Cl,I	B	5	**4a′**	29 (37)
	I, I	C	5.5	**4a″**	(1.6)
Ph–CO–Me	Br,Br	A	3	**4b**	27 (60)
	Cl,I	A	3		(54)
	I,I	A	3		(0)[d)]
Ph–CO–*i*-Pr	Cl,I	A	3	**4c**	(trace)
Ph–CO–CH_2Ph	Cl,I	A	3	**4d**	64
Et–CO–Et	I, I	A	3	**4e**	62 (71)
	Br,Br	A	3		53 (61)
	Cl,I	A	3		44 (53)
	Cl,I	B	4	**4e′**	11 (30)
i-Pr–CO–Me	Br,Br	A	3	**4f**	67 (84)[e)]
	Cl,I	A	2		64 (80)
t-Bu–CO–Me	Br,Br	A	5	**4g**	(0)[d)]
	Cl,I	A	5[f)]	**4h**	21 (66)
	Br,Br	A	3		15 (53)
	Cl,I	B	5	**4h′**	8.8 (34)
n-Hex–CHO	Cl,I	A	3[f)]	**4i**	(48)
	Br,Br	A	3[f)]		8.3 (45)

a) **1**, *ca.* 80 mmol; **1** : **2** : **3** ≈ 1 : 1.2 : 2.4 (molar ratio); THF 100 ml; under reflux. b) A, pyrrolidine (*c*-$(CH_2)_4$NH); B, Et_2NH; C, *i*-Pr_2NH. c) Isolated yields. Figures in parentheses refer to the crude products (see Experimental). d) Resulted tarry material with complete consumption of the substrate. e) Only *i*-Pr–CO-CH_2-CH_2N  was detected. f) Room temp.

As is encountered in literatures,[6] attempts to isolate pure sample by distillation sometimes suffered from poor yields of **4**, probably due to thermal instability of the Mannich base. Although the conventional Mannich reaction with formaldehyde–R_2NH in the presence of acid catalyst,[5] or recent version by means of preformed methyleneiminium reagents,[7] has widely been utilized for the synthesis of amino ketones, the transformation described here may have some synthetic utility because of its operational simplicity and reasonable yields for certain ketone substrates.

The aminomethylation depicted in Eq. 1 seems to proceed *via* initial formation of methyleneiminium species **5** which is formed according to Eq. 2; upon mixing pyrrolidine with CH_2ClI in DMSO-d_6, a new ^1H NMR absorption signal appeared at δ 8.8 (broad), which may be assigned to methylene protons of the iminium species,[8] and the strength of which was reduced gradually on addition of propiophenone. The Mannich reaction of ketones by means of preformed methyleneiminium species such as $Me_2\overset{+}{N}=CH_2,\overset{-}{X}$ has well been precedented in the last decade.[10]

$$R_2NH + CH_2XY \xrightarrow[-HY]{R_2NH} R_2N\text{-}CH_2X \longleftrightarrow \underset{\mathbf{5}}{R_2\overset{+}{N}=CH_2,\overset{-}{X}} \qquad (2)$$

Experimental

Materials and measurements were the same as those described in a previous paper.[1]

The aminomethylation reactions were conducted in essentially the same manner under nitrogen, and the reaction of diethyl ketone is illustrative. To a water-chilled, stirred solution of diethyl ketone (7.13 g, 82.8 mmol) and CH_2Br_2 (16.5 g, 94.9 mmol) in 90 ml of THF was added dropwise 13.7 g (193 mmol) of pyrrolidine in 10 ml THF; the mixture was heated under reflux for 3 h. The cooled reaction mixture was diluted with 100 ml of 2 M HCl.† Non-basic components were extracted with portions of cyclohexane. The aqueous phase was made alkaline with 10% NaOH, and basic products were extracted with ether (100 ml × 3), washed successively with 1 M Na_2CO_3, brine, and water, and then dried over $MgSO_4$. Evaporation *in vacuo* of the solvents, unchanged pyrrolidine, and di(1-pyrrolidinyl)methane, which was formed by the reaction of pyrrolidine and CH_2Br_2, left 8.60 g of the crude Mannich base (61% yield). Trap-to-trap distillation of the residue gave a middle cut boiling at 65—70 °C/6 mmHg†† (**4e**, 7.45 g, 53% yield); IR (neat) 2780 and 1710 cm^{-1}; ^1H NMR (CCl_4, hexamethyldisiloxane) δ 0.7—1.2 (6H, 2× $-CH_3$), 1.4—2.0 (4H, $-CH_2-(C\underline{H}_2)_2-CH_2-$, m), and 2.0—2.8 (9H, m). Found (Calcd for $C_{10}H_{19}NO$): C, 71.06 (70.96); H, 11.45 (11.32); N, 8.58 (8.27)%.

4a: Bp ≈123 °C/3 mmHg; IR (neat) 2780 and 1680 cm^{-1}; MS *m/e* (%) 146 (M−*c*-$(CH_2)_4NH$, 31.1), 118 (10.1), 105 (28.8), and 77 (7.1).

4a′: Bp 105—108 °C/2.2 mmHg; IR (neat) 2800 and 1680 cm^{-1}; MS *m/e* (%) 146 (M−Et_2NH, 12.0), 118 (7.8), 105 (38.9), and 77 (24.9).

4b: Bp 100—110 °C/1—1.5 mmHg; IR (neat) 2800 and 1690 cm^{-1}. Found (Calcd for $C_{13}H_{17}NO$): C, 76.78 (76.81); H, 8.42 (8.42); N, 6.86 (6.89)%.

4c: IR (neat) 2800 and 1680 cm^{-1}.

4d: Mp 98—99 °C; IR (KBr) 2780 and 1685 cm^{-1}. Found (Calcd for $C_{19}H_{21}NO$): C, 82.10 (81.68); H, 7.67 (7.58); N, 4.76 (5.01)%.

4e′: Bp 42 °C/4 mmHg; IR (neat) 2800 and 1710 cm^{-1}. Found (Calcd for $C_{10}H_{21}NO$): C, 69.95 (70.12); H, 12.25 (12.36); N, 8.37 (8.18)%.

4f: Bp 69—70 °C/5—6 mmHg; IR (neat) 2780 and 1710 cm^{-1}. Found (Calcd for $C_{10}H_{19}NO$): C, 71.35 (70.96); H, 11.25 (11.31); N, 8.66 (8.28)%.

4h: Bp 61—64 °C/3—5 mmHg; IR (neat) 2780 and 1710 cm^{-1}; MS *m/e* (%) 181 (M^+, 1.4), 111 (11.7), 84 (58.4), 82 (7.0), and 67 (13.0).

4h′: Bp 62 °C/2.5 mmHg; IR (neat) 2800 and 1710 cm^{-1}; MS *m/e* (%) 111 (11.7), 84 (7.0), and 67 (13.0).

4i: Bp 35—40 °C/1.5 mmHg; IR (neat) 2800 and 1725 cm^{-1}.

References

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8) ^1H NMR of methylene protons of $Me_2\overset{+}{N}=CH_2,\overset{-}{I}$ appears at δ 8.2 in DMSO-d_6.[1,9] See also, "Iminium Salts in Organic Chemistry," ed by H. Böhme and H. G. Viehe, Wiley-Interscience, New York (1976), Part I, pp. 23—105.

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10) For example, Y. Jasor, M. Gaudry, M. J. Luche, and A. Marquet, *Tetrahedron*, **33**, 295 (1977).

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† 1 M = 1 mol dm^{-3}.

†† 1 mmHg ≈ 133.322 Pa.