CHEMISTRY LETTERS, pp. 1035-1038, 1977. Published by the Chemical Society of Japan

THE REACTION OF DIARALKYLGLYCINES: PREPARATION AND CHEMISTRY OF N-CHLOROMETHYLDIBENZYLAMINE HYDROCHLORIDE

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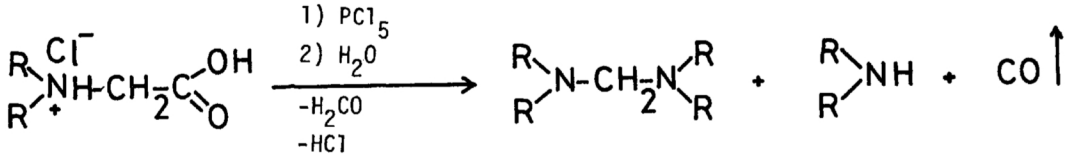
N-Chloromethyldibenzylamine hydrochloride (2a), which is a precursor to N,N-dibenzylimminium salt (3), was obtained from N,N-dibenzylglycine hydrochloride (1a) in the presence of PCl_5 or $(COCl)_2$ in good yields. The reaction mechanism is discussed. 2a was isolated and reacted with dibenzylamine (6a), thiophene, n-buthyllithium and 1-naphthol to give an excellent yield of bis-(N,N-dibenzylamino)methane (5a), 2-(N,N-dibenzylaminomethyl)thiophene (7), N-penthyldibenzylamine (8), and 2-dibenzylaminomethyl-1-naphthol (9), respectively.

Concerning the preparation of imminium salts, there have appeared several publications.[1,2] For example, the synthesis of N,N-dimethyimminium methyl iodide (Eschenmoser's salt) from N-iodomethyltrimethylammonium iodide was published by Eschenmoser et al.[1] But the method requires relatively high temperature (ca. 150°) for the elimination of methyl iodide. Recently, alternative methods were developed for the preparation of imminium salts from glycine derivatives in the presence of $POCl_3$ or $(COCl)_2$.[2a,b] In these cases, the formation of imminium salts proceeds under strong acidic conditions ($HClO_4$). However, little is known about the presence of another interesting and synthetically useful intermediate, which produces the corresponding imminium salt at room temperature under basic conditions, in the reaction. We wish now to report the isolation and chemistry of the intermediate, N-chloromethyldibenzylamine hydrochloride (2a), which should be precursor to imminium salt (3).

We have investigated the reaction of the following four N,N-diaralkylglycines (1); N,N-dibenzylglycine (1a), N,N-di-4-chlorobenzylglycine (1b), N,N-di-3,4-dimethylbenzylglycine (1c) and N,N-di-2-chlorobenzylglycine (1d). The amino group was protected as the corresponding hydrochlorides. The preparation of 1a-1d followed a similar method employed by Velluz et al.[3]

We have found that the reaction of 1a in the presence of PCl_5 or $(COCl)_2$ gave 2a as an isolated

product, which has never been previously observed under the conditions. A typical procedure is shown as follows; to a benzene suspension (15 ml) of PCl_5 (366 mg, 0.172 mmol) was added dried 1a·HCl (500 mg, o.170 mmol) at 5°. After evolution of hydrogen chloride ceased, the volatile phosphorous compounds were removed by co-distillation with benzene at 40-50° under reduced pressure. This process was repeated twice and each time residual glycil chloride (4a, IR(CH_2Cl_2) 1780 cm^{-1}) was cooled and dissolved in dry benzene (10 ml). A benzene solutuion (10 ml) of PCl_5 (360 mg, 0.170 mmol) was added to the residure and the suspention was stirred for 20 min at 60°. On cooling with cold water, 2a crystallized from the solution; it was filtered off on exclution of moisture, washed three times with dry benzene, and was dried under a high vacuum at room temperature: 2a[8] (461 mg, 95 %); dec. 156-158°; NMR ($CDCl_3$/TMS) δ 4.40(s, 4H, Ph-CH_2-), 6.66(s, 2H, $\geq\overset{+}{N}$-CH_2Cl), and 7.55 ppm(s, 10H, Ph-); IR(CH_2Cl_2) $\tilde{\nu}$ 2300, 2400, 2525 and 2670 cm^{-1}($\geq\overset{+}{N}H\cdot Cl^-$). The formation of 2a was accompanied by a evolution of carbon monoxide (IR_{gas} $\tilde{\nu}$ 2250 cm^{-1}) and the total volume of the gas was messured by a measuring cylinder of gas-trapping apparatus (0.98 equiv.). The pseudo-first order rate constants of the gas evolution at 40° from 1a, 1b, 1c and 1d were 2.45, 3.15, 0.81 and 10.9 ($\times 10^4$ sec^{-1}), respectively. The evolution of carbon monoxide in each run was monitored by passing it through a dilute aq. $KMnO_4/AgNO_3$ solution acidified with HNO_3.[7] The amount of the gas evolved was measured by UV absorption at 525 nm (ε 2350) of the resulted solution. We have also found that the reaction of 1a·HCl in the presence of $(COCl)_2$ under similar conditions as above gave 2a in fairly good yield (80%). 2a is very hygroscopic and converted to 5a and dibenzylamine (6a) with moisture. Moreover, after 1 was treated with PCl_5 (2 equiv.) in dry benzene at 40° for 30 min, the reaction mixture was treated with large excess of water to give a mixture of 5a + 6a, 5b + 6b, 5c + 6c, and 5d + 6d, respectively (see Scheme 1).



1

a; R= $C_6H_5CH_2$-
b; R= 4-Cl-$C_6H_4CH_2$-
c; R= 3,4-$(CH_3)_2C_6H_3CH_2$-
d; R= 2-Cl-$C_6H_4CH_2$-

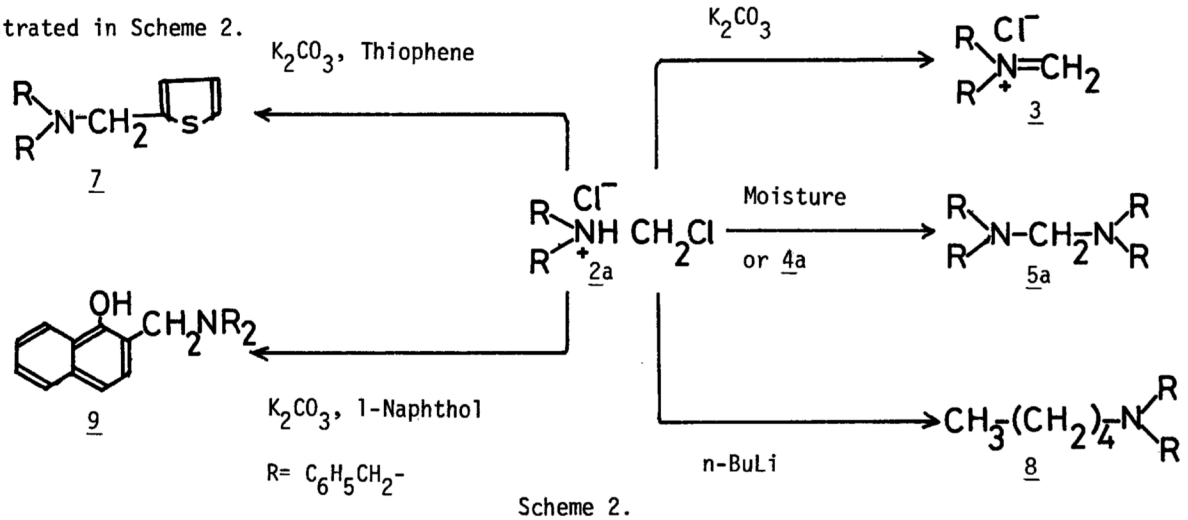
5	(Yield, %)	Mp °C	6	(Yield, %)	(Yield, %)
5a	(43)	98-99[6]	6a	(8)	(98)
5b	(61)	100-101	6b	(8)	(95)
5c	(37)	183-184	6c	(9)	(97)
5d	(60)	126-127	6d	(11)	(100)

Scheme 1

Mannich et al. pointed out that $AlCl_3$ plays an important role for decarbonylation from the hydrochloride of benzyl methylglycilchloride,[4] we have also observed the decarbonylation from 4 in the presence of $SnCl_4$.

It should be noted that the decarbonylation from 4 has shown the following phenomena by an action of PCl_5. The rate of the decarbonylation depends on the substituent on the phenyl group of 1, and the electron-withdrowing group promotes the rate. This result is contrast to the decarbonylation from tertiary acid chlorides.[9]

The utilization of 2a might provide a very useful method for constructing new carbon frameworks, if 2a reacts with nucleophlic reagents under a mild condition. According to the present method,aminomethylation proceeds at room temperature under basic conditions instead of acidic conditions employed by the Mannich reaction.[4,5] When a thiophene (7.5 ml, 9.0 mmol) solution of 2a (510 mg, 0.18 mmol) treat with K_2CO_3 (220 mg, 0.18 mmol) at room temperature for 6 hr, 7 was obtained in 88 % yield (460 mg, mp 81-82°) after usual work-up. Successive treatment of 2a (180 mg, 0.072 mmol) generated in situ with 6a (280 mg, 0.14 mmol), buthyllithium (0.8 ml, 0.20 mmol, 2.45 M solution in hexane) and 1-naphthol (260 mg, 0.18 mmol) at room temperature afforded 5a (270 mg, 98 %), 8 (182 mg, 92 %, bp125-127°/0.25 Torr) and 2-dibenzylaminomethyl-1-naphthol (9) (250 mg, 38 %, mp 139-141°), respectively. Furthermore, the present procedure to treat the intermediate (2a) with weak base (K_2CO_3) provides a convenient preparation of the corresponding imminium salt (3) in high yield. We suggested that the key intermediate formed during the above aminomethylations is imminium salt (3), because 2a (500 mg, 0.18 mmol) undergoes rapid elimination of HCl in the presence of K_2CO_3 (220 mg, 0.18 mmol) to form 3 (350 mg, 80 %);[8] bp 145°/0.2 Torr; NMR($CDCl_3$/TMS) δ 5.04(s, 4H, Ph-CH_2-), 7.43(s, 10H, Ph-), and 8.34 ppm(s, 2H, =CH_2); IR(nujol) $\tilde{\nu}$ 3150($\overset{+}{N}$=CH_2), and 1655 cm^{-1}($\overset{+}{N}$=C<). Representative examples are illustrated in Scheme 2.



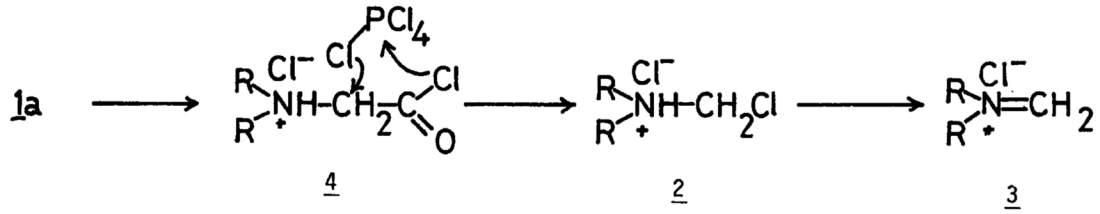
Scheme 2.

Another noteworthy advantages of this new method for aminomethylation are that the reagent (2a) with good leaving groups (such as benzyl) is readily available and that the reaction products derived from 2a produce another useful chemicals.[10] 2-Methylthiophene (10) (98 %, bp 110-113°),

penthyl amine (11) (97 %, bp 102-104°/0.2 Torr), and 2-methyl-1-naphthol (12) (91 %, mp 66-68°) were obtained by removing the benzyl group by hydrogenolysis (Pd/charcoal) of 7, 8, and 9, respectively. Treatment of 7 (270 mg, 0.10 mmol) with ethylchlorocarbonate (330 mg, 0.30 mmol) gave N-ethoxycarbonyl-N-benzyl-n-penthylamine (13) (240 mg, 95 %, bp 112-115°/o.2 Torr).

5a, 6 (6a-6d), 10, 11 and 12 were identified by comparison of these spectral data with those of authentic samples.[6] The structure of 5b, 5c, 5d, 7, 8, 9 and 13 were established on the basis of IR and NMR spectral data.[8]

Though we have few experimental results to clarify the mechanism of these reactions, such results as shown above may allow us to propose the following cyclic mechanism for the decarbonylation and the formation of 3 as shown in Scheme 3.



Scheme 3

Investigation on the scope and limitation of these reaction is currently being continued.

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(Received June 20, 1977)