Sulfuryl Chloride as a Reagent for Selective Chlorination of Symmetrical Ketones and Phenols

Divakar Masilamani and Milorad M. Rogić*

Corporate Research and Development Laboratories, Allied Corporation, Morristown, New Jersey 07960

Received June 25, 1981

Cyclohexanone reacts with sulfuryl chloride in sulfur dioxide, ether, tetrahydrofuran, dioxane, and tetraglyme to give mixtures of mono- and dichlorocyclohexanones. However, when the reaction was carried out in sulfur dioxide solution containing a slight excess of methanol, only monochlorocyclohexanone was obtained in high yield. Almost as good selectivities are obtained in methylene chloride solution in the presence of methanol. A similar procedure with acetone affords monochloroacetone cleanly. While phenols do not react with sulfuryl chloride in methylene chloride even under reflux, the chlorination can be induced by the addition of various organic "bases", resulting in selective monochlorination.

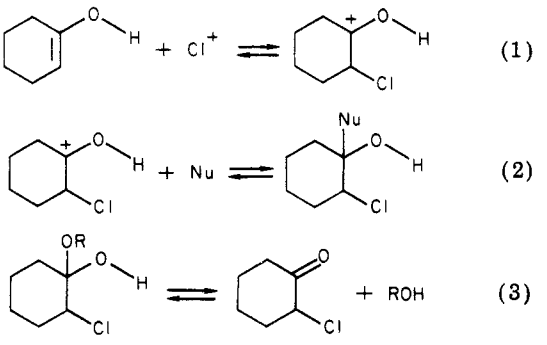
Replacement of hydrogen atoms adjacent to a carbonyl or other activating groups is one of the most frequently encountered synthetic procedures. Nitrosation[1] and halogenation[2] of ketones are typical examples of these transformations. In many instances the synthetic values of these transformations are limited by their low selectivities. This is particularly true for reactions of cyclohexanone and cyclohexanone derivatives in which both adjacent methylene groups are either of equivlent or similar reactivities. Recently, we described a method for achieving mononitrosation of cyclohexanone[3] which led to development of the nitrosolysis reaction.[3-5] In the present paper we describe a method, based on the same principles used in the nitrosolysis reaction,[4] for highly selective monochlorination of cyclohexanone, acetone, and certain phenols.

Results and Discussion

1. Monochlorination of Cyclohexanone. Chlorination of cyclohexanone under typical reaction conditions in various solvents generally leads to polychlorinated cyclohexanones.[6-8] Sulfuryl chloride was used as a chlorinating reagent for the chlorinations of ketones[9] and aldehydes,[10] as well as of several other substrates containing other functional groups.[10] In the case of acetone, methyl ethyl ketone, and diethyl ketone, the reaction with sulfuryl chloride provided polychlorinated products.[9] 2-Methylcyclohexanone, on the other hand, reacted with sulfuryl chloride in carbon tetrachloride to give 2-chloro-2-methylcyclohexanone with high selectivity,[11] which is contrary to the direct chlorination, which apparently was not selective.

The overall chlorination of ketones is undoubtedly another case of electrophilic addition of a chlorinating reagent to the double bond of enol present in the equilibrium (Scheme I, eq 1).[4] Consequently, a key to selective monochlorination of cyclohexanone, by analogy to electrophilic nitrosation,[3,4] also involves an efficient trapping of the resulting 2-chloro-1-hydroxycyclohexanone carbonium ion with an appropriate nucleophile (eq 2, Nu = ROH).

Scheme I



The formation of 2-chloro hemiacetal (eq 2, Nu = ROH), albeit reversible, should suppress the second enolization and hence further chlorination. For further minimization of polychlorination, the concentration and the reactivity of the chlorinating reagent should be as low as possible.

In solution sulfuryl chloride exists, very likely, in an equilibrium with a chloronium ion[12] (eq 4). While typical

$$SO_2Cl_2 \rightleftharpoons Cl^+ + SO_2Cl^- \rightleftharpoons Cl_2 + SO_2 \quad (4)$$

basic solvents,[13] such as ethers, would be expected to promote this dissociation, they should also render the chloronium ion less reactive due to an efficient solvation of the positive charge. The chlorination of cyclohexanone in these solvents (Table I, entries 1-4), indicated (a) that selectivities were not high and (b) that a considerable amount of cyclohexanone remained unreacted, suggesting, as expected, efficient generation of the chloro enols leading to the dichloro derivatives.

Sulfur dioxide solvates effectively negatively charged species, leaving the positive cations unsolvated and hence more reactive in the electrophilic reaction.[14] However,

(1) For a general discussion and summary of the early references, see Touster, O. *Org. React.* **1953**, *7*.
(2) For example, see House, H. O. "Modern Synthetic Methods", 2nd ed; W. A. Benjamin: Melno Park, CA, **1972**; p 459.
(3) Rogić, M. M.; Vitrone, J.; Swerdloff, M. D. *J. Am. Chem. Soc.* **1975**, *97*, 3848.
(4) Rogić, M. M.; Vitrone, J.; Swerdloff, M. D. *J. Am. Chem. Soc.* **1977**, *99*, 1156.
(5) Klein, K. P.; Demmin, T. R.; Oxenrider, B. C.; Rogić, M. M.; Tetenbaum, M. T. *J. Org. Chem.* **1979**, *44*, 275.
(6) Newman, M. S.; Farbman, M. D.; Hipsker, H. "*Organic Syntheses*", Collect. Vol. 3; Wiley: New York, 1955; p 188.
(7) Ebek, F. *Helv. Chim. Acta* **1929**, *12*, 9.
(8) Bartlett, P. D.; Rosenwald, R. H. *J. Am. Chem. Soc.* **1934**, *56*, 1992.
(9) Wayman, D. P.; Kaufman, P. R. *J. Org. Chem.* **1964**, *29*, 1956.
(10) Wayman, D. P.; Kaufman, P. R.; Treeman, W. R. *J. Org. Chem.* **1964**, *29*, 2706.
(11) Wernhoff, E. W.; Johnson, W. S. *J. Am. Chem. Soc.* **1953**, *75*, 494.
(12) For a free radical chlorination with sulfuryl chloride, see Karash, M. S.; Brown, H. C. *J. Am. Chem. Soc.* **1939**, *61*, 2142. Brown, H. C.; Ash, A. B. *Ibid.* **1955**, *77*, 4019. Russell, G. A.; Brown, H. C. *Ibid.* **1955**, *77*, 4031. Cupric halides have also been used for halogenation of ketones: Kochi, J. K. *J. Am. Chem. Soc.* **1955**, *77*, 5274. Kosower, E. M.; Cole, W. J.; Wu, G.-S.; Cardy, D. E.; Meisters, G. *J. Org. Chem.* **1963**, *28*, 630 and references therein.
(13) For a recent study of a product distributions in chlorination of aliphatic ketones in methanol and carbon tetrachloride, see Galbicci, R. R.; Going, R. *J. Org. Chem.* **1981**, *12*, 2532. We are grateful to the referee for bringing this paper to our attention.
(14) For a summary of general and solvent properties of sulfur dioxide, see Markowitz, J. M. *J. Chem. Educ.* **1960**, *37*, 75. Tokura, N. *Synthesis* **1971**, 639. Tokura, N.; Akiyama, F. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 1723.

0022-3263/81/1946-4486$01.25/0

Table I. Reaction of Cyclohexanone with Sulfuryl Chloride in the Presence of Various "Nucleophiles"[a]

no.	ketone/SO_2Cl_2, mmol	solvent	"nucleophile" (mmol)	unreacted ketone	products,[b] % monochloro	dichloro	RCl[c]
1	50/56	Et_2O		0	85	15	
2	50/56	THF		25	66	9	
3	50/56	*p*-dioxane		12	74	14	
4	50/56	tetraglyme		22	67	9	
5	50/56	SO_2			polychlorinated products		
6	50/56	SO_2	MeOH (150)	30	70	*d*	MeCl[f]
7	50/55	SO_2	MeOH (300)	25	75	*d*	MeCl[f]
8	50/62	SO_2	MeOH (225)	0	95	*e*	MeCl[f]
9	50/58	SO_2	MeOH (100)	0	100	*d*	MeCl[f]
10	100/120	SO_2/CH_2Cl_2[g]	MeOH (310)	5-15	85-93		MeCl[f]
11	50/55	CH_2Cl_2	MeOH (150)	100			MeCl[f]
12	50/55	CH_2Cl_2	MeOH (50)	15	85		MeCl[f]
13	50/55	CH_2Cl_2	*i*-PrOH (50)	100			*i*-PrCl[f]
14	50/55	CCl_4	*i*-PrOH (50)	30	70		*i*-PrCl[f]
15	50/55	CH_2Cl_2	MeOH/H_2O (50/50)	tr	99		MeCl[f]

[a] For a detailed experimental procedure, see Experimental Section. [b] GLC analyses. [c] In all instances hydrogen chloride and sulfur dioxide were gaseous byproducts. [d] Traces of 2,2-dimethoxycyclohexyl chloride and 1-methoxy-6-chlorocyclohexene were also formed. [e] About 3% and 2% of the 2,2-dimethoxycyclohexyl chloride and 1-methoxy-6-chlorocyclohexene, respectively. [f] No quantitative analyses for these alkyl chlorides were carried out. [g] A mixture of 100 mL of SO_2 and 40 mL of CH_2Cl_2.

being an acidic solvent, sulfur dioxide should not facilitate the proton removal to generate chloroenols, which are required for subsequent chlorinations. Nevertheless, chlorination of cyclohexanone in sulfur dioxide, just as the nitrotrosation reaction in the same solvent,[3,4] is not selective (Table I, entry 5). Evidently, the increased electrophilic character of the chloronium ion in sulfur dioxide more than compensates for the less efficient generation of the chloroenols, still leading to an overall polychlorination.

Sulfuryl chloride reacts vigorously with methanol at room temperature to give methanesulfuryl chloride, hydrogen chloride, methyl chloride, and dimethyl sulfate. Methanesulfuryl chloride is a relatively stable compound at room temperature and can be distilled at reduced pressure; however, attempted distillation at atmospheric pressure gave methyl chloride and presumably sulfur trioxide. Methanesulfuryl chloride is not a chlorinating reagent either by itself, or in the presence of hydrogen chloride. Consequently, it is not surprising that cyclohexanone cannot be chlorinated by sulfuryl chloride in methanol solution. However, the addition of sulfuryl chloride to a solution of cyclohexanone in sulfur dioxide containing a slight excess of methanol led to an efficient chlorination (Table I, entry 6–9). In all cases only monochlorination of cyclohexanone did take place; small amounts of the 2-chlorocyclohexanone dimethyl ketal and the corresponding enol ether were also formed, but there was no evidence of polychlorination. While methyl chloride was formed, no quantitative analysis was carried out, and only a slight excess of sulfuryl chloride was required to compensate for this side consumption of the chlorinating agent.

The efficient monochlorination can also be carried out in methylene chloride, although the overall conversion was not as good (Table I, entries 10, 12). Apparently, in methylene chloride the reaction of sulfuryl chloride with methanol to give methanesulfuryl chloride (and methyl chloride) occurs more readily than in sulfur dioxide (entries 11, 12). Isopropyl alcohol is less effective in methylene chloride than methanol (entries 12, 13), and cyclohexanone was recovered largely unreacted; substantial amounts of isopropyl chloride were fomed both in methylene chloride and in carbon tetrachloride (entries 13, 14). Interestingly, monochlorination of cyclohexanone with sulfuryl chloride in methylene chloride, containing a molar equivalent each of methanol and water, gave almost quantitatively monochlorocyclohexanone, without formation of the monochloro ketal and the enol ether (entry 15). Clearly, in low concentrations even water can act as a nucleophile in eq 2, providing the chlorocyclohexanone hydrate as intermediate, thus preventing further chlorination.

Reaction of acetone with sulfuryl chloride in methylene chloride in the absence of methanol gives 1-chloroacetone and 1,1-dichloroacetone in a 2:1 ratio and unreacted acetone.[9] However, in the presence of methanol, no polychlorination was observed, and monochloroacetone was obtained in 85% yield, together with unreacted acetone.

2. Sulfuryl Chloride as a Reagent for Chlorination of Phenols. While direct chlorination of phenol with chlorine affords 2,4,6-trichlorophenol, it is usually not too difficult to achieve selective monochlorination of this substrate.[15] It is of interest that sulfuryl chloride does not react with phenol in methylene chloride solution even under reflux. Addition of a molar equivalent of pyridine to such a solution induces the replacement of a chloride ion from sulfuryl chloride by phenol and provides benzenesulfuryl chloride quantitatively. On the other hand, in ether, sulfuryl chloride chlorinates phenol. Furthermore, addition of ether to a solution of phenol and sulfuryl chloride in methylene chloride also induces chlorination of phenol and formation of monochlorophenols. Similarly, addition of methanol and other basic materials such as dimethyl sulfoxide or crown ethers to a solution of phenol and sulfuryl chloride in methylene chloride provided exclusively monochlorophenols. Para-substituted phenols, such as 4-*tert*-butylphenol and bisphenol A, in which the attack at the para position is hindered, provided only *o*-monochloro derivatives in II).

Both pyridine and ether induced the reaction between sulfuryl chloride and phenol in methylene chloride solution. However, while pyridine induced nucleophilic substitution of the chloride ion from the sulfuryl chloride by phenol, ether induced electrophilic chlorination of the aromatic ring. Presumably, pyridine facilitates otherwise inefficient nucleophilic replacement of the chloride ion by

(15) See, for example, Carey, F. A.; Sundberg, R. J. "Advanced Organic Chemistry"; Plenum Press: New York, 1977; p 260 and references therein.

Table II. Reaction of Phenol with Sulfuryl Chloride in the Presence of Organic "Bases"[a]

no.	phenol/SO_2Cl_2, mmol	solvent	"base" (mmol)	unreacted phenol,[b] %	monochlorophenols,[b] %		
					para	ortho	para/ortho
1	100/100	CH_2Cl_2		100			
2	100/100	CH_2Cl_2	Et_2O (100)	3	65.8	31.1	2.1
3	100/100	CH_2Cl_2	MeOH (100)	7.3	51.0	41.7	1.2
4	100/100	CH_2Cl_2	EtOH (100)	10.0	60.0	30.0	2.0
5	100/100	CH_2Cl_2	Me_2SO (50)	50.0	25.0	25.0	1.0
6	100/100	CH_2Cl_2	n-Bu_2S (10)	tr	66.0	33.0	2.0
7	100/100	CH_2Cl_2	18-crown-6 (10)[c]	10	45.0	45.0	1.0

[a] Reactions were carried out at room temperature by addition of organic "base" to a solution of phenol and sulfuryl chloride in 50 mL of methylene chloride. [b] GLC analyses. [c] Dissolved in 10 mL of methylene chloride.

removing hydrogen chloride from the equilibrium (eq 5 and 6). Ether is not as strong a base as pyridine, and evidently

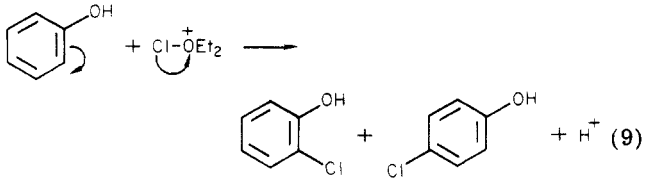
$$PhOH + SO_2Cl_2 \underset{CH_2Cl_2}{\rightleftharpoons} PhOSO_2Cl + HCl \quad (5)$$

$$HCl + Py \rightarrow PyHCl \quad (6)$$

it does not assist in the formation of benzenesulfuryl chloride by removing the acid from the equilibrium (eq 5). Instead, it promotes dissociation of the chloronium ion from sulfuryl chloride[16] (eq 7 and 8), which then undergoes electrophilic reaction with the aromatic ring of phenol to give the observed products (eq 9).

$$SO_2Cl_2 \rightleftharpoons Cl^+ + SO_2Cl^- \quad (7)$$

$$Cl^+ + Et_2O \rightleftharpoons Et_2O^+{:}Cl \quad (8)$$



(9)

Conclusions

Chlorination of ketones with sulfuryl chloride in the presence of a slight molar excess of "nucleophiles", such as methanol or water, provides only monochloro ketones. Mechanistically, the resulting α-chlorohydroxy carbonium ion intermediate is trapped efficiently with the present nucleophile,[3,4] providing the corresponding α-chloro ketone hemiacetal of hydrate. This suppresses formation of the enols of chlorinated ketones and thus the subsequent polychlorination. Consequently, the reaction could also be carried out with chlorine itself. However, because the success of the reaction requires that the chloronium ion electrophile be introduced in low relative concentrations, sulfuryl chloride is simpler to use experimentally than gaseous chlorine.

Moreover, sulfuryl chloride can also be used in selective monochlorination of phenols in the presence of a slight excess of various organic "bases", including methanol and ether.

Experimental Section

The melting points are uncorrected. The ^1H NMR and infrared spectra were recorded on a Varian T-60 and on a Perkin-Elmer spectrometer, respectively. All starting materials (including sulfuryl chloride) were either distilled or crystallized before use. Sulfur dioxide (Matheson high-purity grade) was dried over molecular sieves. Anhydrous alcohols and ethers were used without further purification.

Reaction of Cyclohexanone with Sulfuryl Chloride in Liquid Sulfur Dioxide. A three-neck flask equipped with a dry ice condenser protected by a nitrogen bubbler, an addition funnel, and a mechanical stirrer was placed in a dry ice–acetone bath and charged with dry sulfur dioxide (50 mL). Cyclohexanone (4.9 g, 50 mmol) was introduced, and the dry ice bath was removed; when sulfur dioxide started to reflux, sulfuryl chloride (7.5 g, 56 mmol) was added dropwise with stirring over 15–20 min. The gaseous byproducts were vented out through the nitrogen bubbler, and the reaction mixture was stirred for an additional 10–15 min. To the solution was added 50 mL of precooled chloroform, and sulfur dioxide was removed on a rotary evaporator. The chloroform solution was washed with saturated sodium bicarbonate solution, dried over sodium sulfate, and then analyzed by GLC, using a 6-ft column of 10% OV-1 on Chromosorb. Besides unreacted cyclohexanone, there were six other products, the dichlorocyclohexanones predominating.

Reaction of Cyclohexanone with Sulfuryl Chloride in Ether Solvents. The reactions were carried out in a similar apparatus as above at 10–15 °C. Cyclohexanone (4.9 g, 50 mmol) was dissolved in 50 mL of ether, tetrahydrofuran, p-dioxane, or tetraglyme, and sulfuryl chloride 7.5 g, 56 mmol) was added dropwise with stirring. After a similar workup procedure, the reaction mixture was analyzed, and the results are summarized in Table I.

Reaction of Cyclohexanone with Sulfuryl Chloride in Liquid Sulfur Dioxide in the Presence of Methanol. The reactions were carried out as above under gentle reflux by adding sulfuryl chloride to a solution of cyclohexanone in liquid sulfur dioxide containing various amounts of methanol. After complete addition of sulfuryl chloride, the reaction mixture was worked up as before and then analyzed by GLC. The results are summarized in Table I.

Reaction of Cyclohexanone with Sulfuryl Chloride in Sulfur Dioxide/Methylene Chloride in the Presence of Methanol. The reaction was carried out in a sulfur dioxide/methylene chloride solution (100 mL/40 mL) containing cyclohexanone (9.8 g, 100 mmol) and methanol (310 mmol) by slow addition of sulfuryl chloride (15.5 g, 120 mmol) under gentle reflux (dry ice condenser). After complete addition and usual workup, the reaction mixture was analyzed by GLC. The results are summarized in Table I.

Reactions of Cyclohexanone with Sulfuryl Chloride in Methylene Chloride in the Presence of Alcohol. To a solution of cyclohexanone (4.9 g, 50 mmol) in methylene chloride (50 mL) at 25 °C was added sulfuryl chloride (7.5 g, 55 mmol), followed by dropwise addition of an alcohol (50–150 mmol, see Table I). After complete addition (gas evolution), the solution was refluxed

(16) Both ether and pyridine would be expected to promote the dissociation of sulfuryl chloride (eq 7). However, being a weaker base than pyridine, ether should form a weaker conjugate acid with the chloronium ion, which should have higher concentration of the "free" chlororinum ion at the equilibrium (eq 8) than the corresponding conjugate acid with pyridine. Evidently, methanol, dimethyl sulfoxide, and crown ethers (and presumably other similar organic "bases" also behave as ether and induce the electrophilic chlorination of the aromatic nucleus rather than the nucleophilic substitution of the chloride ion from sulfuryl chloride.

for 1 h, worked up, and analyzed by GLC (Table I).

Reaction of Acetone with Sulfuryl Chloride in Methylene Chloride in the Presence of Methanol. To a solution of acetone (5.8 g, 100 mmol) and methanol (9.6 g, 300 mmol) in methylene chloride (50 mL) was added sulfuryl chloride (14.8 g, 110 mmole) dropwise over 10 min. After the evolution of gases stopped (HCl, SO_2, CH_3Cl), GLC analysis indicated that only unreacted acetone and monochloroacetone were present. After the solution was washed with the saturated solution of sodium bicarbonate and dried over the magnesium sulfate, distillation gave 85% yield of monochloroacetone and unreacted acetone.

When the reaction was carried out in the absence of methanol, a 2:1 mixture of monochloroacetone/1,1-dichloroacetone and unreacted acetone was obtained.

Reaction of Phenol with Sulfuryl Chloride in the Presence of Ether and Other Organic "Bases". Phenol (9.4 g, 100 mmol) and sulfuryl chloride (13.5 g, 100 mmol) were dissolved in methylene chloride (50 mL). Dropwise addition of ether (7.4 g) led to an instantaneous and exothermic reaction with evolution of hydrogen chloride and sulfur dioxide (when an alcohol was used instead of the diethyl ether, the corresponding alkyl chlorides were also formed). GLC analysis indicated that only monochlorophenols were produced. Usual workup followed by the evaporation of the solvent afforded the products. A similar reaction procedure was followed when other organic "bases" different than ether (alcohols, thioethers, sulfoxides, and crown ethers) were used. The results are summarized in Table II. In the absence of the "base" there was no reaction between phenol and sulfuryl chloride in methylene chloride solution even under reflux.

Reaction of Bisphenol A with Sulfuryl Chloride in Ether. To a solution of bisphenol A (17.2 g, 75 mmol) in ether (100 mL) was added slowly sulfuryl chloride (22.3 g, 165 mmol) at room temperature with stirring. The reaction is exothermic, and initially the temperature rose to 30 °C. However, the evolution of gaseous byproducts maintained the temperature below 30 °C. When evolution of gases stopped, the solution was refluxed for 1 h. After the solution was washed with the saturated solution of sodium bicarbonate and dried over sodium sulfate, evaporation of the solvent gave 75% yield of 3,3'-dichloro-4,4'-isopropylidenediphenol.

Reaction of 4-*tert*-Butylphenol with Sulfuryl Chloride in Methyene Chloride in the Presence of Methanol. To a solution of 4-*tert*-butylphenol (15 g, 100 mmol) in methylene chloride (50 mL) was added methanol (3.2 g, 100 mmol) dropwise at room temperature. After the usual workup, 2-chloro-4-*tert*-butylphenol was obtained in 95% yield.

Acknowledgment. We thank Mr. Edward H. Manahan for his valuable assistance in all phases of this work.

Registry No. Sulfuryl chloride, 7791-25-5; cyclohexanone, 108-94-1; bisphenol A, 80-05-7; 4-*tert*-butylphenol, 98-54-4; acetone, 67-64-1; phenol, 108-95-2.

N-Substituted (Sarcosylamino)benzophenones. Their Synthesis and Conversion into Heterocycles[1,2]

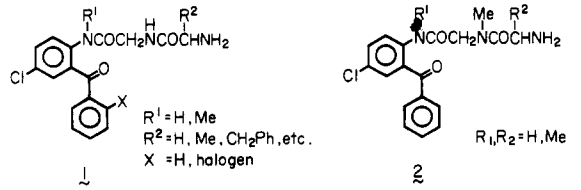
Kentaro Hirai,* Teruyuki Ishiba, Hirohiko Sugimoto, and Toshio Fujishita

Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

Received May 5, 1981

A synthetic study of N-substituted (sarcosylamino)benzophenones **2** is described. The target molecules **2** were found to be reactive under neutral conditions, affording intramolecularly cyclized products. Compounds **6a** and **13a** were converted into pyrazino[2,1-*b*]quinazoline **9a** and pyrazino[2,3-*b*]quinoline **18a**, respectively. The new heterocycles were characterized, and possible mechanisms are proposed for their formation.

Recently we have reported the synthesis of a novel series of (peptidoamino)benzophenones **1**[1,3] as ring-opened de-



1 **2**

rivatives of 1,4-benzodiazepine. These compounds possess significant central nervous system (CNS) activities. We thought that appropriate modification of this system would produce compounds with qualitatively different pharmacological profiles.

A marked difference in the CNS activities between aniline N-Me and N-H derivatives in **1** has been observed. Furthermore, release of terminal amino acid from **1** followed by cyclization leads to 1,4-benzodiazepine. Introduction of a methyl group to the nitrogen atom in dipeptide bond part of **1** would change its activities by affecting the dipeptide bond (N(Me)-CO) cleavage in vivo as well as inhibiting the formation of 1,4-benzodiazepine. Thus, preparation of **2** is of interest from the synthetic and pharmacological points of view. We found that the target molecules **2** were particulary reactive in solution, undergoing cyclization to afford pyrazino[2,1-*b*]quinazoline or pyrazino[2,3-*b*]quinoline derivatives and/or cleavage of anilide bond to give aminobenzophenones depending on the substituent (R^1, R^2). A noteworthy feature of this cyclization is that it takes place essentially under neutral condition, whereas the cyclization of [[(iodoacetyl)-glycyl]amino]benzophenone and [[(cyanoacetyl)glycyl]-amino]benzophenone to form oxazolo[3,2-*d*][1,4]benzo-

(1) This paper is part 5 of a series on "Benzophenone Related Compounds". Part 4: Hirai, K.; Ishiba, T.; Sugimoto, H.; Fujishita, T.; Tsukinoki, Y.; Hirose, K. *J. Med. Chem.* **1981**, *24*, 20.

(2) A part of this paper was presented at the 12th Congress of Heterocyclic Chemistry, Tokyo, Japan, 1979. For an abstract, see: *Heterocycles* **1980**, *14*, 121.

(3) (a) Hirai, K.; Ishiba, T.; Sugimoto, H.; Sasakura, K.; Fujishita, T.; Tsukinoki, Y.; Hirose, K. *Chem. Pharm. Bull.* **1978**, *26*, 1947. (b) Hirai, K.; Ishiba, T.; Sugimoto, H.; Sasakura, K.; Fujishita, T.; Toyoda, T.; Tsukinoki, Y.; Jōyama, H.; Hatakeyama, H.; Hirose, K. *J. Med. Chem.* **1980**, *23*, 764.

0022-3263/81/1946-4489$01.25/0