September, 1984] © *1984 The Chemical Society of Japan* *Bull. Chem. Soc. Jpn.*, *57, 2479—2483 (1984)*

Selective Protection of Carbonyl Groups by Taking Advantage of a Combination of Solid Support and Girard's Reagent

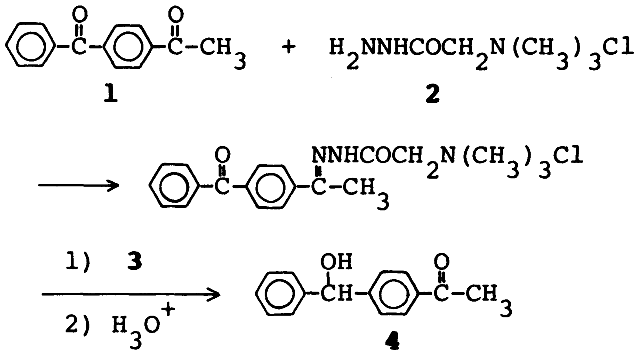
Teiji Chihara, Erika Waniguchi,[†] Tamie Wakabayashi,[†] and Kazuo Taya*,[†]
The Institute of Physical and Chemical Research, Wako, Saitama 351-01
[†]*Department of Chemistry, Tokyo Gakugei University, Koganei, Tokyo 184*
(Received February 21, 1984)

Some Girard's derivatives of 4-phenylbenzophenone were prepared in ethanol solution, in the presence of Amberlite IRC-50 as a catalyst. Supported samples of the derivatives were then prepared by addition of silica gel to the solution, followed by evaporation of the ethanol. The supported samples were reduced with lithium tri-*t*-butoxyhydroaluminate by being suspended in THF solution. Hydrolysis, followed by extraction of the product, yielded 4-acetyl-α-phenylbenzyl alcohol in an 80% selectivity. In the same way, 4-acetylbenzaldehyde yielded 1-(4-formylphenyl)ethanol in an 81% selectivity. Relatively unhindered carbonyl groups were preferentially protected. Utilization of Girard's reagents was successfully made as a protecting reagent and also as an extracting reagent of carbonyl compounds.

Many chemical reactions occur homogeneously, while various reactions occurring on solid surfaces are also known. Recently, solid adsorbents have been used as reaction media on which the reactions occur heterogeneously.[1] In almost all cases reagents were adsorbed on them, and some concepts for application of the adsorbents can be seen in the reports. In one concept, inorganic reagents such as potassium permanganate, sodium periodate, iron(III) nitrate, and iron(III) chloride were brought into an organic reaction system on solid adsorbents.[2–5] These inorganic reagents are insoluble in organic solvents, so they were adsorbed, forming monomolecular-like layers on the solid adsorbents. In addition, isolation of the products became easy by use of adsorbents, because inorganic byproducts and tarry matter remain on the adsorbents.

We have reported the case in which a substrate was adsorbed.[6] Sodium hydrogensulfite adducts of carbonyl compounds are usually not soluble in organic solvents, but were stably adsorbed on silica gel and alumina in the absence of water. The adducts adsorbed on solid adsorbents could be brought into an organic reaction system. In this way, sodium hydrogensulfite was used for protection of the carbonyl groups in the organic reaction system.

From the same stand point the use of Girard's reagents for protection of carbonyl groups has been studied. Girard's reagents condense with carbonyl compounds to form water-soluble products. The carbonyl compounds are then recovered from the aqueous layer by hydrolysis or carbonyl exchange reaction.[7] While a semicarbazide hydrochloride is used to protect the carbonyl groups, Girard's reagent, a member of the substituted hydrazine group, has not been used to protect them because of the low solubilities of the derivatives in the usual organic solvents. We tried to use Girard's reagent for protection of the carbonyl groups by using it with adsorbents. As a representative of dicarbonyl compounds, 4-acetylbenzophenone (**1**) was chosen. It has two carbonyl groups. One of these, the benzoyl group, was reported not to react with Girard's reagent because of steric hindrance.[8] First, the derivative of **1** with Girard-T (**2**), α-(trimethylammonio) acetohydrazide chloride, was prepared. Then it was supported on silica gel and reduced with lithium tri-*t*-butoxyhydroaluminate (**3**). Analysis of the product showed that 4-acetyl-α-phenylbenzyl alcohol (**4**) was obtained in an 80% selectivity. Part of the results of this investigation was preliminary reported in an earlier paper,[9] and the details are given here.



Results and Discussion

Selective Protection of the Acetyl Group of 4-Acetylbenzophenone (1). The effect of reaction time on the Girard's derivative formation was examined. Equal moles of **1** and **2** were allowed to react in the presence of Amberlite IRC-50 (**5**) as a catalyst to produce the derivative. After removal of the catalyst, silica gel was added to the solution, and the ethanol was evaporated. The derivative supported on silica gel was reduced with an excess of **3**. After hydrolysis the product was analyzed. The compositions of the products were plotted against the reaction time for the derivative formation in Fig. 1. This figure shows that the products of insufficient reaction time contained considerable amount of diol, 4-(1-hydroxyethyl)-α-phenylbenzyl alcohol (*6*). This is because considerable amount of **1** was left intact and was then reduced. Figure 1 also shows that the compositions of the products attained constant values after two hours. So the selectivity for **4** was about 80%. Two hours was sufficient to complete the formation of the derivative. In this way the reaction time was determin-

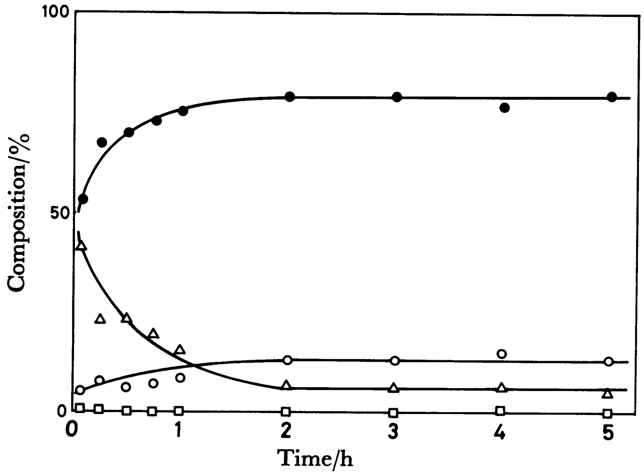


Fig. 1. Effect of reaction time for Girard-T derivative formation on selective protection of **1**.
Reaction temperature: 70 °C, **1** : **2**=1 : 1(mol/mol), **1**: silica gel=1 : 35(w/w), ○: **1**, ●: **4**, △: **6**, □: **11**.

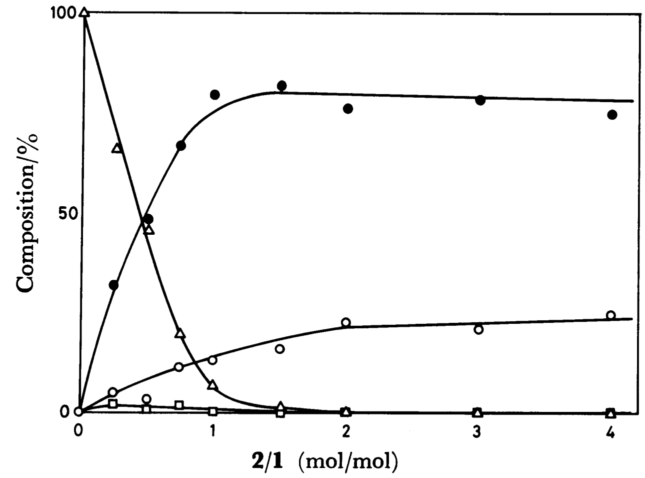


Fig. 2. Effect of amount of **2** on selective protection of **1**.
1: silica gel=1:35 (w/w), ○: **1**, ●: **4**, △: **6**, □: **11**.

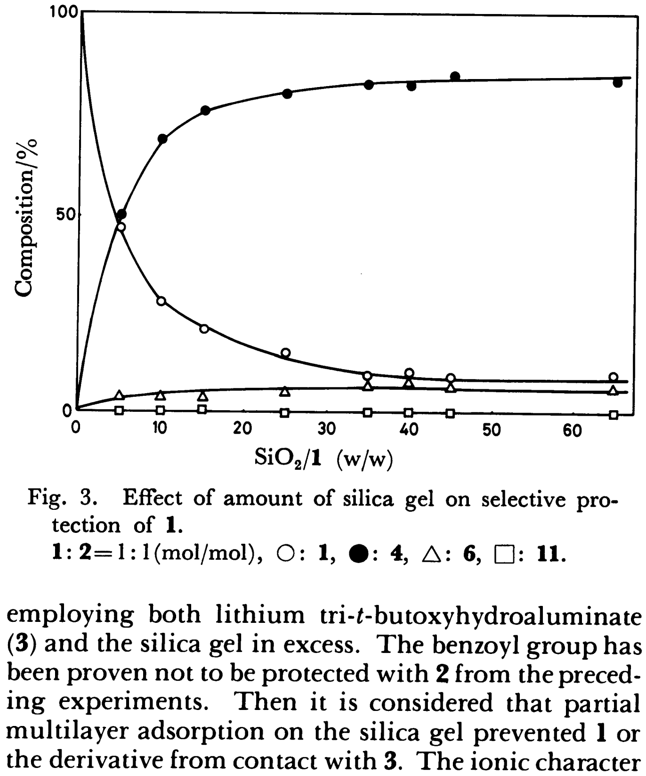


Fig. 3. Effect of amount of silica gel on selective protection of **1**.
1: **2**=1:1(mol/mol), ○: **1**, ●: **4**, △: **6**, □: **11**.

ed for each substrate or pair of substrates in competitive reaction at an appropriate reaction temperature. Milder reaction conditions were adopted unless a benzoyl group was contained. As Fig. 1 shows, the products contained about 13% of the starting material, **1**, unreduced, though equal mole of **2** and sufficient amount of **3** were used. Two cases are proposed for the explanation: (1) The benzoyl group of **1** was also protected by **2**. (2) Compound **1** or the derivative on the silica gel was covered with other molecules and prohibited from reacting with **3**.

The effect of the amount of Girard-T (**2**) on the selectivity was examined. The derivatives were prepared in varying ratios of **2** to 4-acetylbenzophenone (**1**), using **5** as a catalyst, and treated in the way described above. The compositions of the products were plotted against the amounts of **2** in Fig. 2. When more than equal moles of **2** to **1** was used, 4-acetyl-α-phenylbenzyl alcohol (**4**) was obtained in about 80% selectivity. An equal mole amount of **2** was sufficient for the selective protection of the acetyl group of **1**. The benzoyl group of **1** was not protected, for more than 75% of the benzoyl group was reduced in spite of the addition of **2** in excess.

The effect of the amount of silica gel was also examined. The derivatives were prepared from equal moles of **1** and **2** as described above. Then the adsorbed samples were prepared with varying amounts of silica gel and treated with the procedure described above. The compositions of the products are plotted against the amount of silica gel in Fig. 3. This figure shows that a significant amount of unreduced **1** was recovered when the amount of silica gel was little. The figure also shows that the amount of 4-acetyl-α-phenylbenzyl alcohol (**4**) increased with increasing amount of the silica gel up to 35 times that of **1**. Not less than 10 times silica gel is required for monolayer adsorption of the derivative: this comes from a rough estimate using simple molecular models.[10] Rough agreement was obtained amoung these values. In the reaction products, **1** was contained in more than 13% selectivity in spite of employing both lithium tri-*t*-butoxyhydroaluminate (**3**) and the silica gel in excess. The benzoyl group has been proven not to be protected with **2** from the preceding experiments. Then it is considered that partial multilayer adsorption on the silica gel prevented **1** or the derivative from contact with **3**. The ionic character of the derivative may facilitate the formation of the multi layer adsorption.

Girard-P (**7**), α-(1-pyridino) acetohydrazide chloride, and rarely Girard-D (**8**), α-(dimethylammonio) acetohydrazide chloride, are also used as the condensation reagents.[7] The effectiveness of these reagents was examined according to the manner described above. As presented in Table 1, **7** was a useful reagent for protection of the acetyl group of **1**, but **8** was not.

Acetic acid (**9**), as well as Amberlite IRC-50 (**5**), is known as a catalyst for the condensation of Girard's reagents with carbonyl compounds. The effect of **9** on the selective protection was examined. As can be seen from Table 1, **9** was not a suitable reagent for the selective protection, because a significant amount of

TABLE 1. SELECTIVE PROTECTION OF **1** WITH GIRARD'S REAGENTS

Girard's reagent[a]	Catalyst	Adsorbent	Product composition/%			
			1	**4**	**11**	**6**
2	**9**	SiO$_2$	41.4	51.8	0.6	6.2
2	**9**[b]	SiO$_2$	39.4	54.0	0.5	6.1
2	**5**	SiO$_2$	13.2	79.5	0.8	6.5
7	**5**	SiO$_2$	14.3	73.1	2.3	10.2
8	**5**	SiO$_2$	17.1	14.1	22.0	46.7
2	**5**	Celite	9.6	82.5	0.3	7.6
2	**5**	Al$_2$O$_3$	25.8	68.6	0.6	5.0

a) Equal moles of Girard's reagent and **1** were used. b) **9** was neutralized with sodium hydroxide.

TABLE 2. SELECTIVITY FOR PROTECTION OF CARBONYL GROUPS WITH **2**

Entry	Carbonyl compounds[a]		Recovery/%[b]		Conversion/%[c]		Selectivity for B[d]
	A	B	A	B	A	B	
1	4-phenylacetophenone	benzophenone	95	81	16.1	96.3	5.98
2	benzaldehyde	**17**	74	82	10.1	61.1	6.05
3	undecanal	2-undecanone	83	96	9.6	60.7	6.32
4	undecanal	3-undecanone	75	96	0.8	77.9	97.4
5	2-undecanone	3-undecanone	80	91	38.5	71.2	1.85
6	**15**	**16**	89	95	6.7	73.3	10.9

a) Equal moles of A, B, and **2** were used. b) Combined amount of unreduced substrate and product. c) Based on recovered products. d) (Conversion of B)/(Conversion of A).

4-acetylbenzophenone (**1**) was recovered without reduction. It is difficult to remove **9** completely from the adsorbed sample because of its relatively low vapor pressure and high polarity. The incomplete reduction of **1** could be attributed to the deposit of insoluble products produced by the reaction of **9** with tri-*t*-butoxyhydroaluminate (**3**) on the silica gel surface. A calculated amount of sodium hydroxide was added to neutralize **9** and to prevent the effect after condensation reaction. Then the adsorbed sample was prepared and reduced. As shown in Table 1, no improvement was observed. Consequently **9** was proven not to be a suitable catalyst for this purpose. In contrast to **9**, **5** brought about good selectivity. Moreover **5** could be easily removed from the reaction mixture by decantation. All the following experiments were undertaken by use of **5** as the catalyst.

Celite gave good selectivity, as Table 1 shows. Alumina was another effective adsorbent for the reaction, though the selectivity decreased a little. A similar result was obtained when silica-alumina (13% or 28% Al_2O_3) was used as adsorbent.

An attempt was made to utilize the Girard's reagent for protection of the carbonyl group in an aqueous solution without using solid support. Sodium borohydride (**10**) was used, for it can reduce carbonyl groups in aqueous solution. The derivative of **1** with **2** was prepared. Reduction of the derivative with **10** in the aqueous solution yielded 4-ethyl-α-phenylbenzyl alcohol preferentially and failed to yield **4**. Reductive cleavage occurred at the carbon-nitrogen double bond of the derivative.[11] Though this attempt was unsuccessful, another reducing agent can be utilized for this procedure.

It has been confirmed that the acetyl group of 4-acetylbenzophenone (**1**) had higher reactivity with **3** than the benzoyl group. When **3** was added to the THF solution of **1**, 4-(1-hydroxyethyl) benzophenone (**11**) was produced in a maximum 68% selectivity, while 4-acetyl-α-phenylbenzyl alcohol (**4**) was produced in a 19% maximum selectivity.

*Protection Selectivity of Girard-T (**2**) for Carbonyl Groups.* 4-Acetylbenzaldehyde (**12**) and 7-oxooctanal (**13**) were chosen as representatives of dicarbonyl compounds. The selective protection of the carbonyl groups with Girard-T (**2**) was examined by the method described above. When equal moles of **12** and **2** were allowed to react, 1-(4-formylphenyl) ethanol (**14**) was obtained in an 81.0% selectivity after reduction with **3**. When equal moles of **13** and **2** were allowed to react, 7-hydroxyoctanal was obtained in an 82.1% selectivity by the same procedure. In both cases the acetyl groups which existed together with the formyl groups were reduced preferentially. On the other hand, the acetyl group of 4-acetylbenzophenone (**1**) which existed together with the benzoyl group was not reduced. The treatment of **12** with twice the number of moles of **2** gave unreduced **12** in an 80.5% selectivity after reduction with **3**, which indicates that both carbonyl groups of **12** were protected with **2**. The protection of carbonyl groups depended both on the reactivity of the carbonyl groups and on the amount of **2** used.

The protection selectivity of **2** for other carbonyl groups was examined by a competitive reaction method combining two different kinds of carbonyl compounds. Table 2 presents the results. An acetyl group was selectively protected in the presence of a benzoyl group (entry 1), as can be expected from the result of **1**. Formyl groups in the presence of acetyl groups (entries 2 and 3), the aldehyde in the presence of an ethyl ketone (entry 4), and the methyl ketone in the presence of the ethyl ketone (entry 5) of similar molecular structures were selectively protected. 4-Phenylcyclohexanone (**15**) in the presence of 2-methyl-4-phenylcyclohexanone (**16**) was also selectively protected (entry 6). Consequently, **2** responded sensitively to the differences of steric hindrance of the carbonyl groups, and hence **2** was effective as a reagent for selective protection of the unhindered carbonyl groups.

Application of Girard-T (2) as a Protective as well as an Extractive Reagent. An experiment was undertaken in which **2** acted as a protective reagent of a carbonyl group, in addition to acting as the usual extractive reagent. To 9.4 mmol of 4-acetylbenzaldehyde (**12**), 9.4 mmol of acetophenone (**17**) was added deliberately as an impurity. To a solution of the mixture, 9.4 mmol of **2** was added; this produced the derivative in the presence of **5**. The product was washed with water. The adsorbed sample of the derivative on silica gel was prepared from the aqueous solution. After reduction with **3** followed by hydrolysis, the products were extracted with benzene. The following compounds were identified by analysis: 1-(4-formylphenyl) ethanol (**14**) (85% wt), **12** (5.6% wt), **17** (1.7% wt) and 1-phenylethanol (**18**, 6.9% wt). In this stage, about 90% of the impure substances (**17** and **18**) were removed. After purification of this product by column chromatography, 6.6 mmol (69% yield) of **14** was obtained.

Conclusion

Girard's reagents were found to be effective reagents for protection of carbonyl groups in a nonaqueous reaction system when they were used with the solid supports. The solid support was used as a reaction media on which the reaction took place. Another example can be seen in our study of protecting carbonyl groups with sodium hydrogensulfite, in which the substrates were supported on the silica gel or alumina.[6] Other examples can be seen in many cases in which the reagents were supported.[1] A solid support will provide an effective reaction environment if suitable solvents which dissolve both the substrate and reagent are not available.

Experimental

Materials. 4-Acetylbenzophenone (**1**, mp 83—84 °C),[12] 4-acetylbenzaldehyde (**12**, bp 155 °C/15 mmHg, 1 mmHg=133.322 Pa),[13] 7-oxooctanal (**13**, bp 126 °C/16 mmHg),[14] 4-phenylacetophenone (**19**, mp 121—122 °C),[15] 4-phenylcyclohexanone (**15**, mp 78 °C),[16] and 2-methyl-4-phenylcyclohexanone (**16**, mp 139 °C)[17] were prepared by the reported methods. THF was dried over calcium hydride. Lithium tri-*t*-butoxyhydroaluminate (**3**) was prepared by the reported method.[18] Silica gel and alumina were Wakogel C-200 and activated alumina 200 mesh, respectively (Wako Pure Chemical Industries, Ltd.). Finely divided Celite 545 (Johns-Manville Sales Corp.) was used. Other materials were commercial products.

Methods. *Typical Reaction*: Equal moles of **1** (44.8 mg, 0.2 mmol) and Girard-T (**2**, 33.5 mg, 0.2 mmol) were added to ethanol (1.3 mmol) suspending Amberlite IRC-50 (**5**, 10 mg) and stirred for 2 h at 70 °C. After removal of **5** by decantation silica gel (1.6 g) was added and the ethanol was evaporated under reduced pressure (*ca.* 10 mmHg) at 60 °C. After the evaporation had apparently completed, the sample was evacuated for an additional 10 min. The recovery of **1** from this adsorbed sample was 98%, and hence only a small amount of **1** was lost in this evaporation procedure. The adsorbed sample thus obtained contained a trace amount of the ethanol, but was used for further reaction as such. To a solution of **3** (2 mmol) in THF (7 cm^3), the adsorbed sample was added and well mixed for 1 h; then the mixture was hydrolyzed with dilute hydrochloric acid or treated with formaldehyde.[19] The product was extracted with benzene and analyzed by GLC or HPLC. The reactant was recovered in a 98% yield, based on the adsorbed sample. Selectivity for the formation of 4-acetyl-α-phenylbenzyl alcohol (**4**) was 79.5%.

Competitive Reaction: Typically **19** (39.2 mg, 0.2 mmol), benzophenone (36.4 mg, 0.2 mmol), and **2** (33.5 mg, 0.2 mmol) were added to ethanol (1.3 cm^3) which included **5** (10 mg) in suspension. The mixture was stirred for 2 h at 80 °C to produce the derivatives. Hereafter the sample was treated by the procedures described above.

Analysis. Reaction products were identified with the authentic samples obtained commercially or synthesized independently. Product compositions were determined by GLC or HPLC. GLC analyses were carried out on Shimadzu gas chromatographs Model GC-7A and GC-4MPTF using columns packed with 10% polyethylene glycol 20000 on Chromosorb WAW, and columns packed with 10% Apiezon grease L on Chromosorb WAW. HPLC analyses were performed on a Waters liquid chromatograph consisting of a Model 6000A pump, a Model U6K injector, and a Model 440 absorbance detector equipped with a Radial-PAK C_{18} column and a Hitachi 635A liquid chromatograph equipped with a Waters Model 440 absorbance detector and a Radial-PAK C_{18} column. Forty percent methanol in water and 25% methanol in water with 1% triethylamine adjusted at pH 7.3 with phosphoric acid were used as the mobile phase. Recoveries of the substrate from the adsorbed samples were determined by the GLC analyses above described. For the substrates bearing aromatic nuclei, the data were confirmed by UV absorbance measurement using a Hitachi 124 Spectrophotometer. The results agreed with a difference of less than 2%.

References

1) A. McKillop and D. W. Young, *Synthesis*, **1979**, 401; G. H. Posner, *Angew. Chem., Int. Ed. Eng.*, **17**, 487 (1978).

2) S. L. Regen and C. Koteel, *J. Am. Chem. Soc.*, **94**, 4024 (1972).

3) K.-T. Liu and Y.-C. Tong, *J. Org. Chem.*, **43**, 2717 (1978).

4) A. Corneris, P.-Y. Herze, and P. Laszlo, *Tetrahedron Lett.*, **23**, 5035 (1982).

5) E. Kainan and Y. Mazur, *J. Org. Chem.*, **43**, 1020 (1978).

6) T. Chihara, T. Wakabayashi, and K. Taya, *Chem. Lett.*, **1981**, 1657.

7) A. Girard and G. Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936); O. H. Wheeler, *J. Chem. Educ.*, **45**, 435 (1968).

8) O. H. Wheeler, *J. Chem. Educ.*, **45**, 435 (1968). Another paper reported that the benzoyl group reacted with **2** (L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley, New York (1967), p.410.) Even if it is so, the benzoyl group seemed to be more difficult to react with **2** than the acetyl group.

9) T. Chihara, E. Waniguchi, T. Wakabayashi, and K. Taya, *Chem. Lett.*, **1983**, 1647.

10) The specific surface area of the silica gel was 350 m^2 per g by BET measurement. The Girard-T derivative of **1** was approximated to a rectangular plate of 200 nm×50 nm. The estimation was made by arranging this plate without gap or overlap on a plane, and repulsive or attractive interactions among the molecules were disregarded.

11) L. Caglioti and P. Grasselli, *Chem. Ind. (London)*, **1964**, 153.

12) R. P. Zelinski, B. W. Turnquest, and E. C. Martin, *J. Am. Chem. Soc.*, **73**, 5521 (1951); J. Cason, *J. Am. Chem. Soc.*, **68**, 2078 (1946).

13) L. Friedman and H. Shechter, *J. Org. Chem.*, **26**, 2522 (1961); P. Tinappe and E. Möltgen, *Arch. Pharm. (Weinheim, Ger.)* **309**, 766 (1976).

14) J. F. Oughton, U. S. Patent 3112330 (1963); *Chem. Abstr.*, **60**, 4011g (1964).

15) J. Luche and A. L. Gemal, *J. Am. Chem. Soc.*, **101**, 5848 (1979).

16) L. M. Long and H. R. Henze, *J. Am. Chem. Soc.*, **63**, 1939 (1941).

17) A. G. Cook, "Enamines," Marcel Dekker, New York (1969), p. 2 and p. 346.

18) H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.*, **80**, 5372 (1958).

19) C. L. Teitelbaum, *J. Org. Chem.*, **23**, 646 (1958).