The Favorskii Rearrangement of α-Chloro Ketimines

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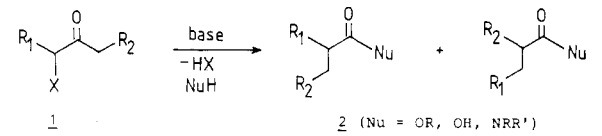
The Favorskii rearrangement of α-chloro ketimines has been studied. It was shown that the base-induced rearrangement of α-chloro ketimines afforded imidates or amides via a mechanism involving 1,3-dehydrochlorination and ring-opening of the resulting cyclopropylideneamines. The ring-opening occurred in such a way as to produce the most stable carbanion. The entire mechanism paralleled the well-known cyclopropanone mechanism of the Favorskii rearrangement of the corresponding oxygen analogues, i.e., α-halo ketones. Evidence has been presented that the semibenzilic-type mechanism is not operative in the cases studied. Depending upon the reaction conditions and the substrate, the Favorskii rearrangement was accompanied by various side reactions including nucleophilic substitution, 1,2-dehydrochlorination, rearrangement via intermediate α-alkoxyaziridines, and self-condensation.

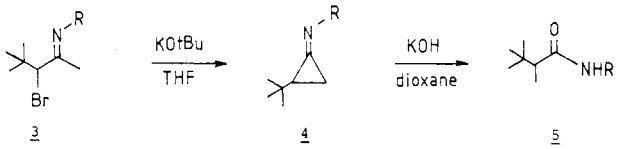
The Favorskii rearrangement of α-halo ketones **1**, entailing a base-induced skeletal rearrangement to afford carboxylic acid derivatives **2**, has been studied extensively in recent years (Scheme I). In the majority of cases, the reaction proceeds via a cyclopropanone intermediate and the mechanism is referred to as the cyclopropanone mechanism. In a number of cases, especially when no α′-hydrogens are available and when extreme ring tension prohibits formation of a cyclopropanone intermediate, the formation of carboxylic acid derivatives from α-halo ketones is explained by a mechanism which resembles the benzilic rearrangement, and, therefore, this mechanism is referred to as the semibenzilic mechanism.[2,3] The paramount interest in this well-studied rearrangement originates from its potential in the synthesis of highly branched carboxylic acid derivatives, the stereospecific synthesis of α,β-unsaturated carboxylic acid derivatives, and the ring-contraction of α-halo cycloalkanones into cycloalkanecarboxylic acid derivatives. In addition, the theoretical interest in the mechanism of the reaction has resulted in numerous studies. Accordingly, a large number of review articles on this topic have already appeared in the literature in which detailed mechanistic and synthetic aspects have been treated.[3-8]

From the theoretical viewpoint, α-halo ketimines, which are the nitrogen analogues of the corresponding α-halo ketones, are also suitable substrates to undergo a base-induced Favorskii-type rearrangement. As compared to α-halo ketones, α-halo imines are less reactive due to the weaker electronegativity of nitrogen with respect to oxygen. This would certainly influence both possible Favorskii mechanisms in which the cyclopropanone mechanism would be influenced by the reduced acidity of the α-hydrogens while the weaker electrophilic character of the imino function would have impact on the semibenzilic-type mechanism.

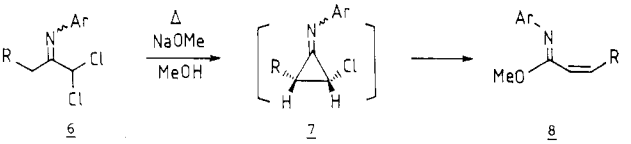
Scheme I



Scheme II



Scheme III



α-Halo imines have only been studied extensively in the last decade,[9-11] but their Favorskii rearrangement has been reported in very few cases. The first 1,3-dehydrobromination of an α-halo ketimine was reported for a sterically hindered substrate (**3**) which afforded isolable cyclopropylideneamines **4**. The latter were opened with hydroxide in a Favorskii fashion to yield carboxylic amides **5** (Scheme II).[12]

The net result of this two-step process entailed the Favorskii rearrangement, which was later extended to two cases in the alicyclic series.[13,14] The first one-step Fa-

(1) Onderzoeksleider (Senior Research Associate) of the Belgian Nationaal Fonds voor Wetenschappelijk Onderzoek (National Fund for Scientific Research).
(2) Kende, A. S. *Org. React.* **1960**, *11*, 261.
(3) Warnhoff, E. W.; Wong, C. M.; Tai, W. T. *J. Am. Chem. Soc.* **1968**, *90*, 514.
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(5) Rappe C. In *The Chemistry of the Carbon–Halogen Bond*; Patai, S., Ed.; Wiley: New York, 1973; p 1071.
(6) Sato, K.; Oohashi, M. *Yuki Gosei Kagaku Kyokai Shi* **1974**, *32*, 435.
(7) Chenier, P. J. *J. Chem. Educ.* **1978**, *55*, 286.
(8) Baretta, A.; Waegell, B. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1982; Vol. 2, p 527.
(9) De Kimpe, N.; Schamp, N. *Org. Prep. Proced. Int.* **1979**, *11*, 115.
(10) De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *Org. Prep. Proced. Int.* **1980**, *12*, 49.
(11) De Kimpe, N.; Verhé, R. In "α-Halogenated Imines"; Chapter 13 in *The Chemistry of Functional Groups—Supplement D: The Chemistry of Halides, Pseudo-Halides and Azides*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1983; p 549.
(12) Quast, H.; Frank, R.; Schmitt, E. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 329.

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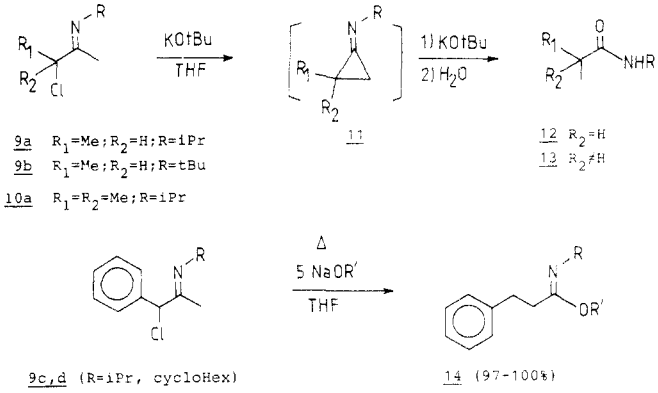
Scheme IV

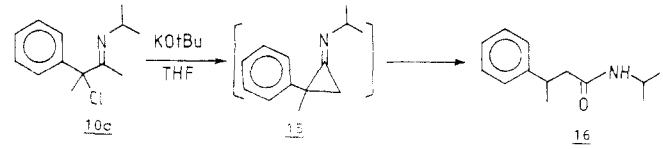


vorskii-rearrangement sensu strictu was described a decade ago as the rearrangement of *N*-aryl α,α-dichloromethyl ketimines **6** with sodium methoxide in methanol to afford α,β-unsaturated imidates **8** in a regiospecific and stereospecific way (Scheme III).[15,16] Recently, in a preliminary communication we reported the first Favorskii rearrangement of α-monochloro ketimines.[17] We have extended this study to various other substrates and have determined the scope and limitations of this reaction of α-halo imines. In addition, various side reactions occurring during the reaction of α-halo imines under so-called Favorskii conditions are discussed.

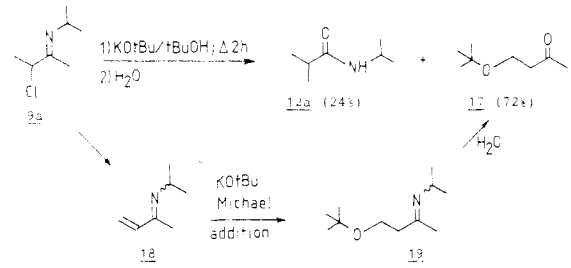
Results and Discussion

Although the reaction of *N*-alkyl α,α-dichloromethyl ketimines with alkoxides in the corresponding alcohols afforded nucleophilic substitution yielding the corresponding α,α-dialkoxyketimines,[18] the reaction of aliphatic *N*-alkyl α-monochloro ketimines **9a,b** (R_2 = H) and **10a** ($R_2 \neq$ H) with potassium *tert*-butoxide in tetrahydrofuran afforded branched carboxylic amides **12a,b** and **13a**, respectively (Table I). Secondary α-chloro ketimines **9** (R_2 = H) reacted under mild reaction conditions (room temperature) but tertiary α-chloro ketimines **9a** ($R_2 \neq$ H) required an extended period of reflux in order to complete the rearrangement. Yields of amides **12** and **13** are rather moderate probably due to losses during recrystallization (only isolated yields of recrystallized amides are reported in the table). A strong base such as potassium *tert*-butoxide or potassium hydroxide in dioxane is necessary for the rearrangement of aliphatic α-chloro ketimines **9**. Other base/solvent systems did not give any conversion of starting material **9a** (reagents used were sodium methoxide in diethyl ether, diisopropyl ether, THF or Dabco in THF, or benzene; all experiments were run under reflux). *N*-Alkyl α-chloro-α-phenyl ketimines **9c,d** reacted with a 5 molar excess of sodium alkoxides in tetrahydrofuran under reflux in a straightforward manner to provide nonbranched rearranged carboxylic imidates **14** in a nearly quantitative yield (Scheme IV). After completion of the reaction, the rearranged compounds were isolated by filtration of salts and unreacted alkoxide and evaporation of the solvent. Surprisingly, the tertiary α-chloro-α-phenyl ketimine **10c** (R_1 = Ph; R_2 = Me; R = *i*-Pr) did not react with sodium

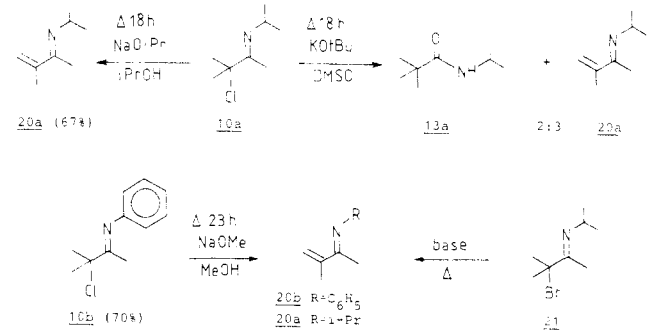
Scheme V



Scheme VI



Scheme VII

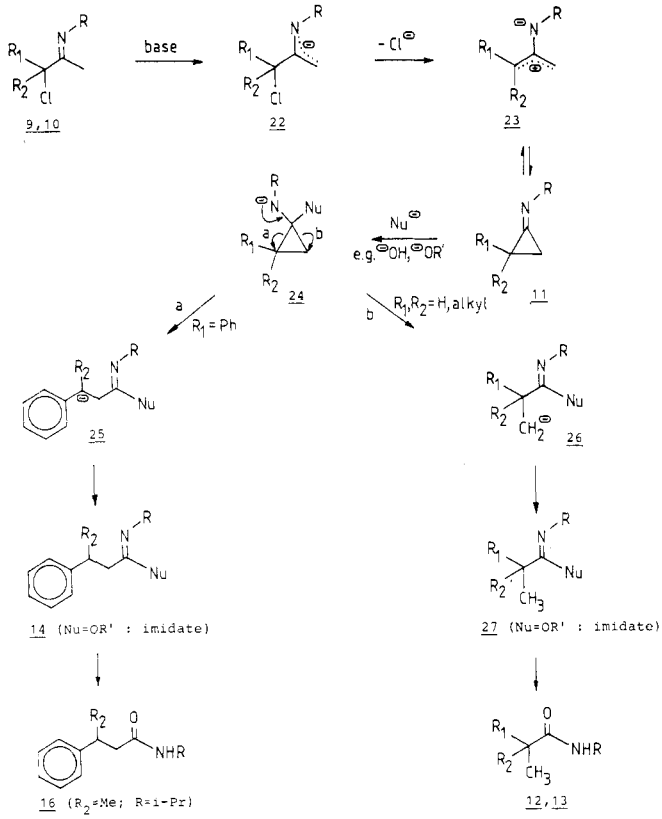


methoxide in tetrahydrofuran under reflux, but with the more strongly basic potassium *tert*-butoxide in the same solvent at room temperature a low yield (15%) of the rearranged amide **16** was isolated (Scheme V) (the mechanism will be discussed later). The latter reaction mixture contained a large portion of cyclopropylideneamine **15**, which was characterized by the typical high stretching vibration of the strained imino function ($\nu_{C=N}$ 1775 cm^{-1}). However, due to the instability of this compound, all attempts (TLC, column chromatography) to isolate it were unsuccessful. The intermediacy of cyclopropylideneamines will be discussed further in the section dealing with the mechanistic aspects of the Favorskii rearrangement. In more polar medium (3-chloro-2-butylidene)isopropylamine (**9a**) reacted with potassium *tert*-butoxide in a partially different manner. After 2 h of reflux with potassium *tert*-butoxide in *tert*-butyl alcohol, aqueous workup revealed the presence of a 1:3 mixture of Favorskii amide **12a** and 4-*tert*-butoxy-2-butanone (**17**) (Scheme VI). The formation of the latter ketone can be explained by initial 1,2-dehydrochlorination after which the resulting 1-azabutadiene **18** underwent Michael addition of *tert*-butoxide to provide β-*tert*-butoxy ketimine **19**. Alkoxy ketimines hydrolyze very easily and therefore it is not surprising the ketone **17** to be isolated exclusively after aqueous treatment.

Tertiary *N*-alkyl α-chloro ketimines **10** showed also this elimination reaction (1,2-dehydrochlorination), especially when base–solvent systems other than potassium *tert*-butoxide–tetrahydrofuran were used. (3-Chloro-3-methyl-2-butylidene)isopropylamine (**10a**) provided some Favorskii amide **13a** (33%) when treated with potassium *tert*-butoxide in dimethyl sulfoxide but the major compound was the 1-azabutadiene **20a** (Scheme VII). On the other hand, the α,β-unsaturated ketimine **20a** was obtained

(13) Quast, H.; Frank, R.; Heublein, A.; Schmitt, E. *Liebigs Ann. Chem.* **1980**, 1814.
(14) Quast, H.; Frank, R. *Liebigs Ann. Chem.* **1980**, 1939.
(15) De Kimpe, N.; Schamp, N. *Tetrahedron Lett.* **1974**, 3779.
(16) De Kimpe, N.; Schamp, N. *J. Org. Chem.* **1975**, *40*, 3749.
(17) De Kimpe, N.; Verhé, R.; De Buyck, L.; Moëns, L.; Schamp, N. *Tetrahedron Lett.* **1981**, *22*, 1837.
(18) De Kimpe, N.; Schamp, N. *Bull. Soc. Chim. Belg.* **1974**, *83*, 507.

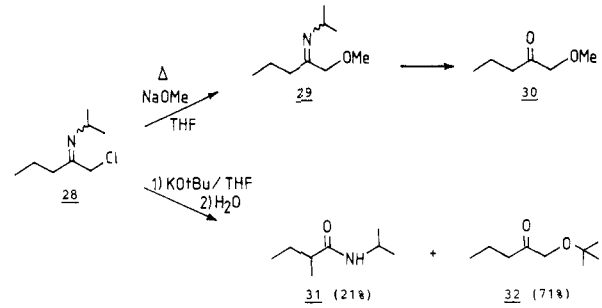
Scheme VIII



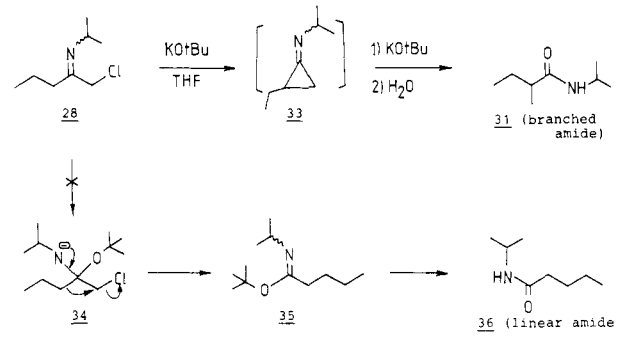
exclusively when sodium isopropoxide in isopropyl alcohol under reflux was used. The same 1,2-dehydrochlorination was observed rather unexpectedly (cf. ref 15 and 16) in the reaction of *N*-(3-chloro-3-methyl-2-butylidene)aniline (**10b**) with sodium methoxide in methanol under reflux (Scheme VII). This elimination reaction is the preferred reaction of α-bromo ketimine **21** with a variety of strong bases, e.g., sodium methoxide or potassium *tert*-butoxide in tetrahydrofuran or benzyltrimethylammonium hydroxide (Triton B) in isopropyl alcohol (Table I).

Mechanism of the Favorskii-Type Rearrangement of α-Chloro Ketimines. It has been shown previously[12] that the reaction of sterically hindered α-bromo ketimines with potassium *tert*-butoxide in tetrahydrofuran can be stopped at the stage of the 1,3-dehydrohalogenation products, i.e., cyclopropylideneamines **4**. Therefore it is reasonable to accept the mechanism of the Favorskii conversion of α-chloro ketimines with bases into amides or imidates in terms of an analogue of the so-called cyclopropanone mechanism of α-halo ketones. The base abstracts a proton at the α′-position of the α-chloro ketimine to form delocalized anion **22**, which by loss of a chloride anion produces zwitterion **23** (Scheme VIII). This species might be viewed in equilibrium with the cyclopropylideneamine **11** according to a disrotative ring-closure in accordance with the rules of Woodward and Hoffmann concerning the conservation of orbital symmetry. The reactive cyclopropylideneamine **11** undergoes then rapid addition across the strained imino function after which the resulting adduct anion **24** is opened in such a way as to produce the most stable carbanion. When R_1 and R_2 are alkyl groups (or also if R_2 = H), the primary carbanion **26** is the most stable form and this explains the opening via path b. In these cases (aliphatic series) branched derivatives are formed exclusively. If a phenyl substituent is present in the α-position of the starting α-chloro ketimine (R_1 = Ph) the exclusive opening of adduct **24** occurs via path a because the resulting benzylic carbanion **25** is more stable than the primary one. This results in the production of linear imidates **14** or linear amides **16**. It should be mentioned that all our attempt to trap the intermediate cyclopropylideneamines **11** with furan or 1,3-diphenylisobenzofuran were unsuccessful.

Scheme IX



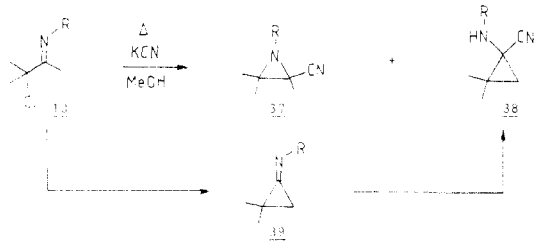
Scheme X



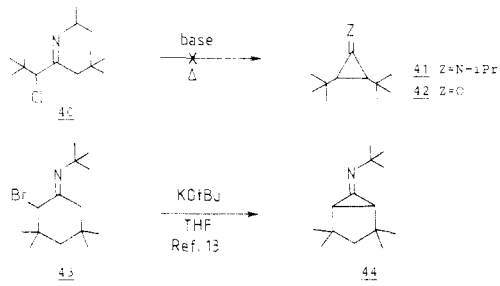
An alternative explanation for the base-induced rearrangement of α-chloro ketimines into amides or imidates is the semibenzilic-type mechanism. Experimental evidence for the exclusion of this mechanistic alternative can be gained in some series of reactions. The reaction of α-chloromethyl ketimine **28** with potassium *tert*-butoxide in tetrahydrofuran (room temperature, 2 h) afforded, after aqueous workup, a mixture of rearranged amide **31** (21%) and 1-*tert*-butoxy-2-pentanone (**32**) (71%) (Scheme IX). It is worth noting that less sterically hindered alkoxides, e.g., sodium methoxide, yielded nucleophilic substitution (**30**), exclusively. The semibenzilic rearrangement of α-chloromethyl ketimine would give addition of *tert*-butoxide across the imino function (see **34**) which would be followed by regeneration of an imino moiety and concomitant migration of the propyl group with expulsion of the chloride anion (Scheme X). This process would provide linear amide **36** (or imidate **35**), which is not isolated. Instead, the branched amide **31** was isolated and this product analysis is sufficient to accept the cyclopropylideneamine mechanism as the operating process (**28** → **33** → **31**) (Scheme X). Further support for the proposed cyclopropylideneamine mechanism of the Favorskii rearrangement of α-chloro ketimines was recently found in the reaction of tertiary *N*-alkyl α-chloro ketimines **10** (R = Et, *i*-Pr, cyclohexyl, allyl, neopentyl) with potassium cyanide in methanol which afforded 1-(alkylamino)cyclopropanecarbonitriles **38** along with the major product, α-cyanoaziridines **37**.[19,20] The formation of these geminally substituted cyclopropanes **38** pointed again to a Favorskii-type 1,3-dehydrochlorination and subsequent trapping of the

(19) De Kimpe, N.; Moëns, L.; Verhé, R.; De Buyck, L.; Schamp, N. *J. Chem. Soc., Chem. Commun.* **1982**, 19.
(20) De Kimpe, N.; Sulmon, P.; Verhé, R.; De Buyck, L.; Schamp, N. *J. Org. Chem.* **1983**, *48*, 4320.

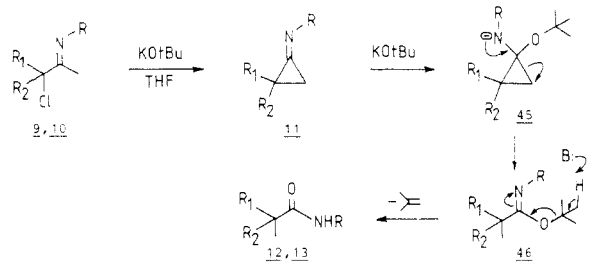
Scheme XI



Scheme XII



Scheme XIII



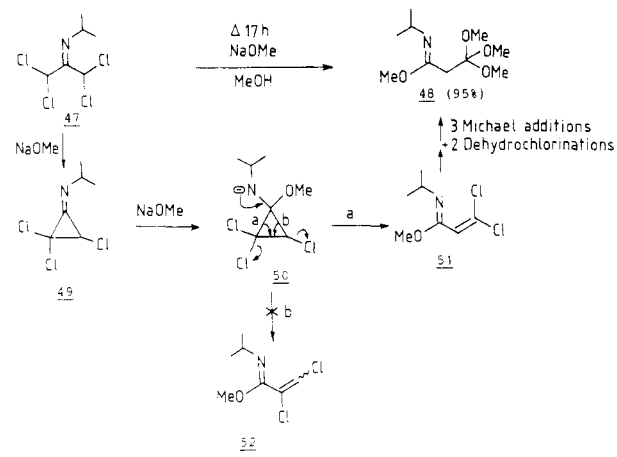
intermediate cyclopropylideneamines **39** as their stable adducts **38** (Scheme XI).

Concerning the mechanism of the Favorskii rearrangement of α-chloro ketimines, it should be pointed out that a major limiting factor is certainly the acidity of the α'-hydrogens in the starting material. Lowering this acidity by alkyl substitution reduced the tendency for Favorskii rearrangement.[20] This fact, in addition to steric factors, may explain that *N*-(3-chloro-2,2,6,6-tetramethyl-4-heptylidene)isopropylamine (**40**) did not undergo any reaction with strong bases such as potassium *tert*-butoxide in tetrahydrofuran (Δ, 24 h), potassium hydroxide in dioxane (Δ, 50 h), or 2 N sodium methoxide in methanol (Δ, 7 days) (Scheme XII). This would have been an entry to 2,3-di-*tert*-butylcyclopropylideneamine (**41**) (Z = N-*i*-Pr) in analogy to the known synthesis of 2,3-di-*tert*-butylcyclopropanone (**42**) (Z = O) under Favorskii conditions.[21-23] Recently however, a cyclic α-bromo ketimine with analogous double neopentylic structure (**43**) has been converted in such a similar strained cyclopropylideneamine (**44**).[13]

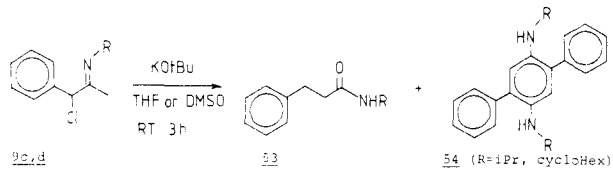
The mechanistic explanation of the formation of Favorskii rearrangement products still lacks the interpretation of the occurrence of carboxylic amides instead of imidates, when the reactions were performed with potassium *tert*-butoxide. Via opening of the cyclopropylideneamine adduct **45** a *tert*-butyl imidate (e.g., **46**) is formed (but not isolated) which is further transformed into amides **12** and **13**. *tert*-Butyl imidates are rare in the literature, and in

(21) Pazos, J. F.; Greene, F. D. *J. Am. Chem. Soc.* **1967**, *89*, 1030.
(22) Wharton, P. S.; Fritzberg, A. R. *J. Org. Chem.* **1972**, *37*, 1899.
(23) Pazos, J. F.; Pacifici, J. G.; Pierson, G. O.; Sclove, D. B.; Greene, F. D. *J. Org. Chem.* **1974**, *39*, 1990.

Scheme XIV



Scheme XV



analogy with precedents in the literature[24,25] it is postulated that 2-methylpropene is expelled by means of the base-induced process as given in Scheme XIII. This alkene expulsion of imidates is better known under pyrolytic conditions.[26-28] With simpler alkoxides, such as methoxide and ethoxide, however, stable alkyl imidates were indeed isolated, which proves the validity of the imidate consideration.

Further Examples of the Favorskii Rearrangement of α-Chloro Ketimines. The Favorskii-type rearrangement is not limited to α-monochloro or α,α-dichloro ketimines as exemplified for tetrachloro ketimine **47**, which reacted with excess sodium methoxide in tetrahydrofuran under reflux (17 h) to afford ortho esters **48** in 95% yield (Scheme XIV). The structure of the rearranged ortho ester **48** was established by spectrometric methods and by acidic hydrolysis (aqueous HCl) into dimethyl malonate. It is plausible and reasonable to interpret this rearrangement as a regiospecific process in view of the end product formed. The addition of methoxide across cyclopropylideneamine **49** gives adduct **50** which is regiospecifically opened with formation of the intermediate β,β-dichloro-α,β-unsaturated imidate **51** (path a). If the reaction would take place via path b, then the resulting α,β-dichloro-α,β-unsaturated imidate **52** could also afford ortho ester **48** but could also suffer reactions in which the α-halogen is displaced by methoxide (after Michael addition). However, the latter side reaction was not observed.

A side reaction worth focusing on was observed during the reaction of α-chloro-α-phenyl ketimines **9c,d** with potassium *tert*-butoxide in tetrahydrofuran or dimethyl sulfoxide. Besides the expected Favorskii amide **53**, crystalline compounds of high molecular weight were isolated (22–41%), which, based on spectrometric data, were identified as *N,N'*-dialkyl-2,5-diphenyl-*p*-phenylenediamines **54** (R = *i*-Pr, cycloHex) (Scheme XV). An un-

(24) Deyrup, J. A.; Greenwald, R. B. *Tetrahedron Lett.* **1966**, 5091.
(25) Ichimura, K.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1874.
(26) Wiberg, K. B.; Rowland, B. L. *J. Am. Chem.* **1955**, *77*, 2207.
(27) Ralls, J. W.; Ellinger, C. A. *Chem. Ind. (London)* **1961**, 20.
(28) Al-Awadi, N.; Ballam, J.; Hemblade, P. R.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2*, **1982**, 1175.

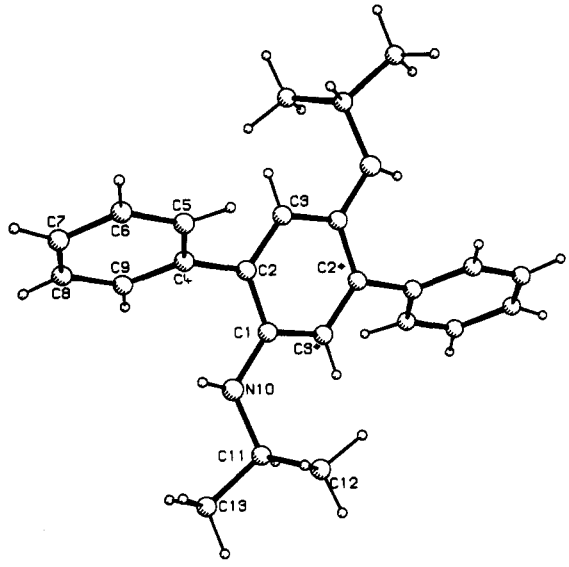
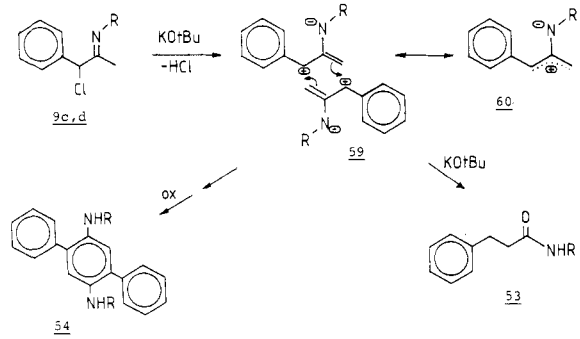


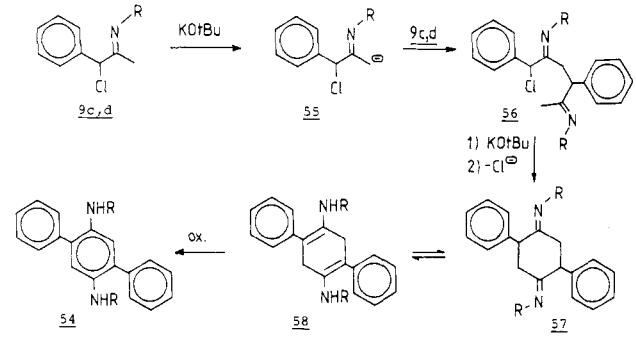
Figure 1. X-ray crystallographic structure of *N,N'*-diisopropyl-2,5-diphenyl-*p*-phenylenediamine (**54**) (R = *i*-Pr).

Scheme XVI

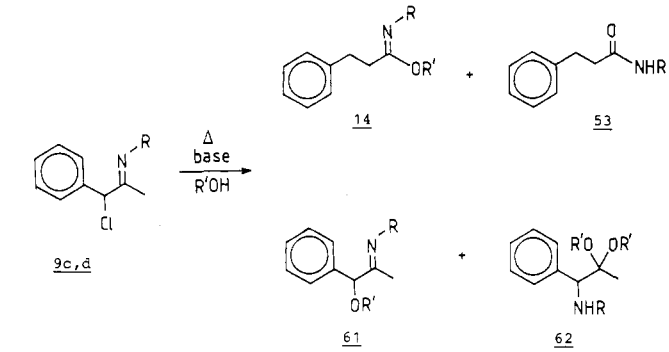


ambigous structural assignment was obtained from an X-ray crystallographic analysis of the isopropyl derivative **54** (R = *i*-Pr), which was crystallized from acetone. The stereoscopic view of this compound is given in Figure 1.[29] From the mechanistic viewpoint the formation of the *p*-phenylenediamine derivatives **54** can be considered as arising from an intermolecular nucleophilic substitution of the α'-anion **55** onto the double activated chloride **9c,d** (Scheme XVI). Subsequent intramolecular nucleophilic substitution of the same type produces 1,4-diimine **57**, which could not be isolated. Instead, the aromatic compound **54** is isolated which is understood in terms of an oxidation of the electron-rich cyclohexadiene **58** which is the tautomer of diimine **57**. A plausible explanation for this aromatization might be the air-oxidation of **58** into **54**. However, experiments under nitrogen did not reduce the yield of **54** substantially. It should be mentioned that the air-oxidation of bis-enamines of 1,4-cyclohexanediones into *p*-phenylenediamines is a known facile process.[30] There might be a similarity between the conversion of α-chloro ketimines **9c,d** into *p*-phenylenediamines **54** and the (very recently) reported transformation of the dianion of 1-phenyl-2-propanone and 1,3-diphenyl-2-propanone with iodine into 2,5-diphenylhydroquinone and 2,3,5,6-tetraphenylhydroquinone, respectively.[54] In addition, the earlier reported condensation of 1,3-dibromo-1,3-diphenyl-2-propanone with cuprates into 2,3,5,6-tetra-

Scheme XVII



Scheme XVIII



phenyl-1,4-cyclohexanedione may be viewed in relation to the reactions of α-chloro ketimines **9c,d**.[32] A few related base-induced self-condensations leading to six-membered rings have been reported in the field of α-halo ketones.[31-37] α-Bromoalkyl aryl ketones showed sometimes the tendency for self-condensation (e.g., with sodium amide in liquid ammonia) but of course could not give rise to an analogous cyclization.[38-40] An alternative mechanism for the generation of *p*-phenylenediamine derivatives **54** entails the formation of zwitterion **60**, according to the normal Favorskii rearrangement (vide supra), and subsequent cyclocondensation as indicated in Scheme XVII.

Other types of side reactions were found when α-chloro-α-phenyl ketimines **9c,d** were reacted with bases (sodium methoxide, triethylamine, potassium hydroxide) in alcohols (Scheme XVIII). The Favorskii rearrangement is the prime reaction (amide **53** as well as imidate **14**) but is always accompanied by the substitution product **61** and the rearranged acetal **62**. The latter compound is formed via a sequence of steps involving nucleophilic addition of the alcohol across the imino function, intramolecular nucleophilic substitution to produce an α-alkoxyaziridine, and the following alcoholysis of the three-membered ring.[41] An increasing amount of substitution product **61** was observed with increasing concentration of sodium methoxide in

(29) Full details of the crystallographic analysis of *N,N'*-diisopropyl-2,5-diphenyl-1,4-phenylenediamine (**54**) (R = *i*-Pr) will be published in a forthcoming report.

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Table I. Favorskii Rearrangement of α-Halo Ketimines

entry	R_1	R_2	R	α-halo ketimine	reaction conditions[a]	Favorskii product	other reaction products	physical data and remarks[e]
1	Me	H	*i*-Pr	**9a**	2E KO-*t*-Bu/THF RT/1 h	64% amide **12a**		mp 104–105 °C (lit.[46] mp 102 °C)
2	Me	H	*t*-Bu	**9b**	2E KO-*t*-Bu/THF RT/1 h	66% amide **12b**		mp 118–119 °C (lit.[47] mp 118–120 °C)
3	Me	H	*i*-Pr	**9a**	10E KOH/dioxane Δ 19 h	57% amide **12a**		mp 104–105 °C (lit.[46] mp 102 °C)
4	Me	H	*i*-Pr	**9a**	various bases[b]	no reaction		
5	Me	H	*i*-Pr	**9a**	2E KO-*t*-Bu/*t*-BuOH Δ 2 h	24% amide **12a**	72% β-*tert*-butoxy ketone **17**	GLC analysis; ^{1}H NMR analysis
6	Me	Me	*i*-Pr	**10a**	2E KO-*t*-Bu/THF Δ 48 h	62% amide **13a**		mp 106–107 °C
7	Me	Me	*i*-Pr	**10a**	2E KO-*t*-Bu/Me_2SO Δ 18 h	33% amide **13a**	67% α,β-unsaturated ketimine **20a**	
8	Me	Me	*i*-Pr	**10a**	2E NaO-*i*-Pr/*i*-PrOH 1 N Δ 18 h		67% α,β-unsaturated ketimine **20a**	
9	Me	Me	Ph	**10b**	2E NaOMe/MeOH 1 N Δ 23 h		70% α,β-unsaturated ketimine **20b**	
10	Me	Me	*i*-Pr	**21**	4E NaOMe/THF Δ 22 h		81% α,β-unsaturated ketimine **20a**	
11	Me	Me	*i*-Pr	**21**	2E KO-*t*-Bu/THF Δ 4 h		80% α,β-unsaturated ketimine **20a**	
12	Me	Me	*i*-Pr	**21**	2E Triton B/*i*-PrOH Δ 2 h		82% α,β-unsaturated ketimine **20a**	
13	Ph	H	*i*-Pr	**9c**	5E NaOMe/THF Δ 24 h	97% imidate **14c** (R′ = Me)		bp 57–59 °C/0.02 mmHg
14	Ph	H	*i*-Pr	**9c**	5E NaOEt/THF	98% imidate **14c** (R′ = Et)		yield of crude product; purity ≥98%
15	Ph	H	*i*-Pr	**9c**	various bases[c]	no reaction		
16	Ph	H	*i*-Pr	**9c**	2E NaO-*i*-Pr/*i*-PrOH 1 N Δ 18 h	100% imidate **14c** (R′ = *i*-Pr)		when additional column chromatography was performed (in order to remove some colored material) the yield dropped to 85% (neutral Al_2O_3; ether–pentane, 1:1)
17	Ph	H	cyclohexyl	**9d**	5E NaOMe/THF Δ 22 h	100% imidate **14d** (R′ = Me)		bp 96–100 °C/0.1 mmHg
18	Ph	H	cyclohexyl	**9d**	NaO-*i*-Pr/*i*-PrOH 1 N Δ 18 h	100% imidate **14d** (R′ = *i*-Pr)		column chromatography (see entry 16): 86% yield
19	Ph	Me	*i*-Pr	**10c**	5E NaOMe/THF Δ 20 h	no reaction		
20	Ph	Me	*i*-Pr	**10c**	2E KO-*t*-Bu/THF RT 3 h	15% amide **16**		preparative TLC (2 mm thickness), silica gel, ether/pentane (1/4) R_f 0.15–0.27
21				**28**	10E NaOMe/THF Δ 4 h		89% **30**	
22				**28**	2E KO-*t*-Bu/THF RT 2 h	21% amide **31**	71% **32**	GLC analysis
23				**40**	various bases[d]	no reaction		
24				**47**	10E NaOMe/THF Δ 17 h	95% imidate **48**		purity ≥98%
25	Ph	H	*i*-Pr	**9c**	2E KO-*t*-Bu/THF RT 3 h	15% amide **53**	41% **54** (R = *i*-Pr)	**53**: mp 90 °C **54** (R = *i*-Pr): mp 154 °C
26	Ph	H	*i*-Pr	**9c**	2E KO-*t*-Bu/Me_2SO RT 3 h		22% **54** (R = *i*-Pr)	**54** (R = *i*-Pr): mp 154 °C
27	Ph	H	cyclohexyl	**9d**	2E KO-*t*-Bu/Me_2SO RT 3 h		23% **54** (R = cyclohex)	**54** (R = cyclohexyl): mp 187 °C
28	Ph	H	*i*-Pr	**9c**	2E 0.1 N NaOMe/MeOH Δ 20 h	36% imidate **14** 36% amide **53c**	24% α-amino acetal **62**, 4% α-methoxy ketimine **61**	GLC; ^{1}H NMR analysis R′ = Me

Table I (Continued)

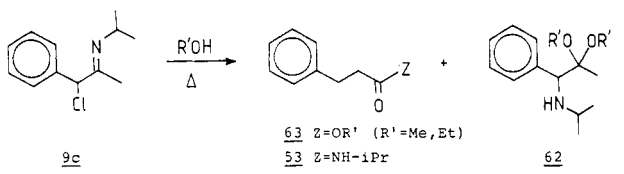
entry	R_1	R_2	R	α-halo ketimine	reaction conditions[a]	Favorskii product	other reaction products	physical data and remarks[e]
29	Ph	H	*i*-Pr	**9c**	2E 0.5N NaOMe/MeOH Δ 20 h	38% imidate **14** 24% amide **53c**	29% α-amino acetal **62**, 9% α-methoxy ketimine **61**	GLC; ^{1}H NMR analysis R′ = Me
30	Ph	H	*i*-Pr	**9c**	2E 1 N NaOMe/MeOH Δ 20 h	37% imidate **14** 27% amide **53c**	24% α-amino acetal **62**, 12% α-methoxy ketimine **61**	GLC; ^{1}H NMR analysis R′ = Me
31	Ph	H	*i*-Pr	**9c**	2E 2 N NaOMe/MeOiH Δ 20 h	40% imidate **14** 21% amide **53c**	19% α-amino acetal **62**, 20% α-methoxy ketimine **61**	GLC; ^{1}H NMR analysis R′ = Me
32	Ph	H	*i*-Pr	**9c**	2E 4 N NaOMe/MeOH Δ 20 h	37% imidate **14** 12% amide **53c**	56% α-methoxy ketimine **61**	GLC; ^{1}H NMR analysis R′ = Me
33	Ph	H	*i*-Pr	**9c**	4E KOH/MeOH Δ 18 h	70% amide **53c**	16% α-amino acetal **62**, 16% α-methoxy ketimine **61**	GLC; ^{1}H NMR analysis R′ = Me
34	Ph	H	*i*-Pr	**9c**	2E Et_3N/MeOH Δ 24 h	36% imidate **14**	64% α-amino acetal **62**	during workup the imidate **14** was transformed into the corresponding ester **63**; R′ = Me
35	Ph	H	*i*-Pr	**9c**	MeOH Δ 24 h	28% amide **53** 36% ester **63**	36% α-amino acetal **62**	GLC; ^{1}H NMR analysis R′ = Me
36	Ph	H	*i*-Pr	**9c**	EtOH Δ 20 h	85% ester **63**	10% α-amino acetal **62**	GLC; ^{1}H NMR analysis R′ = Et

[a] E = equivalents; Δ = reflux; RT = room temperature. [b] NaOMe/ether; NaOMe/*i*-Pr_2O; NaOMe/THF; Dabco/THF; Dabco/C_6H_6 (each time 2 E; Δ 4–6 h). [c] NaOMe/ether; NaOMe/*i*-Pr_2O; NaOMe/THF (each time 5 E/Δ 24 h); 1 E NaH/THF (Δ 6 h). [d] KO-*t*-Bu/THF, Δ 24 h; 2 N NaOMe/MeOH, Δ 7 days; KOH/dioxane (Δ 50 h). [e] All N-containing compounds gave N analyses in agreement with the proposed structure.

methanol (from 0.1 N up to 4 N), while the amount of Favorskii rearrangement seemed to be independent of the base concentration (Table I). The occurrence of α-alkoxy ketimine **61** can be completely eliminated by using triethylamine as the base, but the major reaction product became the α-alkylamino acetal **62**. The latter rearranged compound **62** and the α-alkoxy ketimine **61** can be both eliminated in the reaction mixture by using sodium isopropoxide in isopropyl alcohol which afforded the Favorskii rearrangement (imidate **14**) quantitatively (Table I). The reaction mixtures from the reaction of α-chloro-α-phenyl ketimine **9c** (R_1 = Ph; R_2 = H; R = *i*-Pr) under Favorskii conditions were analyzed by GLC analysis and ^{1}H NMR spectrometry. It was found that α-amino acetal **62** (R = *i*-Pr; R′ = Me) underwent loss of methanol during GLC analysis to produce (2-methoxy-1-phenyl-1-propylidene)-isopropylamine. It proved to be advantageous to analyze the reaction mixtures after acidic hydrolysis (aqueous HCl) which converted α-amino acetal **62** (R = *i*-Pr; R′ = Me) and α-methoxy ketimine **61** (R = *i*-Pr; R′ = Me) into 1-(isopropylamino)-1-phenyl-2-propanone and 1-methoxy-1-phenyl-2-propanone, respectively. The structure of imidates **14** was further proven by acidic hydrolysis (5 molar equiv of 4 N HCl during 1 h under reflux) into amides **53**. As an example isopropyl *N*-isopropyl-3-phenylpropanimidate (**14**) (R = R′ = *i*-Pr) was converted into *N*-isopropyl-3-phenylpropanamide (**53**) (R = *i*-Pr) in 90% yield under these reaction conditions. Basic hydrolysis did not occur under comparable conditions (5 molar equiv of 4 N NaOH during 1 h under reflux).

A remarkable result in this context is that α-chloro ketimine **9c** (R = *i*-Pr) underwent the *Favorskii rearrangement* in alcohols (methanol, ethanol) *without the use of added base*! In this case, esters **63** and/or amide **53** were formed in addition to the rearranged α-alkylamino acetal **62** (Scheme XIX). The α-chloro ketimine has of course intrinsic basic properties but it remains still a unique case in the field of the Favorskii rearrangement. For comparative purposes, the corresponding α-chloro ketone, i.e., 1-chloro-1-phenyl-2-propanone, was reacted with methanol (reflux 50 h) to provide no trace of Favorskii rearrangement, but instead 85% of 1-methoxy-1-phenyl-2-propanone was formed. Only 2-bromocyclobutanone has ever been reported to undergo a Favorskii rearrangement in neutral aqueous or alcoholic medium,[42,43] but it has to be stressed that this transformation occurred via a semibenzilic-type rearrangement.

Scheme XIX



This study of the Favorskii rearrangement of α-halo imines demonstrates the synthetic potential of this reaction, but also points to limitations in terms of various side reactions which occur under a variety of conditions (including nucleophilic substitution, 1,2-dehydrohalogenation, rearrangement via transient α-alkoxyaziridines, and self-condensation). The results of this research also prove that heteroallylic halides in general are apt to undergo 1,3-dehydrohalogenation to afford cyclopropanes with exocyclic double bonds. This fairly general reaction of α-halo ketones is also operative for α-halo imines but has been seldom reported for allylic halides sensu strictu (i.e., the carbon analogues).[44,45]

As compared to α-halo ketones, α-halo ketimines showed some characteristics toward Favorskii reaction conditions by which substantial deviations in reaction patterns were noticed. Aliphatic α-chloro ketimines and α-halo ketones[48,49] underwent regiocontrolled Favorskii rearrangements with alkoxides but α-halo ketones afforded more

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Table II. Spectrometric Data of Compounds Obtained by Treatment of α-Halo Imines under Favorskii-Rearrangement Conditions

compound	IR (NaCl) cm^{-1}	^1H NMR	mass spectrum (70 eV)
14c (R = *i*-Pr; R′ = Me)	1680 $\nu_{C=N}$	δ (CCl_4) 0.88 (6 H, d, J = 6 Hz, Me_2), 2.3–3.0 (4 H, m, CH_2CH_2), 3.53 (3 H, s, OMe), 7.17 (5 H, s, C_6H_5), 3.40 (1 H, septet, J = 6 Hz, NCH)	205 (M^+, 19), 190 (11), 132 (3), 131 (4), 114 (6), 105 (6), 104 (6), 103 (3), 100 (8, MeOC≡N^+-*i*-Pr), 91 (45), 86 (12), 78 (6), 77 (8), 65 (11), 60 (6), 59 (8), 58 (100), 57 (6), 51 (11), 44 (61), 43 (56), 42 (21), 41 (31), 40 (7)
14c (R′ = *i*-Pr; R′ = Et)	1677 $\nu_{C=N}$	δ (CCl_4) 0.90 (6 H, d, J = 6 Hz, Me_2), 1.20 (3 H, t, J = 7 Hz, $OCCH_3$), 2.2–3.0 (4 H, m, CH_2CH_2), 3.37 (1 H, septet, J = 6 Hz, NCH), 3.98 (2 H, q, J = 7 Hz, CH_2O), 7.13 (5 H, s, C_6H_5)	219 (M^+, 5), 191 (3), 190 (3), 132 (6), 131 (6), 106 (3), 105 (15), 104 (9), 103 (4), 100 (10), 91 (68), 86 (9), 79 (4), 78 (9), 77 (8), 73 (5), 65 (14), 63 (3), 60 (3), 59 (3), 58 (100), 57 (3), 51 (11), 50 (4), 46 (5), 45 (10), 44 (84), 43 (64), 42 (22), 41 (37), 40 (8), 39 (25)
16	1645 $\nu_{C=N}$	δ ($CDCl_3/CCl_4$, 1:1) 0.95 and 1.05 (each 3 H, d, J = 6.5 Hz, Me_2), 1.32 (3 H, d, J = 7 Hz, CH_3CPh), 2.32 (2 H, d, J = 7.5 Hz, CH_2), 3.28 (1 H, ~sextet, J ~ 7 Hz, PhCH), 3.90 (1 H, m, NCH), 5.4 (1 H, s br, NH), 7.17 (5 H, s, Ph)	
17	1719 $\nu_{C=O}$	δ (CCl_4) 1.15 (9 H, s, *t*-Bu), 2.08 (3 H, s, CH_3CO), 2.48 (2 H, *t*, J = 6.5 Hz, CH_2CO), 3.53 (2 H, t, J = 6.5 Hz, CH_2O)	130 (M^+, 1), 115 (2), 100 (4), 87 (4), 75 (1), 59 (4), 58 (4), 57 (100, Me_3C^+), 56 (6), 55 (4), 43 (8), 41 (29)
20a	1620 $\nu_{C=N}$	δ (CCl_4) 1.12 (6 H, d, J = 6 Hz, Me_2), 1.90 (3 H, br, CH_3C=), 1.98 (3 H, s, CH_3), 3.73 (1 H, septet, J = 6 Hz, NCH), 5.40 (2 H, m, CH_2=C)	125 (M^+, 71), 110 (36), 84 (29), 69 (43), 68 (71), 43 (29), 42 (100, CH_3C≡N^+H), 41 (57), 40 (29)
20b	1625 $\nu_{C=N}$	δ (CCl_4) 1.97 (3 H, s, CH_3), 2.04 (3 H, m, CH_3C=), 5.54 (2 H, m, CH_2=), 6.4–7.4 (5 H, m, C_6H_5)	
32	1720 $\nu_{C=O}$	δ (CCl_4) 1.20 (9 H, s, *t*-Bu), 0.92 (3 H, t, J = 7 Hz, Me), 1.6 (2 H, m, CH_2), 2.46 (2 H, t, J = 6 Hz, CH_2CO), 3.75 (2 H, s, OCH_2)	158 (M^+, 1), 143 (1), 129 (12), 128 (6), 114 (8), 101 (11), 86 (12), 71 (28), 57 (62), 44 (100), 43 (87), 42 (15), 41 (41)
48	1690 $\nu_{C=N}$	δ ($CDCl_3$) 1.09 (6 H, d, J = 6 Hz, Me_2), 2.73 (2 H, s, CH_2), 3.6 (1 H, septet, J = 6 Hz, NCH), 3.63 (3 H, S, OMe), 3.32 (9 H, s, $(OMe)_3$)	no M^+, 156 (11), 126 (27), 100 (29, MeOC≡N^+-*i*-Pr), 84 (10), 75 (8), 74 (7), 69 (16), 68 (23), 58 (100, MeOC≡N^+H), 57 (11), 56 (9), 44 (21), 43 (48), 42 (37), 41 (25), 40 (8), 39 (18)
54 (R = *i*-Pr)	3400 (KBr) ν_{NH}	δ ($CDCl_3$) 1.07 (12 H, d, J = 6.5 Hz, 2 Me_2), 3.2 (2 H, s, br, 2NH), 3.53 (2 H, septet, J = 6.5 Hz, 2NCH), 6.62 (2 H, s, CH=), 7.46 (10 H, s, $2C_6H_5$)	344 (M^+, 0.7), 329 (0.3), 301 (0.2), 270 (0.1), 259 (0.2), 191 (0.2), 157 (0.2), 105 (0.2), 91 (0.2), 58 (50), 57 (2), 43 (100), 42 (7), 39 (3)
54 (R = cyclohexyl)	3390 ν_{NH}	δ ($CDCl_3$) 0.8–2.2 (20 H, m, 2 × C_6H_{10}), 2.6–3.4 (4 H, m, 2 × NCH and 2 × NH), 6.67 (2 H, s, CH=), 7.50 (10 H, s, 2 × C_6H_5)	424 (M^+, 6), 231 (7), 105 (10), 98 (12), 91 (13), 83 (13), 56 (47), 43 (30), 40 (100)
62 (R = *i*-Pr; R′ = Me)	3320 ν_{NH}	δ (CCl_4) 0.96 and 1.01 (6 H, 2 × d, J = 6 Hz, Me_2), 1.03 (3 H, s, CH_3), 2.56 (1 H, septet, J = 6 Hz, NCH), 3.11 and 3.20 (6 H, 2 × s, $(OMe)_2$), 3.90 (1 H, br s CH), 7–7.5 (5 H, m, C_6H_5), NH invisible	
14c (R = R′ = *i*-Pr)	1675 $\nu_{C=N}$	δ ($CDCl_3$) 0.97 (6 H, d, J = 6.5 Hz, Me_2CHN), 1.18 (6 H, d, J = 6 Hz, Me_2CHO), 2.2–3 (4 H, m, CH_2CH_2), 3.45 (1 H, septet, J = 6.5 Hz, NCH), 5.10 (1 H, septet, J = 6 Hz, OCH), 7.23 (5 H, s, C_6H_5)	no M^+, 190 (19), 133 (5), 131 (5), 105 (25), 104 (15), 100 (26), 91 (40), 87 (5), 79 (6), 78 (8), 77 (10), 65 (8), 60 (5), 58 (20), 57 (6), 51 (18), 44 (100, $^+NH_2$=C=O), 43 (32), 42 (8), 41 (13), 40 (10), 39 (9)
14d (R = cyclohexyl; R′ = *i*-Pr)	1676 $\nu_{C=N}$	δ (CCl_4) 1.17 (6 H, d, J = 6 Hz, Me_2CH), 1–2 (10 H, m, C_6H_{10}), 2.2–3 (4 H, m, CH_2CH_2), 3.8 (1 H, m, NCH), 5.01 (1 H, septet, J = 6 Hz, OCH), 7.17 (5 H, s, C_6H_5)	
14d (R = cyclohexyl; R′ = Me)	1684 $\nu_{C=N}$	δ ($CDCl_3$) 0.9–2 (10 H, m, C_6H_{10}), 2.3–2.6 (2 H, m, CH_2C=N), 2.7–3 (2 H, m, CH_2Ph), 3.6 (1 H, m, NCH), 3.56 (3 H, s, OMe), 7.16 (5 H, s br, C_6H_5)	245 (M^+, 5), 154 (7), 131 (7), 117 (5), 105 (18), 104 (9), 98 (86), 91 (100), 83 (23), 82 (7), 81 (11), 79 (9), 78 (7), 77 (18), 70 (12), 67 (18), 65 (22), 58 (20), 57 (12), 56 (22), 55 (66), 54 (22), 53 (14), 51 (18), 44 (12), 43 (20), 42 (24), 41 (94), 39 (40)
53 (R = *i*-Pr)	1655 $\nu_{C=O}$ 3200–3500 ν_{NH}	δ ($CDCl_3$) 1.06 (6 H, d, J = 6.5 Hz, Me_2), 2.43 (2 H, m, CH_2CO), 2.7–3 (2 H, m, CH_2Ph), 4.01 (1 H, septet, J = 6.5 Hz, NCH), 5.4 (1 H, s, NH), 7.24 (5 H, s, C_6H_5)	191 (M^+, 38), 106 (10), 105 (34), 104 (20), 103 (8), 100 (32), 91 (48), 86 (6), 79 (8), 78 (10), 77 (16), 65 (10), 60 (6), 58 (26), 57 (10), 51 (10), 44 (100, $^+NH_2$=C=O), 43 (40), 42 (8), 41 (14), 40 (22), 39 (10)

various side reactions (e.g., solvolyses, rearrangements via oxiranes, etc.). The direction of the opening of the intermediate cyclopropanones (from α-halo ketones)[50] and cyclopropylideneamines (from α-halo ketimines) was determined by carbanion stabilities. α-Bromo ketimines gave preferentially 1,2-dehydrohalogenation under Favorskii conditions while the corresponding α-bromo ketones yielded more complex reaction patterns involving (mixtures of) solvolyses (mainly), Favorskii rearrangement (minor portion), and 1,2-dehydrobromination.[54] The Favorskii rearrangement of 1-chloro-1-aryl-2-propanones with sodium methoxide in methanol, as extensively studied by Bordwell,[51] yielded methyl 3-arylpropionate but was always accompanied by the corresponding α-hydroxy acetal, $ArCHOHC(OMe)_2CH_3$. The corresponding α-chloro-α-phenyl ketimines **9** (R_1 = Ph, R_2 = H) similarly rearranged into imidates **14** or amides **53** (major reaction), while variable amounts of α-alkylamino acetals **62** (i.e., the N-analogue of α-hydroxy acetals) were formed. Contrary to the α-halo ketone case, substantial amounts (4–56%) of substitution products (i.e., α-methoxy ketimines) were formed depending upon the concentration of methoxide. Finally, α,α,α′,α′-tetrachloroacetone with methoxide rearranged into methyl 3,3-dichloroacrylate[52] and the result paralleled the rearrangement of the corresponding tetrachloro ketimine **47** (in the latter case subsequent Michael additions and dehydrohalogenations took place).

Experimental Section

IR spectra were measured with a Perkin-Elmer Model 1310 spectrophotometer. ^1H NMR spectra were recorded with a Varian T-60 spectrometer (60 MHz), while ^{13}C NMR spectra were obtained from a Varian FT-80 spectrometer (20 MHz). Mass spectra were recorded with a Varian-MAT 112 mass spectrometer (direct inlet system, 70 eV). Melting points were determined with a Kofler hot stage apparatus. Gas chromatographic analyses were performed with Varian 1700 and Varian 920 gas chromatographs using preparative stainless steel columns (SE 30, 3 m).

Preparation of the Starting Materials. α-Chloro ketimines **9a–c**, **10a,b**, and **28** were prepared as previously described.[53] Analogously, the new α-chloro ketimines **9d**, α,α,α′,α′-tetrachloro ketimine **47**, and α-bromo ketimine **21** were synthesized by condensation of the appropriate α-halo ketone and a primary amine in the presence of titanium(IV) chloride.[53] These novel α-halo ketimines gave the following spectrometric data (all compounds gave correct N analyses).

(1-Chloro-1-phenyl-2-propylidene)cyclohexylamine (9d): IR (NaCl) 1660 cm^{-1} ($\nu_{C=N}$); ^1H NMR (CCl_4), *E* isomer exclusively, 0.9–2 (10 H, m, C_6H_{10}), 1.73 (3 H, s, $CH_3C{=}N$), 3.3 (1 H, m, NCH), 5.55 (1 H, s, CHCl), 7.2–7.6 (5 H, m, C_6H_5). The compound decomposed on high vacuum distillation but was obtained in 94% yield (purity >97%) by the normal workup procedure.

(1,1,3,3-Tetrachloro-2-propylidene)isopropylamine (47): IR (KBr) 1660 cm^{-1} ($\nu_{C=N}$); ^1H NMR ($CDCl_3$) δ 1.22 (6 H, d, *J* = 6 Hz, Me_2), 4.70 (1 H, septet, *J* = 6 Hz, NCH), 6.23 (1 H, s, $CHCl_2$ trans with respect to N-*i*-Pr), 6.53 (1 H, s, $CHCl_2$ cis with respect to N-*i*-Pr); mass spectrum, *m/e* (relative abundance) 235/37/39/41/43 (M^+, 0.3), 220 (1), 152/54/56 (8), 110/12/14 (2), 83/85/87 (4), 75 (3), 73 (3), 43 (100), 41 (18), 39 (7); yield 64%, mp 71 °C. Anal. Calcd: N, 5.91. Found: N, 5.73.

(3-Bromo-3-methyl-2-butylidene)isopropylamine (21): IR (NaCl) 1655 cm^{-1} ($\nu_{C=N}$); ^1H NMR (CCl_4) δ 1.05 (6 H, d, *J* = 6 Hz, Me_2CN), 1.83 (6 H, s, Me_2), 2.03 (3 H, s, $CH_3C{=}N$), 3.59 (1 H, septet, NCH); mass spectrum, *m/e* (relative abundance) 205/7 (M^+, 0.2), 126 (9), 125 (17), 111 (4), 110 (19), 84 (41, $CH_3C{\equiv}N^+$-*i*-Pr), 69 (15), 68 (25), 67 (4), 57 (5), 55 (5), 54 (3), 53 (5), 43 (21), 42 ($CH_3C{\equiv}N^+H$, 100), 41 (31), 40 (5); bp 55–59 °C/11 mmHg, yield 64%. Anal. Calcd: N, 6.80. Found: N, 6.59.

The synthesis of (3-chloro-2,2,6,6-tetramethyl-4-heptylidene)isopropylamine (**40**) was accomplished in the following way. Dineopentyl ketone was synthesized from *tert*-butylacetic acid using the iron carboxylate method.[23] Halogenation (Br_2, SO_2Cl_2) resulted in the α-halo and α,α′-dihalo ketone but the condensation with isopropylamine in the presence of $TiCl_4$ was not successful. Therefore an alternative route involving halogenation of the corresponding ketimine was used. Reaction of dineopentyl ketone (0.02 mol) with isopropylamine (20 molar equiv) in the presence of $TiCl_4$ (1 molar equiv) in benzene (24 h, reflux) afforded (2,2,6,6-tetramethyl-4-heptylidene)isopropylamine in 85% yield with no detectable impurity (purity >98%).

(2,2,6,6-Tetramethyl-4-heptylidene)isopropylamine: ^1H NMR (CCl_4) δ 0.94 (9 H, s, *t*-Bu), 0.97 (9 H, s, *t*-Bu), 1.04 (6 H, d, *J* = 6 Hz, Me_2), 2.04 (2 H, s, CH_2), 2.12 (2 H, s, CH_2), 3.67 (1 H, septet, *J* = 6 Hz, NCH); IR (NaCl) 1649 cm^{-1} ($\nu_{C=N}$). This ketimine was chlorinated with *N*-chlorosuccinimide (1.1 equiv) in CCl_4 (room temperature, 4 h) to give (after filtration and evaporation) (3-chloro-2,2,6,6-tetramethyl-4-heptylidene)isopropylamine (**40**) in 98% yield (95% purity as given by GLC).

(3-Chloro-2,2,6,6-tetramethyl-4-heptylidene)isopropylamine (40): ^1H NMR (CCl_4) δ 1.01 (9 H, s, *t*-Bu), 1.06 (9 H, s, *t*-Bu), 1.03 (6 H, Me_2 covered by the two *t*-Bu signals), 1.96 and 2.47 (2 H, AB system, *J* = 13.5 Hz, CH_2), 3.73 (1 H, septet, *J* = 6.5 Hz, NCH), 4.04 (1 H, s, CHCl); mass spectrum, *m/e* (relative abundance) 245/7 (M^+, 0.2), 230/2 (1), 194 (2), 189 (1), 174/6 (1), 154 (1), 153 (1), 152 (1), 140 (8), 138 (4), 133/5 (13), 132/4 (3), 118 (1), 110 (3), 98 (100), 82 (14), 70 (4), 69 (6), 57 (62), 55 (15), 43 (27), 42 (62), 41 (60). Anal. Calcd: N, 5.70. Found: N, 5.58.

General Procedure for the Reactions of α-Chloro Ketimines under Favorskii Conditions. Most reactions were run on a 0.01 molar scale but those reactions which afforded interesting results (e.g., the synthesis of carboxylic amides **12**, imidates **14**, ortho ester **48**, *p*-phenylenediamines **54**, and the rearrangement of α-chloro-α-phenyl ketimines **9c,d**) were performed afterward on a much larger scale (0.05 mol). The reactions were executed, as outlined in Table I, by treating α-chloro ketimines with the basic reagents in the appropriate solvent under magnetic stirring. After the reaction was carried out at the given temperature during the indicated period of time, the reaction mixture was poured into water and extraction (3 times) was performed with dichloromethane or diethyl ether. The combined extracts were dried over $MgSO_4$ (most of all cases) or K_2CO_3 (if imino compounds are expected in the reaction mixture). After evaporation of the solvent under vacuum, the residual mixture was weighed, investigated by ^1H NMR analysis, and analyzed by preparative gas chromatography. It was assured that the ratios found in the GLC analysis were consistent with those found in the ^1H NMR analysis. If possible, solid reaction products were first isolated by crystallization (e.g., amide **53** R = *i*-Pr). The analysis of the reaction products of the rearrangements of α-chloro-α-phenyl ketimines **9c,d** was executed in the following way. After the usual workup and analysis (vide supra), the reaction mixture was treated with aqueous 1 N HCl (2 h, room temperature). Extraction with dichloromethane afforded a mixture of 1-methoxy-1-phenyl-2-propanone, ester **63** (R′ = Me), and imidate **14** (R′ = Me). After basification with aqueous sodium hydroxide, extraction with dichloromethane afforded nearly pure 1-(isopropylamino)-1-phenyl-2-propanone.

(2-Methoxy-1-phenyl-1-propylidene)isopropylamine: IR (NaCl) 1650 cm^{-1} ($\nu_{C=N}$); ^1H NMR (CCl_4) δ 0.98 and 1.01 (6 H, 2 × d, *J* = 6 Hz, Me_2), 1.07 (3 H, d, *J* = 7 Hz, CH_3), 3.37 (3 H, s, OMe), 3.95 (1 H, q, *J* = 7 Hz, CHO), 7–7.5 (5 H, m, C_6H_5), 3.4 (1 H, NCH covered).

1-Methoxy-1-phenyl-2-propanone was identical in all aspects with the compound (85% yield) resulting from methanolysis of 1-chloro-1-phenyl-2-propanone (reflux, 50 h).

1-(Isopropylamino)-1-phenyl-2-propanone: IR (NaCl) 3340 cm^{-1} (ν_{NH}), 1720 cm^{-1} ($\nu_{C=O}$); ^1H NMR (CCl_4) δ 0.95 and 0.99 (6 H, 2 × d, *J* = 6 Hz, Me_2), 1.97 (3 H, s, CH_3), 2.64 (1 H, septet, *J* = 6 Hz, NCH), 2.4 (1 H, s, br, NH), 4.37 (1 H, s, br, CHN), 7.33 (5 H, s, C_6H_5).

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Methyl 3-phenylpropionate (63, Z = OMe) was identical with the compound described in the literature.[51]

***N*-Isopropyl-2-methylbutanamide (31)** obtained from α-chloro ketimine **28** was identical in all aspects (^{1}H NMR, IR, MS) with an authentic sample prepared from 2-methylbutyric acid via the acid chloride ($SOCl_2$, reflux 30 min) and subsequent reaction with isopropylamine in dichloromethane. Table II gives a compilation of the ^{1}H NMR, IR, and mass spectral data of various reaction products resulting from the reaction of α-chloro ketimines under Favorskii conditions. In addition, the following ^{13}C NMR data support the structural elucidation.

Methyl *N*-isopropyl-3-phenylpropanimidate (14c) (R = *i*-Pr; R′ = Me): ($CDCl_3$) 160.47 (s, C=N), 141.48 (s, quaternary aromatic C), 128.50 and 128.38 (each d, ortho and meta C), 126.21 (d, para C), 32.86 (t, CH_2Ph), 30.36 (t, CH_2C=N), 51.83 (q, OMe), 48.58 (d, NCH), 24.79 (q, Me_2).

Ethyl *N*-isopropyl-3-phenylpropanimidate (14c) (R = *i*-Pr; R′ = Et): δ ($CDCl_3$) 160.29 (s, C=N), 141.76 (s, quaternary aromatic C), 128.43 and 128.39 (each d, ortho and meta C), 126.14 (d, para C), 32.86 (t, CH_2Ph), 30.34 (t, CH_2C=N), 59.83 (t, OCH_2), 14.33 (q, CH_3CO), 48.55 (d, NCH), 24.76 (q, Me_2).

***N*-Isopropyl-3-phenylbutanamide (16)**: δ ($CDCl_3$) 170.82 (s, C=O), 146.10 (s, quaternary aromatic C), 128.52 and 126.86 (d, ortho and meta C), 126.35 (d, para C), 41.12 (d, NCH), 45.95 (t, CH_2), 37.17 (d, CHPh), 21.57 (q, Me), 22.52 and 22.64 (each q, Me_2).

Methyl *N*-isopropyl-3,3,3-trimethoxypropanimidate (48): δ ($CDCl_3$) 155.85 (s, C=N), 113.87 (s, $C(OMe)_3$), 51.93 (q, CH_3O), 50.03 (q, $(OCH_3)_3$), 49.06 (d, NCH), 32.06 (t, CH_2), 24.69 (q, Me_2).

***N*,*N*′-Diisopropyl-2,5-diphenyl-*p*-phenylenediamine (54) (R = *i*-Pr)**: δ ($CDCl_3$) 140.0 (s, =CN), 136.34 (s, quaternary C of Ph substituent), 115.87 (d, ortho C with respect to N), 129.51, 128.72 and 126.98 (each d, aromatic CH=), signal of C-2 covered, 45.66 (d, NCH), 23.26 (q, CH_3). Anal. Calcd: C, 83.68; H, 8.19; N, 8.13. Found: C, 83.74; H, 8.09; N, 8.25.

***N*,*N*′-Dicyclohexyl-2,5-diphenyl-*p*-phenylenediamine (54) (R = cyclohexyl)**: δ ($CDCl_3$) 140.45 (s, =CN), 136.12 (s, quaternary C of Ph substituent), 115.73 (d, =CH), 128.71 (d, ortho C of Ph substituent), 129.34 (d, para C of Ph substituent), 53.02 (d, NCH), 33.68 (t, CH_2CN), 24.97 (t, CH_2CCN), 26.05 (t, CH_2CCCN). Anal. Calcd: C, 84.86; H, 8.55; N, 6.60. Found: C, 84.71; H, 8.79; N, 6.69.

Isopropyl *N*-isopropyl-3-phenylpropanimidate (14c) (R = R′ = *i*-Pr): δ ($CDCl_3$) 158.68 (s, C=N), 141.35 (s, quaternary aromatic), 128.40 (d, ortho and meta), 126.09 (d, para), 65.28 (d, OCH), 48.51 (d, NCH), 32.85 (t, CH_2Ph), 30.30 (t, CH_2C=N), 24.77 (q, CH_3CO), 21.84 (q, CH_3CN).

Methyl *N*-cyclohexyl-3-phenylpropanimidate (14d) (R = cyclohexyl; R′ = Me): δ ($CDCl_3$) 160.15 (s, C=N), 141.30 (s, quaternary aromatic), 128.35 and 128.45 (d, ortho and meta C), 126.18 (d, para C), 56.76 (d, NCH), 51.74 (q, OCH_3), 32.93 (t, CH_2Ph), 30.35 (t, CH_2C=N), 35.00 (t, CH_2CN), 24.83 (t, CH_2CCN), 25.96 (t, CH_2CCCN).

Isopropyl *N*-cyclohexyl-3-phenylpropanimidate (14d) (R = cyclohexyl; R′ = *i*-Pr): δ ($CDCl_3$) 158.76 (s, C=N), 141.22 (s, quaternary aromatic), 128.43 and 128.36 (d, ortho and meta), 126.06 (d, para), 65.37 (d, OCH), 56.67 (d, NCH), 34.95 (t, $(CH_2)_2$), 32.93 (t, CH_2Ph), 30.39 (t, CH_2C=N), 25.98 (t, CH_2), 24.75 (t, $(CH_2)_2$), 21.82 (q, CH_3).

***N*-Isopropyl-3-phenylpropanamide (53) (R = *i*-Pr)**: δ ($CDCl_3$) 171.28 (s, C=O), 141.15 (q, quaternary aromatic), 128.50 and 128.44 (each d, ortho and meta), 126.21 (d, para), 41.28 (d, NCH), 38.64 (t, CH_2Ph), 31.98 (t, CH_2C=O), 22.69 (q, CH_3).

Hydrolysis of Ortho Ester 48. A solution of 1.1 g (0.005 mol) of ortho ester **48** in 11 mL of dichloromethane was vigorously stirred with 10 mL of 2 N HCl during 5 h at room temperature. The dichloromethane phase was isolated, washed with brine, dried ($MgSO_4$), and evaporated to yield 0.58 g of a liquid substance which was shown to be dimethyl malonate by spectrometric methods (^{1}H NMR, IR) and comparison with an authentic sample.

Synthesis of *N*,*N*′-Dialkyl-2,5-diphenyl-*p*-phenylenediamines 54. The experimental procedure applied for the synthesis of compound **54** (R = *i*-Pr) is representative. A stirred solution of 2.1 g (0.01 mol) of (1-chloro-1-phenyl-2-propylidene)isopropylamine (**9c**) in 20 mL of dry tetrahydrofuran was treated portionwise with 2.24 g (0.02 mol) of potassium *tert*-butoxide. After being stirred 3 h at room temperature, the reaction mixture was poured into water, extracted twice with pentane, dried ($MgSO_4$), and evaporated in vacuo to give the *p*-phenylenediamine **54** (R = *i*-Pr) as a yellow solid. Recrystallization from pentane/ether afforded 0.7 g (41%) of **54** (R = *i*-Pr), mp 154 °C. If the reaction mixture, after pouring into water, was extracted with ether, the Favorskii amide **53** (R = *i*-Pr) could be isolated from the evaporated extract after trituration with pentane: mp 90 °C, yield 15%.

Registry No. **9a**, 78827-36-8; **9b**, 78827-37-9; **9c**, 78827-43-7; **9d**, 87207-67-8; **10a**, 78827-38-0; **10b**, 103818-60-6; **10c**, 87207-66-7; **12a**, 869-07-8; **12b**, 7472-49-3; **13a**, 14278-30-9; **14c** (R^1 = CH_3), 78827-39-1; **14c** (R^1 = CH_3CH_2), 103818-64-0; **14c** (R^1 = $CH(CH_3)_2$), 103818-65-1; **14d** (R^1 = $CH(CH_3)_2$), 103818-66-2; **14d** (R^1 = CH_3), 103818-67-3; **15**, 103818-77-5; **16**, 103818-68-4; **17**, 51930-93-9; **20a**, 103818-63-9; **20b**, 101219-17-4; **21**, 87207-68-9; **28**, 78827-41-5; **30**, 103274-71-1; **31**, 78827-40-4; **32**, 78827-42-6; **40**, 103818-61-7; **47**, 103818-62-8; **48**, 103818-69-5; **53c**, 56146-87-3; **54** (R = $CH(CH_3)_2$), 103818-70-8; **54** (R = C_6H_{11}), 103818-71-9; **61** (R^1 = CH_3), 103818-73-1; **62** (R^1 = CH_3), 103818-72-0; **63** (R^1 = CH_3CH_2), 2021-28-5; **63** (R^1 = CH_3), 103-25-3; 1,1,3,3-tetrachloroacetone, 632-21-3; isopropylamine, 75-31-0; dineopentyl ketone, 4436-99-1; (2,2,6,6-tetramethyl-4-heptylidene)isopropylamine, 103818-74-2; 1-(isopropylamino)-1-phenyl-2-propanone, 103818-75-3; (2-methoxy-1-phenyl-1-propylidene)isopropylamine, 103818-76-4; 1-methoxy-1-phenyl-2-propanone, 7624-24-0; 1-chloro-1-phenyl-2-propanone, 4773-35-7; dimethyl malonate, 108-59-8; cyclohexylamine, 108-91-8; 3-methyl-3-bromo-2-butanone, 2648-71-7.