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ORGANOMETALLIC INDUCED SELF-CONDENSATION OF CARBOXAMIDES

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Abstract—N,N-Disubstituted carboxamides containing α-hydrogen atoms undergo self-condensation reaction simply on treatment with Grignard reagents or n-BuLi in THF at room temp. The reaction is considerably influenced by steric hindrance at the α-carbon and the condensing agent utilized. A possible Claisen-type mechanism is also reported.

Reactions of carboxamides with organometallic reagents have been quite extensively investigated. Indeed, it has been reported that N,N-disubstituted carboxamides react with alkyl lithium or Grignard reagents providing, depending upon the structure of the amide, ketones,[1,2] tertiary alcohols,[2] enamines[3] or carbinolamines,[4a,b] which all arise from the direct nucleophilic attack of the organometallic reagent on the carbonyl function.

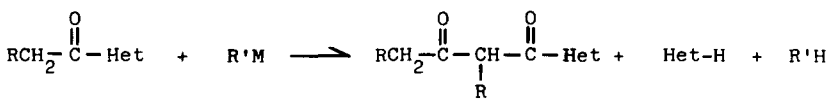
Moreover, the reactivity of carboxamides due to the acidity of the hydrogens in the α-position to the carbonyl has also been described and the α-carbanions generated by abstraction of these protons have been utilized to accomplish cross-condensation with carbonyl compounds like aldehydes or ketones to form β-hydroxycarboxamides.[5]

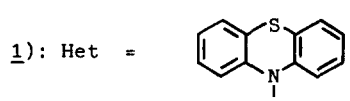
On the contrary, the possibility that α-hydrogen containing N,N-disubstituted carboxamides, as analogues of the carboxylic esters, may give Claisen-type self-condensation, has not been studied. There is no report concerning self-condensation of carboxamides, except for N,N-diethylacetamide, which has been shown to give this kind of reaction in the presence of EtMgBr.[6]

Since we have found recently[7] that 10-acylphenothiazine and 4 - acyl - 2,3 - dihydrobenzo - 1,4 - thiazine undergo easy self-condensation simply on treatment with n-BuLi or Grignard reagents, it appeared to be of interest to extend the investigation to other N,N-disubstituted carboxamides; this paper describes the self-condensation of these amides and the mechanism which we believe is operating.

RESULTS AND DISCUSSION

10-Acylphenothiazine **1** and 4 - acyl - 2,3 - dihydrobenzo - 1,4 - thiazine **2** have been found to react with n-BuLi or Grignard reagents in THF at room temp affording 10-acylacetylphenothiazine **3** and 4 - acylacetyl - 2,3 - dihydrobenzo - 1,4 - thiazine **4** respectively, the ease of the reaction being dependent on the bulk of the acyl group: **1a** > **1b** ≫ **1c**. Products **3** (or **4**), which, at least formally, can be regarded as Claisen-type condensation products, and the free amine **5** (or **6**) formed in equimolecular amount (see Experimental) as illustrated in the following scheme:





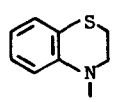
1): Het =

a: R=H
b: R=CH_3
c: R=CH_2Ph

3

a: R=H
b: R=CH_3

5



2): Het =

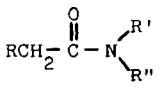
R=H

4: R=H

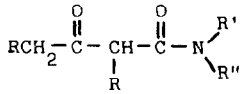
6

This rather surprising reaction (particularly in view of the fact that 10-acylphenothiazines have been reported to react with organometallic compounds in an entirely different route[4b]) led us to extend the investigation to a wide range of amides in order to determine whether the chemical behaviour discovered by us for acylphenothiazines and acylbenzothiazines was a general process. Thus we have examined the reaction between a number of carboxamides (namely **8–16**) and n-BuLi or Grignard reagents in THF or ether or benzene at room temp.

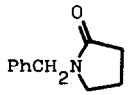
In all cases we obtained the corresponding β-ketoamides **17–24** in very good yields (see Table), al-

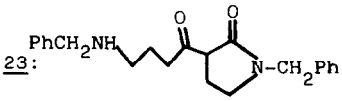


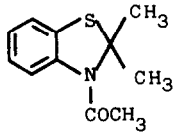
8: R=H; R'=R"=CH_3
10: R=H; R'=R"=C_2H_5
11: R=H; R'=R"=Ph
12: R=H; R'=Ph; R"=CH_2Ph
13: R=H; R'=CH_3; R"=CH_2Ph
14: R=CH_3; R'=R"=Ph



17: R=H; R'=R"=CH_3
18: R=H; R'=R"=C_2H_5
19: R=H; R'=R"=Ph
20: R=H; R'=Ph; R"=CH_2Ph
21: R=H; R'=CH_3; R"=CH_2Ph
22: R=CH_3; R'=R"=Ph

15: 

23: 

16: 

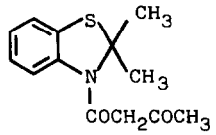
24: 

Table 1. Condensation reaction of N,N-disubstituted carboxamides with organometallic reagents at room temp (≃20).

Compound	Condensing Agent	Solvent	Reactants Ratio	Reaction Time(h)	Condensation Product(%)
1a	n-BuMgBr	THF	1:1	1	3a (90)
"	"	Benzene	"	1	" (85)
"	PhMgBr	THF	"	0.5	" (90)
"	EtMgBr	"	"	1.5	" (85)
"	"	Ether	"	3	" (83)
"	"	THF/Ether	1:3	1.5	" (75)
"	n-BuLi	THF	1:1	20	" (71)
"	LiTMP	"	"	24	" (92)
1b	n-BuMgBr	"	"	20	3b (74)
2	"	"	"	1	4 (83)
"	"	Benzene	"	1	" (80)
"	"	Ether	"	3	" (85)
"	n-BuLi	THF	"	16	" (80)
"	LiTMP	"	"	20	" (75)
1c	n-BuMgBr	"	"	20	No reaction
7	"	"	"	20	No reaction
7+8	n-BuLi	"	"	1	9* (60)
8	n-BuMgBr	"	"	1.5	17 (54)
10	"	"	"	1.5	18 (86)
11	"	"	"	3	19 (73)
12	"	"	"	2	20 (72)
13	"	"	"	0.5	21 (84)
14	"	"	"	60	22 (83)
15	"	"	"	1.5	23 (85)
16	"	"	"	2	24 (72)

* This reaction has been carried out at -78°.

though many of the carboxamides by us investigated have been reported to react with the same organometallic reagents in a quite different way.[1-4] At the moment we have no explanation for this but it might be that our somewhat different experimental conditions are responsible for the discrepancy.

In contrast, no reaction could be observed when n-BuMgBr was added, in the same conditions, to 10-benzoylphenothiazine **7**, which, therefore, was recovered practically unchanged even after long reaction time.

However, the same compound **7**, when treated with N,N-dimethylacetamide **8** in the presence of n-BuLi, underwent cross-condensation reaction leading smoothly to benzoyl - N,N - dimethylacetamide **9**. Self-condensation of N,N-dimethylacetamide did not occur under the experimental conditions in which this experiment has been carried out.

In no case have we observed the formation of ketones or tertiary alcohols, which are expected to form as a consequence of the nucleophilic attack of the organometallic reagent on the carbonyl of the amide.

These findings clearly indicate that under our experimental conditions the organometallic reagent behaves as a base rather than as a nucleophile, abstracting hydrogen atoms in α position to the carbonyl of the amide, thus giving rise to the formation of the amide anion[5] stabilized by resonance (see eqn (1) of scheme 1). A few other reagents have been examined to carry out the self-condensation; among them, LiTMP ("proton harpoon") has been found to react with some of the carboxamides above affording the expected self-condensed products, while t-BuO^- in t-BuOH and NaH in THF gave an intractable mixture of many products, and CH_3ONa in CH_3OH, DABCO and DBU in THF did not give any reaction. Furthermore, reactions carried out with Grignard reagents were faster than those with n-BuLi or LiTMP. Concerning the carboxamide, reactions have been found to be remarkably influenced by the structural features at the α-carbon. In fact, α-unsubstituted carboxamides were more reactive than the α-substituted compounds, with the exception of 1 - benzyl - 2 - pyrrolidone **14**, which as a α-substituted-like carboxamide, has been found to be unusually reactive.

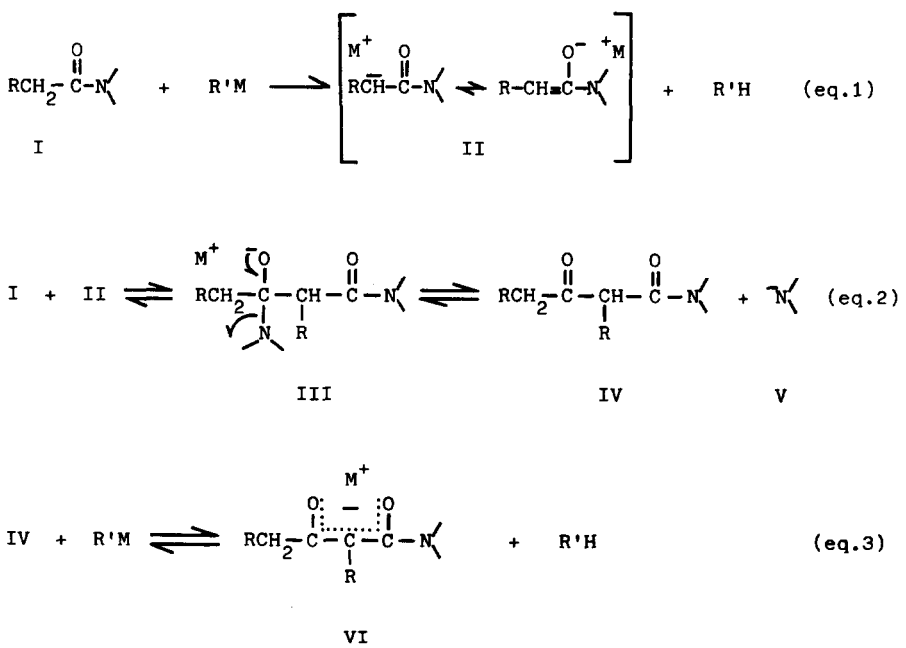
Finally, as for the solvent effect, no appreciable change in the yields of products has been observed when ether or benzene were used instead of THF; however, reactions carried out in THF were faster than those in ether, in which a precipitate (very likely the amide enolate) is observed just after mixing the reactants.

On the basis of the experimental results and by considering the nature of the reaction products, a three step ionic mechanism, similar to that commonly accepted for the Claisen condensation of esters,[8] is proposed.

According to this mechanism, in the first step the amide anion II is generated; to this end, the use of strong bases such as n-BuLi or Grignard reagents or LiTMP seems to be of fundamental importance, no reaction in fact occurring with bases like MeONa, DABCO and DBU and no condensation taking place with NaH or t-BuOK. The second step involves the nucleophilic attack of the enolate II on the carbonyl function of the parent amide I to form an anion intermediate III, which on release of the anion V leads to the self-condensed product IV.

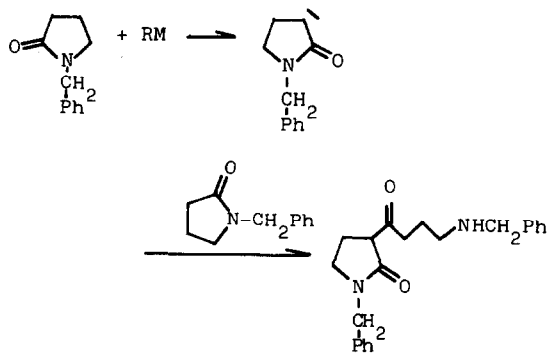
That condensation reactions carried out in the presence of Grignard reagents are faster than those with n-BuLi or LiTMP might likely be explained by considering that the amide enolate-MgX pair is less tightly associated and therefore more reactive than the amide enolate-Li.[9]

Furthermore, the observed low solubility of the enolate-MgX in ether might be responsible for the lower speed of the reactions carried out in ether in respect to those performed in THF. Steric hindrance exerted by the



Scheme 1.

groups at the α position of the carbonyl is expected to operate either in the attacking α-carbanion II or in the amide I which couple in the second step; therefore this step would be strongly influenced by the structure of the amide, as actually confirmed by the following observation: α-unsubstituted carboxamides are much more reactive than the α-substituted ones. In this connection, the fact that 1 - benzyl - 2 - pyrrolidone is unusually ready to undergo self-condensation might be reasonably explained either by assuming that the corresponding α-carbanion is rather exposed (because of the "tying back" of the two groups linked at the carbanion center into a ring structure) and therefore more reactive or by taking into account the fact that the carbon–carbon bond formation step, that is the attack of the α-carbanion above on the carbonyl of the starting lactam, proceeds with angle strain relief.[10]



On the contrary, the nature of the substituents bonded at the nitrogen atom of the amide does not seem to affect the reactivity of the amide. The third step is the driving force of the whole process, in which the removal of a hydrogen at the α-carbon of the β-ketoamide IV by any basic species present in solution leads to the β-ketoamide anion VI, strongly stabilized by chelation.

Our results show that, at least under our experimental conditions, any α-hydrogen containing carboxamides can undergo self-condensation, thus leading to β-ketoamides, which are particularly useful in synthesis. Moreover, the same self-condensation, when applied to heterocyclic amides such as acylbenzothiazole, acylphenothiazine and acylbenzothiazine, allows the synthesis of new derivatives which are expected to be of great interest in the pharmaceuticals area.

EXPERIMENTAL

^{1}HNMR spectra were recorded on a Varian EM 360A spectrometer in $CDCl_3$ and chemical shifts are reported in parts per million (δ) from internal Me_4Si. IR spectra were obtained on a Perkin–Elmer 177 spectrometer. Microanalyses were performed on a Hewlett–Packard C, H, N analyser. M.ps, taken on electrothermal apparatus, were uncorrected.

Materials. Diethyl ether and THF from commercial sources (RS Carlo Erba) were purified by distillation (twice) from sodium wire in a N_2 atmosphere. Phenothiazine, N,N - dimethyl - ,N,N - diethyl - acetamide, 1 - benzyl - 2 - pyrrolidone were good commercial quality products (Fluka). 4 - Acetyl - 2,3 - dihydrobenzo - 1,4 - thiazine,[11] 2,3 - dihydrobenzo - 1,4 - thiazine[11] 10 - acetyl-,[12] 10 - propionyl-,[13] 10 - phenylacetyl-,[12] 10 - benzoyl - phenothiazine,[14] N,N - diphenyl-,[15] N,N - benzylphenyl - acetamide,[16] N,N - diphenylpropionamide,[17] 3 - acetyl - 2,2 - dimethylbenzothiazoline[18] were prepared by the reported procedure. n-BuLi was a commercial reagent (Aldrich), while Grignard reagents[19] and LiTMP[20] were made following the reported procedure.

Preparation and characterization of products

10-Acetoacetylphenothiazine **3a**, 10 - (α - propionyl) propionylphenothiazine **3b**, 4 - acetoacetyl - 2,3 - dihydrobenzo - 1,4 - thiazine **4**, N,N - dimethyl, N,N - diethyl,- N,N-diphenyl-, N,N-benzylphenyl - acetamide, N,N - diphenyl (α-propionyl) propionamide, 1 - benzyl - 3 (γ - benzylaminobutyryl) - 2 - pyrrolidone, 3 - acetoacetyl - 2,2 - dimethylbenzothiazoline were all prepared by a procedure which is here described for the compound **3a**. Structures of unknown compounds were assigned by elemental analysis and IR and NMR spectroscopy. Only ^{1}HNMR data are reported for known compounds.

10-*Acetoacetylphenothiazine* **3a**

1 g (0.0041 mole) of **1a** in 50 ml of dry THF was added dropwise to an equivalent amount of the organometallic reagent with stirring and under nitrogen at room temp ($\simeq$20°). Stirring was continued until tlc (ether–light petroleum 3:7) showed complete disappearance of the starting material. Then the soln was quenched with sat NH_4Cl, extracted with ether, the organic layer separated, dried over Na_2SO_4 and the solvent removed *in vacuo* leaving a residue (1.1 g, oil), which was a mixture of two products. These were separated by column chromatography on silica gel, using ether: petrol (3:7) as eluent. The first product (0.4 g, m.p. 182–3°) was the unsubstituted phenothiazine **5** (IR and ^{1}HNMR consistent, mixed m.p. undepressed). The second product (0.51 g, oil, 90%) was the compound **3a**; IR and ^{1}HNMR spectra clearly indicated the presence of an enolic form in equilibrium with the carbonyl form; IR: C=O stretch at 1720 and 1640 cm^{-1}; ^{1}HNMR($CDCl_3$, δ): carbonyl form, 2.2 (s. 3H), 3.6 (s. 2H), 7.2–7.7 (m. 8H); enolic form, 1.9 (s. 3H), 5.3 (s. 1H), 14.1 (b. s. 1H). (Found: C, 68.1; H, 4.8; N, 4.8. Calc. for $C_{16}H_{13}NO_2S$: C, 68.0; H, 4.6; N, 4.9%.)

N-(α-propionyl)Propionylphenothiazine **3b**. IR; C=O stretch at 1720 and 1650 cm^{-1}. ^{1}HNMR($CDCl_3$, δ): 1.0 (t. 3H), 1.4 (d. 3H), 2.5 (q. 2H), 4.0 (q. 1H), 7.3–7.7 (m. 8H). (Found: C, 69.5; H, 5.6; N, 4.4. Calc. for $C_{18}H_{17}NO_2S$; C, 69.5; H, 5.5; N, 4.5%.)

N - Acetoacetyl - 2,3 - dihydrobenzo - 1,4 - thiazine **4**. IR, C=O stretch at 1720 and 1640 cm^{-1}; ^{1}HNMR($CDCl_3$, δ); carbonyl form: 2.2 (s. 3H), 3.1–3.3 (m. 2H), 3.7 (s. 2H), 3.9–4.1 (m. 2H), 7.1–7.3 (m. 4H); enolic form: 1.9 (s. 3H), 3.1–3.3 (m. 2H), 3.9–4.1 (m. 2H), 5.3 (s. 1H), 7.1–7.3 (m. 4H), 14.5 (b. s. 1H). (Found: C, 60.9; H, 5.9; N, 5.6. Calc. for $C_{12}H_{13}NO_2S$; C, 61.0; H, 5.9; N, 5.5%.)

N,N-Dimethylacetylacetamide **17**. ^{1}HNMR($CDCl_3$, δ); carbonyl form: 2.2 (s. 3H), 2.9 (s. 6H), 3.5 (s. 2H); enolic form: 1.9 (s. 3H), 2.9 (s. 6H), 5.0 (s. 1H), 13.8 (b. s. 1H).

N,N-Diethylacetylacetamide **18**. ^{1}HNMR($CDCl_3$, δ); carbonyl form: 1.15 (t. 3H), 1.18 (t. 3H), 2.3 (s. 3H), 3.3 (q. 2H), 3.43 (q. 2H), 3.5 (s. 2H); enolic form: 1.15 (t. 3H), 1.18 (t. 3H), 1.95 (s. 3H), 3.3 (q. 2H), 3.43 (q. 2H), 5.1 (s. 1H), 14 (b. s. 1H).

N,N-Diphenylacetylacetamide **19**. ^{1}HNMR($CDCl_3$, δ); carbonyl form: 2.1 (s. 3H), 3.5 (s. 2H), 6.9–7.7 (m. 10H); enolic form: 1.8 (s. 3H), 4.9 (s. 1H), 14.2 (b. s. 1H).

N,N-Benzylphenylacetylacetamide **20**. ^{1}HNMR($CDCl_3$, δ); carbonyl form: 2.1 (s. 3H), 3.3 (s. 2H), 4.9 (s. 2H), 6.9–7.6 (m. 10H); enolic form: 1.8 (s. 3H), 4.6 (s. 1H), 4.9 (s. 2H), 6.9–7.6 (m. 10H), 14.4 (s. 1H).

N,N-Benzylmethylacetylacetamide **21**. IR: C=O stretch at 1725 and 1640 cm^{-1}. ^{1}HNMR($CDCl_3$, δ); carbonyl form: 2.2 (s. 3H), 2.8–2.9 (two signals, 3H), 3.6 (s. 2H), 4.4–4.6 (two signals, 2H), 7.2 (b. s. 5H); enolic form: 1.9 (s. 3H), 2.8–2.9 (two signals, 3H), 4.4–4.6 (two signals, 2H), 5.1 (s. 1H), 7.2 (b. s. 5H), 14.9 (b. s. 1H). (Found: C, 70.1; H, 7.2; N, 6.8. Calc. for $C_{12}H_{15}NO_2$: C, 70.2; H, 7.3; N, 6.8%.)

N,N - Diphenyl(α - propionyl)propionamide **22**. ^{1}HNMR($CDCl_3$, δ); carbonyl form: 0.9–1.5 (c. m. 6H), 2.2–2.7 (m. 2H), 3.5–4.1 (m. 1H), 7.1–7.6 (m. 10H).

1 - Benzyl - 3(γ - benzylaminobutyl) - 2 - pyrrolidone **23**. M.p. 65–7°. (Found: C, 75.3; H, 7.4; N, 7.9. Calc. for $C_{22}H_{26}N_2O_2$: C, 75.4; H, 74; N, 8%.) ^{1}HNMR($CDCl_3$, δ): 1.9 (t. 2H), 2.2 (b. s. 1H), 2.7–3.6 (c.m. 9H), 4.4 (s. 2H), 4.6 (s. 2H), 7.1–7.4 (m. 10H).

3 - *Acetoacetyl - 2,2 - dimethylbenzothiazoline* **24**. IR: C=O stretch at 1730 and 1640 cm^{-1}. ^{1}HNMR($CDCl_3$, δ); carbonyl form: 1.9 (s. 6H), 2.2 (s. 3H), 3.7 (s. 2H), 6.8–7.2 (m. 4H); enolic form: 1.9 (s. 9H), 5.4 (s. 1H), 6.8–7.2 (m. 4H), 13.8 (b. s. 1H).

Benzoyl - N,N - dimethylacetamide **9**. 0.15 g (0.0017 mole) N,N-dimethylacetamide in 15 ml of THF was added with 1 ml of n-BuLi 2N (0.002 mole) at −78° under N_2 and with stirring. After 10 min the yellow soln was added dropwise with 0.5 g (0.0017 mole) of **7** in 20 ml of THF and kept at −78° for about 30 min. The reaction mixture was then warmed to ambient, quenched with sat NH_4Cl and extracted with ether. Drying and removal of the solvent gave a residue (0.35 g). Column chromatography afforded 0.1 g of unsubstituted phenothiazine **5**, 0.1 g of the starting material (N-Benzoylphenothiazine **7**) and 0.15 g (60%) of an oil which was identified as **9**. ^{1}HNMR($CDCl_3$, δ), carbonyl and enolic forms: 3.0–3.1 (group of signals, 6H), [4.1 (s.) + 5.8(s) + 15.5(b.s.) = 2H], 7.4–8.2 (m. 5H). (Found: C, 69.2; H, 6.8; N, 7.4. Calc. for $C_{11}H_{13}NO_2$: C, 69.1; H, 6.8; N, 7.3%.)

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REFERENCES

[1a]E. E. Royals, *Advanced Organic Chemistry*, p. 582. Prentice Hall, Englewood Cliffs, New Jersey (1954); [b]B. Castro, *Bull. Soc. Chim. France* 1540 (1967); [c]E. A. Evans, *J. Chem. Soc.* 4691 (1956); P. T. Izzo and S. R. Safir, *J. Org. Chem.* **24**, 701 (1959); [d]D. C. Owsley, J. M. Nelke and J. J. Blomfield, *J. Org. Chem.* **38**, 901 (1973); [e]Scilly, *Synthesis*, 160 (1973).

[2]A. I. Meyers and D. L. Comins, *Tetrahedron Letters* 5179 (1978).

[3]R. Lukes and O. Cervinka, *Coll. Czech. Chem. Comm.* 1893 (1961).

[4a]F. P. Hanck and J. E. Sundeen, *Chem. Abstr.* **87**, 152168v (1977); [b]W. J. Coates, A. M. Roe and R. A. Slater, *Chem. Abstr.* **87**, 23316t (1977).

[5]P. Hullot, T. Cuvigny, M. Larcheveque and H. Normant, *Can. J. Chem.* **55**, 266 (1977) and Refs. cited therein.

[6]M. M. V. Grignard and R. Lienard, *Bull. Soc. Chim. France* 2081 (1935).

[7]F. Ciminale, L. Di Nunno and S. Florio, *Tetrahedron Letters* 3001 (1980).

[8]C. R. Hauser and B. E. Hudson, *Organic Reactions*, Vol. 1, p. 262. Wiley, New York (1947).

[9]C. A. Brown, *J. Org. Chem.* **39**, 3913 (1974).

[10]P. v. R. Schleyer, *J. Am. Chem. Soc.* **86**, 1854 (1964) and Refs. therein cited.

[11]R. N. Prasad and K. Tietje, *Can. J. Chem.* **44**, 1247 (1966).

[12]H. Gilman and R. D. Nelson, *J. Am. Chem. Soc.* **75**, 5422 (1953).

[13]M. Siska, L. Szporny and O. Clander, *Acta Pharm. Hung.* **31**, 91 (1961).

[14]A. Mackie and A. A. Cutler, *J. Chem. Soc.* 2577 (1954).

[15]V. Merz and W. Weith, *Chem. Ber.* **6**, 1511 (1873).

[16]T. M. Siddall III and C. A. Prohaska, *J. Am. Chem. Soc.* **88**, 1172 (1966).

[17]T. Gramstad and W. J. Fuglevik, *Acta Chem. Scand.* **16**, 1369 (1962).

[18]F. Chioccara and G. Prota, *Synthesis* 876 (1977).

[19]R. Quelet, P. Bercot and J. d'Angelo, *Bull. Soc. Chim. France* 3258 (1966).

[20]R. A. Olofson and C. M. Dougherty, *J. Am. Chem. Soc.* **95**, 581 (1973).