Nucleophilic Attack at Heterocyclic Nitrogen: Unusual Reactivity of the Benzotriazole Heterocyclic Ring

Alan R. Katritzky*, Stanislaw Rachwal, Rick J. Offerman, Zbigniew Najzarek, Ahmed K. Yagoub, and Yongmin Zhang

Department of Chemistry, University of Florida,
Gainesville, FL 32611, USA

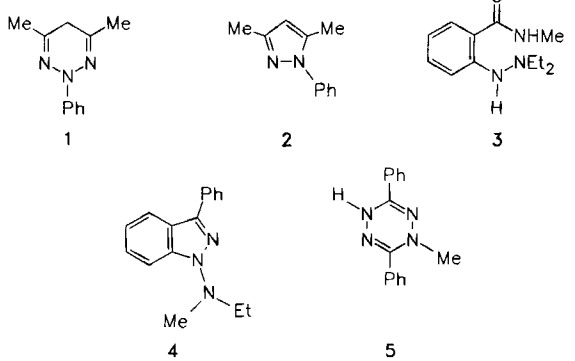
Received January 16, 1990

Key Words: Benzotriazole / 1-Imidoylbenzotriazoles / Grignard reactions / Ring cleavage / Ring nitrogen electrophilicity

Grignard reagents attack 1-imidoylbenzotriazoles at the imidoyl carbon atom and also at the benzotriazolyl N-2 and N-3 atoms leading to complex reaction mixtures, the composition of which allowed identification of the main reaction paths. Mechanisms are discussed. Previous examples of nucleophilic attack on pyridine-like nitrogen atoms are reviewed. The 1-imidoylbenzotriazoles were prepared from amides with benzotriazole and phosphoryl chloride. Amides derived from secondary amines give α-(benzotriazol-1-yl) enamines.

Introduction

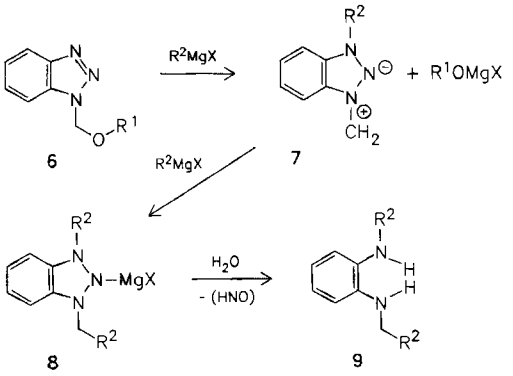
The typical reaction of pyridine-like heterocyclic nitrogen atoms is with electrophiles to give cationic products[1]. By contrast, examples of nucleophilic attack at pyridine-like nitrogen are extremely rare. To our knowledge, the only known examples of nucleophilic attack on heterocycles at nitrogen atoms involve Grignard reagents and the strongly electron-deficient 1,2,3-triazine[2,3] and tetrazine[4] systems. Thus, reaction of 4,6-dimethyl-1,2,3-triazine with phenylmagnesium bromide afforded[2], in addition to the expected 2,5-dihydro-4,6-dimethyl-5-phenyl-1,2,3-triazine (6%), two products of attack at nitrogen: the dihydro derivative **1** (37%) and the pyrazole **2** (10%). Treatment of 3-methyl-1,2,3-benzotriazin-4(3*H*)-one[3] with ethylmagnesium iodide gave the amidohydrazine **3** in 35% yield. 4-Phenyl-1,2,3-benzotriazine[3] was converted by ethylmagnesium iodide, followed by methyl iodide, into the indazole **4** (44%). Reaction of 3,6-diphenyl-*s*-tetrazine[4] with methylmagnesium iodide gave 1,4-dihydro-1-methyl-3,6-diphenyl-*s*-tetrazine (**5**) in 67% yield. These are the sole examples of this reaction type that we have located.



In open-chain analogs, a few examples of the "umpolung" of C = N bonds are known; e.g., the reaction of fluorenimines with alkyllithium reagents gives *N*-alkylated 9-aminofluorenes[5] in high yield. 1,4-Diaza-1,3-diene systems are *N*-alkylated with *n*-butyllithium, ethylmagnesium bromide, and triethylaluminum[6] giving 1,4-addition products together with the isomeric 1,2-derivatives found by nucleophilic attack at carbon. Nucleophilic attack at acyclic nitrogen is also characteristic of di-*tert*-butyl azodicarboxylate[7–9]; however, normal azo compounds react with Grignard reagents by single electron transfer[10].

In our work in the benzotriazole field, we have encountered by-products which have arisen from the nucleophilic attack of organometallic reagents at pyridine-like nitrogen atoms of the benzotriazole ring. Thus, N-3 atom is attacked by Grignard reagents in (benzotriazol-1-yl)methyl ethers[11] **6** to give *N,N'*-disubstituted 1,2-phenylenediamines **9** (Scheme 1) in 5–10% yield and in (benzotriazol-1-yl)methylammonium salts[12] to form 1,2-phenylenediamines **9** in 10–40% yield.

Scheme 1



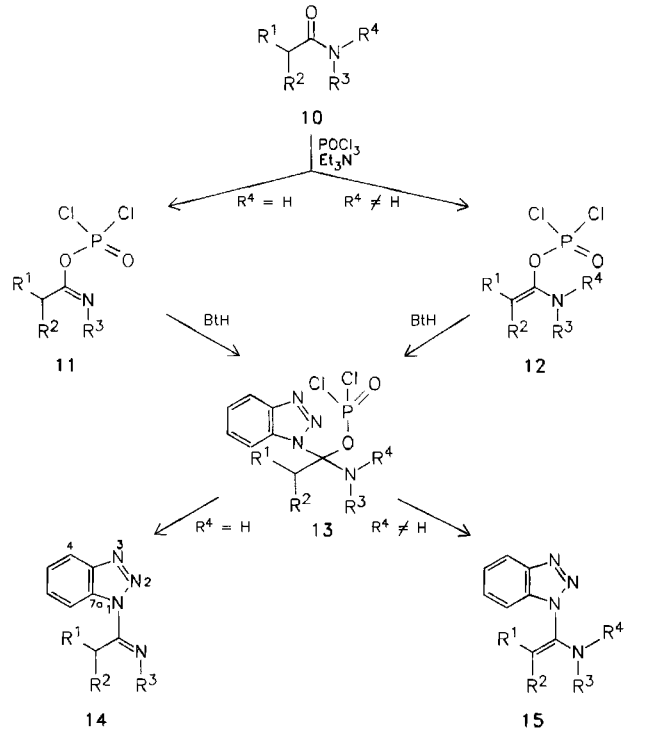
It seemed possible that a more electron-attracting group attached to the benzotriazole 1-position could induce greater susceptibility of the ring nitrogen towards electrophilic attack, provided attack by the Grignard reagent at

the 1-substituent was discouraged. We have found that the imidoyl group does indeed behave in this way and now wish to report that 1-(*N*-phenylacetimidoyl)benzotriazole **14a** and its propionimidoyl analog **14b** undergo a range of such reactions.

Synthesis of 1-Imidoylbenzotriazoles

The synthesis of 1-imidoylbenzotriazoles **14** was effected by the reaction of amides **10** with benzotriazole and phosphoryl chloride in the presence of triethylamine in acetonitrile. The reaction probably involves intermediates of type **11** (amides derived from primary amines) or **12** (amides derived from secondary amines), cf. previously postulated reaction intermediates[13–16]. Adducts of phosphorus pentoxide and amides[17,18] have similar structures. Addition of benzotriazole to the C=N (or C=C bond) leads via adducts **13** to stable molecules **14** or **15** (Scheme 2).

Scheme 2



Acetanilide **10a** gave 1-(*N*-phenylacetimidoyl)benzotriazole **14a** in 96% yield. Other amides reacted similarly: thus, octananilide provided imine **14e** (87%). All the steps required for the preparation of **14** from a carboxylic acid can be carried out in one pot without separation of the intermediates. The 1-imidoylbenzotriazoles **14** obtained are described in Table 1. One example of **15** was prepared from the tertiary amide *N*-methyl-*N*-phenyl-octanamide. Attempts to prepare such imines from primary amides gave the corresponding nitrile, e.g., 87% of benzonitrile from benzamide.

Benzotriazolyl can behave as a leaving group similar to a chloro or bromo substituent, but the benzotriazolyl derivatives are usually more stable than the analogous halides. This previously allowed us to synthesize several reactive species bearing a benzotriazolyl substituent α to the functional group, e.g., α-(benzotriazolyl) alcohols[19], ethers[11,19], amines[20,21], amides[22], silanes[23], chloroalkanes[24], and to apply them in reactions with nucleophiles.

Amides derived from arylcarboxylic acids are readily transformed into corresponding imidoyl chlorides by their reactions with thionyl chloride[25–27] or with phosphorus pentachloride[28–30]. In general, imidoyl chlorides derived from aliphatic carboxylic acids are difficult to prepare and unstable due to acidic α protons of the alkyl group which become involved in the reactions[31]. Our synthesis of 1-imidoylbenzotriazoles derived from aliphatic carboxylic acids is therefore complementary to the synthesis of imidoyl chlorides which have been recently recognized as useful reagents[32–39].

NMR Spectra of 1-Imidoylbenzotriazoles

The structures of the adducts **14** and **15** are based on ^{1}H- and ^{13}C-NMR spectroscopy and on C,H,N analyses. The ^{1}H-NMR spectrum (Table 2) for the acetanilide-derived adduct **14a** showed doublets at δ = 8.54 (*J* = 8.3 Hz, 1H), 8.12 (*J* = 8.2 Hz, 1H), and 6.94 (*J* = 8.4 Hz, 2H), a multiplet at δ = 7.61–7.15 (5H), and a singlet at δ = 2.75 (3H). The first two doublets are assignable to 4-H and 7-H of the benzotriazole ring. The third doublet can be assigned to the *ortho* protons of the phenyl ring. High-resolution spectra and selective proton-decoupling techniques allowed separation and assignment of the aromatic multiplets (Table 2). The singlet was assigned to the methyl group. A remarkable downfield shift of the 7-H resonance is characteristic for this group of compounds in comparison with benzotriazol-1-yl derivatives like 1-methylbenzotriazole[40] (δ = 7.48) or *N*-(benzotriazol-1-yl)methylamines[41] (δ = 7.35–7.62). This phenomenon must be caused by a strong diamagnetic deshielding influence of the arylimidolyl group.

In the ^{13}C-NMR spectra of **14**, the imidoyl carbon resonances were observed at δ = 154.0–160.0. The benzotriazole carbon resonances occurred at δ = 116 (C-7), 120 (C-4), 125 (C-5), 129 (C-6), 131 (C-7a), and 146 (C-3a). Again, there was an abnormally strong downfield shift of the resonance of C-7 when compared to 1-methylbenzotriazole[42] (δ = 108.8), to 1-(benzotriazol-1-yl)-1-chloroalkanes[24] (δ = 110–112) or even to 1-acetylbenzotriazole[42] (δ = 114.1) indicating that both the electron-withdrawing and deshielding effects of the imidoyl group were involved. The four remaining aromatic resonances of **14a** were seen at δ = 120.2, 124.3, 129.2, and 147.4. The methyl group resonance of **14a** was assigned to the peak at δ = 16.3 (Table 3).

Reactions of 1-Imidoylbenzotriazoles with Grignard Reagents

1-Imidoylbenzotriazoles **14** reacted rather slowly with Grignard reagents; completed reaction could require several

Table 1. Preparation of 1-imidoylbenzotriazoles **14**

	R^1	R^2	R^3	Yield (%)	Crystal form	M.p. (°C)	Molecular formula	Calcd. Found C H N
14a	H	H	Ph	96	needles	108	$C_{14}H_{12}N_4$	71.17 5.12 23.71 70.78 5.05 23.78
14b	Me	H	Ph	57[a]	prisms	99	$C_{15}H_{14}N_4$	71.98 5.64 22.38 71.76 5.60 22.50
14c	Et	H	Ph	60	–	oil	$C_{16}H_{16}N_4$	72.70 6.10 21.20 72.73 6.15 21.10
14d	Ph	H	Ph	38	needles	109	$C_{20}H_{16}N_4$	76.90 5.16 17.94 76.97 5.07 17.53
14e	hexyl	H	Ph	87	–	oil	$C_{20}H_{24}N_4$	[b]
14f	H	H	4-BrC_6H_4	89	needles	164	$C_{14}H_{11}N_4Br$	53.35 3.52 17.78 53.53 3.48 17.85
14g	H	H	4-MeC_6H_4	88	needles	115	$C_{15}H_{14}N_4$	71.98 5.64 22.38 71.96 5.63 22.58
14h	Me	Me	4-MeC_6H_4	62	cubes	110	$C_{17}H_{18}N_4$	73.35 6.52 20.13 72.96 6.52 20.28

[a] Total yield for the three-step one-pot procedure starting from propionic acid (calcd. for the crude material). – [b] Calcd.: 320.2000 Found: 320.1997 (MS).

Table 2. ^{1}H-NMR data[a] for 1-imidoylbenzotriazoles **14**

	Benzotriazolyl 4-H	5-H	6-H	7-H	R^1	R^2	R^3
a	8.12 (d, 8.2)	7.48 (dd, 8.3, 7.0)	7.60 (dd, 8.2, 7.1)	8.54 (d, 8.3)	2.75 (s, 3H)	2.75 (s)	6.94 (d, 8.4, 2H), 7.19 (t, 7.6, 1H), 7.38 (dd, 8.3, 7.6, 2H)
b	8.11 (d, 8.3)	7.45 (dd, 8.2, 7.0)	7.56 (dd, 8.2, 7.0)	8.50 (d, 8.3)	1.35 (t, 7.5, 3H)	3.15 (q, 7.5)	6.94 (d, 8.5, 2H), 7.17 (t, 7.4, 1H), 7.39 (dd, 8.3, 7.5, 2H)
c	8.09 (d, 8.2)	7.42 (dd, 8.2, 7.1)	7.53 (dd, 8.2, 7.1)	8.50 (d, 8.3)	0.91 (t, 7.3, 3H) 1.80 (m, 2H)	3.10 (t, 7.8)	6.93 (d, 8.5, 2H), 7.15 (t, 7.5, 1H), 7.39 (dd, 8.4, 7.5, 2H)
d	8.04 (d, 8.3)	7.38 (m)	7.50 (dd, 8.2, 7.1)	8.49 (d, 8.3)	7.15 (m, 5H)	4.58 (s)	6.95 (d, 8.3, 2H), 7.15 (m, 1H) 7.38 (m, 2H)
e	8.08 (d, 8.3)	7.42 (dd, 8.3, 6.4)	7.53 (dd, 8.3, 6.4)	8.50 (d, 8.3)	0.83 (t, 6.7, 3H) 1.17 (m, 4H), 1.25 (m, 4H) 1.77 (m, 2H)	3.11 (t, 8.0)	6.93 (d, 8.4, 2H), 7.15 (t, 7.3, 1H) 7.39 (dd, 8.4, 7.3, 2H)
f	8.12 (d, 8.2)	7.48 (dd, 8.2, 7.1)	7.60 (dd, 8.2, 7.1)	8.49 (d, 8.3)	2.75 (s)	2.75 (s)	6.84 (d, 8.7, 2H), 7.53 (d, 8.7, 2H)
g	8.10 (d, 8.2)	7.45 (dd, 8.2, 7.1)	7.57 (dd, 8.3, 7.2)	8.52 (d, 8.4)	2.74 (s)	2.74 (s)	2.38 (s, 3H), 6.85 (d, 8.3, 2H), 7.21 (d, 8.3, 2H)
h	8.10 (d, 8.1)	7.43 (dd, 8.1, 7.6)	7.54 (dd, 8.4, 7.6)	8.46 (d, 8.4)	1.52 (d, 7.0)	1.52 (d, 7.0)	2.37 (s, 3H), 6.81 (d, 7.6, 2H), 7.20 (d, 7.7, 2H)

[a] Chemical shifts δ are given in ppm from the tetramethylsilane signal, coupling constants (in parentheses) are given in Hz; only the largest coupling constants were considered.

days of stirring at 20°C with excess Grignard reagent. The amine (R^3NH_2) was isolated in significant yields from such reactions together with a variety of other products.

Three main reaction pathways were considered (Scheme 3). In the first pathway, nucleophilic attack of the Grignard reagent on the imidoyl carbon atom led to adduct **16** which

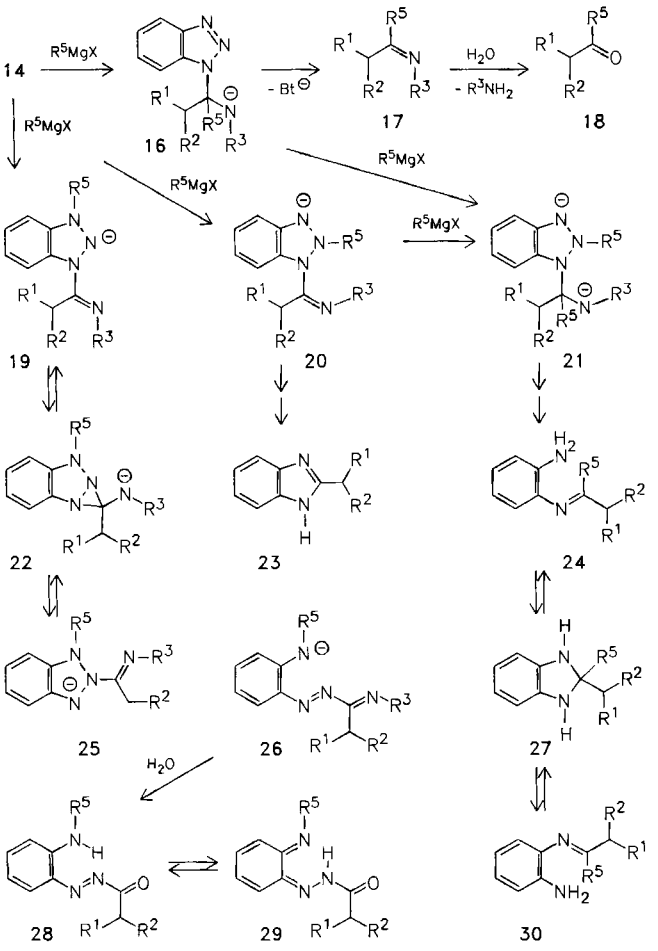
Table 3. ^{13}C-NMR data[a] for 1-imidoylbenzotriazoles **14**

	Benzotriazolyl									
	C-4	C-5	C-6	C-7	C-7a	C-3a	C=N	C-α	R^1	R^3
a	119.7	125.4	129.1	115.7	131.5	146.6	154.0	16.3	–	120.2, 124.3, 129.2, 147.4
b	119.7	125.3	129.2	115.7	131.4	146.5	158.5	22.9	12.8	119.8, 124.0, 129.4, 147.4
c	119.6	125.3	129.2	115.7	131.4	146.4	157.3	31.1	14.0, 21.4	119.8, 124.0, 129.1, 147.3
d	119.7	125.4	129.2	115.5	131.4	146.5	154.6	34.8	126.8, 128.5, 128.7, 135.2	120.1, 124.4, 129.2, 146.9
e	119.9	125.3	129.2	115.7	131.2	146.5	157.6	31.5	14.0, 22.5, 27.9, 28.6, 29.3, 29.4	119.7, 124.0, 128.3, 147.4
f	119.9	123.4	129.4	115.6	131.2	146.4	154.5	16.3	–	117.4, 122.1, 132.3, 146.7
g	119.7	125.3	129.1	115.7	131.3	146.6	153.9	16.2	–	20.9, 120.2, 129.8, 133.8, 144.7
h	119.4	125.2	129.0	115.8	131.9	145.6	160.3	31.3	20.2	20.8, 119.5, 129.8, 133.4, 144.8

[a] Chemical shifts δ are given in ppm from the tetramethylsilane signal for 0.5 M solutions of **14** in $CDCl_3$.

then eliminated a benzotriazole anion to give ketimine **17**. The imine was hydrolyzed during reaction workup to give amine R^3NH_2 and the ketone **18** which could then be isolated from the reaction mixture. Thus, 4-methylpropiophenone (**18**, R^1 = Me, R^2 = H, R^5 = 4-MeC_6H_4) was separated in 17% yield from the reaction of **14b** with 4-tolylmagnesium bromide.

Scheme 3



$Bt^{\ominus}$: anion of benzotriazole

The other pathways are more complex, and involve nucleophilic attack of the Grignard reagents at the ring nitrogen atoms. Attack of the organomagnesium reagent on the benzotriazolyl N-3 is considered to lead to the intriguing colored products **29** isolated in low yield from the reactions of **14** with Grignard reagents. In contrast to the previously reported[11] similar reactions of benzotriazolylmethyl ethers with Grignard reagents leading to *N*-substituted *o*-phenylenediamines (Scheme 1), opening of the benzotriazole heterocyclic ring occurs in the present case without elimination of the N-2 atom. The initially formed anion **19** is considered to rearrange, perhaps via the diaziridine **22** to the successively more stable anions **25** and **26**. Hydrolysis of **26** occurs during chromatography on the silica gel column to yield **29**. Fresh crude material from the Grignard reaction was almost colorless, but a deep orange band slowly developed on the column. The yield of **29** was maximized if elution was effected 24 h after the mixture was put onto the column.

Evidence for the structures of compounds **29** was obtained from C, H, N analyses and from mass and NMR spectra. High-resolution mass spectra of the molecular ions provided the molecular formulas. An ion peak corresponding to $R^1R^2CHC{=}O^+$ supports the presence of the acyl group. Resonance of the carbonyl carbon atom at relatively high field [e.g., δ(C=O) = 172.2 for **29** when R^1 = Me, R^2 = H and R^5 = 4-MeC_6H_4] suggests an amido-type carbonyl group. A relatively strong downfield shift of the aryl *ortho* proton resonances of R^5 in the ^{1}H-NMR spectra of **29** (e.g., δ = 7.74 in the case cited above) supports the tautomeric form **29** rather than **28** (a deshielding effect of the C=N bond). In a similar system to **29**, predominance of the α-hydrazone-oxime over α-azo-hydroxylamine tautomer was previously observed[43].

To explain the formation of products in which the N-2 of the benzotriazole ring has been lost, we postulate that the Grignard reagent can also attack the benzotriazolyl N-2 atom in **14**. This should initially give the anion **20** which can react in two alternative ways. During the reaction workup, **20** undergoes decomposition and cyclization to the 2-substituted benzimidazole **23**: thus, 2-ethylbenzimidazole[44] was isolated from the reaction of **14b** with 4-chlorophenylmagnesium bromide. Isolation of 4-chloro-

aniline from the same reaction of **14b** gave further evidence of the Grignard reagent attachment on N-2. To our knowledge, this is the first observation of such a reaction of the benzotriazole ring. Conjugation of the benzotriazole and C = N group electron systems renders not only N-3 positively charged but also N-2.

However, anion **20** (or possibly anion **16**) is evidently also able to react with a second molecule of the Grignard reagent to give the dianion **21**. Subsequent reactions then gave benzimidazoline **27** and amine R^5NH_2, which were isolated. Thus, from the reaction of **14b** with 4-chlorophenylmagnesium bromide, 2-(4-chlorophenyl)-2-ethylbenzimidazoline (**27**, R^1 = Me, R^2 = H, R^5 = 4-ClC_6H_4) was isolated in 13% yield.

Problems arose with the assignment of the structure of **27**. Elemental analyses and mass spectra gave the molecular formula of **27**, but the ^{13}C-NMR spectra, depending on the solvent used, often exhibited broad peaks. The sharpest signals were obtained in [D_6]DMSO, but were more numerous than the expected number of carbon atoms in the molecule. The phenomenon can be best explained by assuming an equilibration between forms **24**, **27**, and **30**. Benzimidazolines are known to undergo such equilibrations[45-47]. Positions of the ^1H-NMR signals of the *o*-phenylenediamine protons of the product are shifted to lower field (δ = 6.90–7.30) in comparison to the spectra of ordinary benzimidazolines[48,49] suggesting predominance of the "open" forms, **24** and **30**, in the solution.

Experimental

Melting points: Hot-stage microscope. – ^1H NMR: Varian VXR-300 NMR spectrometer (300 MHz) with TMS [δ(TMS) = 0.00] as the internal reference. ^{13}C NMR: Varian VXL-300 NMR spectrometer (75 MHz), referenced to the signal of TMS [δ(TMS) = 0]. $CDCl_3$ was used as the solvent for both ^1H and ^{13}C NMR except when stated otherwise. – High-resolution MS: Kratos/AE1-MS 30 mass spectrometer. – Microanalyses: Dr. R. W. King (University of Florida). – Ether and THF for the Grignard reactions were distilled from sodium/benzophenone prior to use. Octananilide (m.p. 50–51°C, ref.[50] m.p. 51–52°C) was prepared by the reaction of octanoic acid with phenyl isothiocyanate by the method of Rahman and co-workers[51].

General Procedure for the Preparation of 1-Imidoylbenzotriazoles **14**: 13.9 g (100 mmol) of triethylamine was added dropwise to an ice-cold solution of 17.9 g (150 mmol) of benzotriazole and 9.3 ml (100 mmol) of phosphoryl chloride in 200 ml of acetonitrile. To the resulting mixture was added a solution of the amide (50 mmol) in 100 ml of acetonitrile over 30 min. The reaction mixture was stirred until TLC indicated the starting material had been consumed. The solvent was removed in vacuo, and the resulting oil was partitioned between $CHCl_3$ and satd. $NaHCO_3$ solution. The organic phase was separated, and the aqueous phase was extracted with $CHCl_3$. The combined organic extracts were washed with satd. $NaHCO_3$ solution (2 × 200 ml), followed by water and dried with anhydrous $MgSO_4$. The solvent was removed in vacuo, and the residue crystallized (solid products) or chromatographed (oils) to give pure 1-imidoylbenzotriazole **14**.

One-Pot Method for the Synthesis of Imine **14b**: The reaction was carried out in a 1000-ml three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel. The top of the condenser was connected with a HCl/SO_2 trap. To a stirred solution of 18.6 ml (0.25 mol) of propionic acid in 80 ml of benzene was added dropwise 21.9 ml (0.30 mol) of thionyl chloride, and the mixture was heated at reflux for 1 h. A mixture of 22.9 ml (0.25 mol) of aniline and 41.8 ml (0.30 mol) of triethylamine was added dropwise to the refluxing solution, and the stirring at reflux was continued for 2 h. The mixture was cooled to 25°C and then in an ice bath. The stirred mixture was kept in the ice bath while a solution of 59.6 g (0.50 mol) of benzotriazole and 50.2 ml (0.50 mol) of phosphoryl chloride in 120 ml of acetonitrile was added dropwise. Finally, 69.7 ml of triethylamine was added over 2 h. The obtained mixture was stirred at 25°C for 20 h. 200 ml of satd. $KHCO_3$ solution, cooled to −20°C (obtained by dissolving an excess of dry ice in satd. K_2CO_3 solution), was then added, followed by 200 ml of toluene. The resulting mixture was stirred at 25°C for 4 h, and the precipitate was filtered off and washed with toluene (2 × 100 ml). The filtrate and the washings were combined, and the organic phase was separated. The solution was washed with satd. $KHCO_3$ solution (obtained as above) and dried with anhydrous Na_2CO_3. The solvent was evaporated under reduced pressure to give a crude product which was recrystallized from absolute ethanol to give colorless prisms, 30.8 g (49%).

Synthesis of N-[1-(benzotriazol-1-yl)-1-octen-1-yl]-N-methylaniline (**15**; R^1 = hexyl, R^2 = H, R^3 = Ph, R^4 = Me): To a stirred solution of 28.5 g (320 mmol) of benzotriazole in 200 ml of dry acetonitrile was added dropwise 24.5 g (160 mmol) of phosphoryl chloride in 100 ml of acetonitrile followed by 22.3 ml (160 mmol) of triethylamine. 19.0 g (80 mmol) of *N*-methyl-*N*-phenyloctanamide[52] in 100 ml of acetonitrile was added, and the resulting mixture was stirred at 25°C for 20 h. The solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$, and the obtained solution was washed with satd. $NaHCO_3$ solution (4 × 200 ml) to remove benzotriazole. The solution was then dried (Na_2CO_3) and, after concentration, subjected to column chromatography [silica gel; petroleum ether/ethyl ether (1:1)] to give 18.6 g (70%) of enamine **15** (R^1 = hexyl, R^2 = H, R^3 = Ph, R^4 = Me) as a colorless oil. – ^1H NMR: δ = 0.87 (t, *J* = 6.8 Hz, 3H), 1.27 (m, 6H), 1.5 (m, 2H), 2.13 (q, *J* = 7.3 Hz, 2H), 3.14 (s, 3H, CH_3N), 6.01 (t, *J* = 7.3 Hz, 1H, CH = C), 6.84 (t, *J* = 7.3 Hz, 1H, Ph), 6.93 (d, *J* = 7.8 Hz, 2H, Ph), 7.15–7.50 (m, 5H), 8.03 (ddd, *J* = 1.0, 1.5, and 7.8 Hz, 1H, Benzotriazolyl). – ^{13}C NMR: δ = 14.1 (Me), 22.6, 27.0, 28.7, 29.0, 31.6, 37.0 (CH_3N), 110.8, 113.8 (*o*-Ph), 119.2, 120.0, 121.0, 124.1, 128.1, 129.4 (*m*-Ph), 131.9, 136.1, 142.2, 145.9.

$C_{21}H_{26}N_4$ Calcd. 334.2158 Found 334.2161 (MS)

Reaction of Imine **14a** *with Phenylmagnesium Bromide:* To a stirred solution of phenylmagnesium bromide prepared from 5.00 ml (48 mmol) of bromobenzene and 1.44 g (60 mmol) of magnesium in 30 ml of ether was added 2.00 g (8.3 mmol) of imine **14a**. The obtained mixture was stirred and heated at reflux for 4 h. The reaction mixture was poured into 100 g of ice-water and extracted with CH_2Cl_2 (2 × 50 ml). The extract was washed with 100 ml of 10% NaOH solution (100 ml) and dried with anhydrous Na_2SO_4. Evaporation of the solvent afforded a crude product mixture. The NMR spectrum showed that the mixture consisted of many compounds.

Column chromatography of the reaction mixture (silica gel, CH_2Cl_2) did not allow for complete separation of its ingredients; however, one of the fractions was identified by its NMR spectrum as aniline[53]. Another of the fractions attracted more attention because of its interesting orange color. After evaporating off the solvent, the residual oil was triturated with hexane to give an orange

precipitate. The crystals were separated and recrystallized from toluene to give 0.15 g (7.5 %) of analytically pure hydrazone **29a** ($R^1 = R^2 = H$, $R^5 = Ph$) as tiny needles; m.p. 123°C. – ^{1}H NMR: δ = 2.28 (s, 3H), 7.17 (ddd, J = 1.4, 7.3, and 8.5 Hz, 1H), 7.48 (ddd, J = 1.7, 7.3, and 8.6 Hz, 1H), 7.54 (d, J = 7.9 Hz, 2H, Ph), 7.55 (m, 1H, Ph), 7.86 (m, 3H), 8.67 (d, J = 8.4 Hz, 1H), 10.12 (br. s, 1H, NH). – ^{13}C NMR: δ = 25 (CH_3), 120.2, 121.2, 122.8 (Ph), 123.4, 129.3 (Ph), 131.4, 132.9, 135.9, 138.7, 152.4, 168.6 (C = O).

$C_{14}H_{13}N_3O$ Calcd. C 70.28 H 5.48 N 17.56
Found C 70.65 H 5.54 N 17.67

Reaction of Imine **14a** *with Hexylmagnesium Iodide:* A solution of 2.36 g (10.0 mmol) of imine **14a** in 30 ml of dry THF was added to a Grignard reagent prepared from 24.8 g (117 mmol) of hexyl iodide and 2.43 g (100 mmol) of magnesium in 50 ml of ether. This mixture was stirred at 25°C for 16 h. 7.82 ml (110 mmol) of acetyl chloride was added dropwise (exothermic reaction), and the obtained mixture was stirred at 25°C for 1 h. The reaction mixture was poured into 100 g of ice-water and extracted with 100 ml of ether. The ethereal solution was washed with 100 ml of 10% NaOH solution, followed by water, and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded a brown oil. Column chromatography of this oil (silica gel, hexane) gave 11.8 g (47%) of 1-iodo-5-hexanone as the first fraction. Then a mixture of hexane/ethyl acetate (10:1) was used as the eluent to give aniline[53] (0.22 g, 24%) as the second fraction. The third fraction eluted by the same mixed solvent gave 0.82 g (36%) of *N,N*-dihexylacetamide as a colorless oil. – ^{1}H NMR: δ = 0.88 (t, J = 7.0 Hz, 6H), 1.29 (m, 12H), 1.53 (m, 4H), 2.07 (s, 3H, CH_3CO), 3.20 (m, 2H, CH_2N), 3.29 (m, 2H, CH_2N). – ^{13}C NMR: δ = 14.1, 22.6, 26.6, 26.8, 27.8, 29.0, 31.6, 31.7, 45.8 (CH_2N), 48.9 (CH_2N), 170.0 (C = O). The last fraction eluted from the column [hexane/ethyl acetate (3:1)] was identified by ^{1}H NMR to be acetanilide[54] (0.62 g, 46%).

Reaction of 1-(N-Phenylpropionimidoyl)benzotriazole (**14b**) *with 4-Tolylmagnesium Bromide:* To a stirred solution of 4-tolylmagnesium bromide obtained from the reaction of 12.8 g (75.0 mmol) of 4-bromotoluene with 2.43 g (100 mmol) of magnesium in 100 ml of ether was added dropwise a solution of 5.00 g (20.0 mmol) of **14b** in 30 ml of dry THF. The mixture obtained was stirred at 20°C for 36 h and then poured into 100 ml of ice-cold 10% K_2CO_3 solution followed by extraction with ether (3 × 100 ml). The ethereal solution was washed with 100 ml of 10% K_2CO_3 solution, dried with anhydrous K_2CO_3, and the ether was evaporated. Column chromatography (silica gel) of the residual oil with use of hexane as an eluent gave the first fraction (0.60 g, 8%), which was identified by ^{1}H- and ^{13}C-NMR spectra to be 4,4′-dimethylbiphenyl. The second fraction eluted by hexane/ethyl acetate (10:1) gave 0.49 g (17%) of 4-methylpropiophenone[55]. The third fraction, eluted by the same solvent mixture appeared to be **29b** (R^1 = Me, R^2 = H, R^5 = 4-MeC_6H_4) (0.40 g, 7%). The product was recrystallized from methanol to give orange thin needles, m.p. 131°C. – ^{1}H NMR: δ = 1.30 (t, J = 7.6 Hz, 3H, Et), 2.43 (s, 3H, Me), 2.49 (q, J = 7.6 Hz, 2H, Et), 7.13 (ddd, J = 1.3, 7.3, and 8.5 Hz, 1H), 7.31 (d, J = 8.6 Hz, 2H, MeC_6H_4), 7.43 (ddd, J = 1.6, 7.3, and 8.5 Hz, 1H), 7.74 (d, J = 8.6 Hz, 2H, MeC_6H_4), 7.81 (dd, J = 1.6 and 8.1 Hz, 1H), 8.68 (dd, J = 1.3 and 8.4 Hz, 1H), 10.16 (br. s, 1H, NH). – ^{13}C NMR: δ = 9.6 (Et), 21.5 (MeC_6H_4), 31.5 (Et), 120.1, 121.2, 122.6 (MeC_6H_4), 123.2, 129.9 (MeC_6H_4), 132.5, 135.6, 138.6, 142.0, 150.6, 172.2.

$C_{16}H_{17}N_3O$ Calcd. C 71.89 H 6.41 N 15.72
Found C 71.59 H 6.45 N 15.72

The eluent was then changed into more polar hexane/ethyl acetate (4:1) to give 1.36 g (73%) of aniline as the fourth fraction and 0.72 g of a complex, unidentified oily mixture as the last fraction.

Reaction of Imine **14b** *with 4-Chlorophenylmagnesium Bromide:* To a solution of 4-chlorophenylmagnesium bromide prepared from 2.43 g (100 mmol) of magnesium and 14.4 g (75.0 mmol) of 4-bromochlorobenzene in 100 ml of ether was added dropwise a solution of 5.00 g (20.0 mmol) of **14b** in 50 ml of THF and the resulting mixture was stirred under nitrogen at 25°C for 5 d. The reaction mixture was poured into dry ice/water (100 g/500 g), and the precipitate was filtered off, washed with 50 ml of methanol then followed by 50 ml of $CHCl_3$. The filtrate and the washings were collected and extracted with $CHCl_3$ (2 × 100 ml). The $CHCl_3$ solution was washed with 100 ml of water, dried with anhydrous $MgSO_4$, and the solvent was evaporated. The obtained residue (brown oil) was subjected to column chromatography (silica gel). The eluted fractions were identified by their ^{1}H- and ^{13}C-NMR spectra. The new compounds were additionally characterized by their C,H,N analyses or high-resolution mass spectra.

The first fraction (1.15 g, eluted by toluene) appeared to be a mixture of 4,4′-dichlorobiphenyl[56], chlorinated triptycenes, and higher polyphenylenes. The second fraction (0.30 g, eluted by toluene) was a complex mixture which was not investigated further. The third fraction [0.25 g, (10%), eluted by toluenc] was found to be 4-chloroaniline.

The fourth fraction [0.45 g, eluted by toluene/ethyl acetate (10:1)] appeared to be a mixture of 4-chloroaniline and hydrazone **29c** (R^1 = Me, R^2 = H, R^5 = 4-ClC_6H_5) in a molar ratio of 2:1. Subsequent column chromatography of this mixture (silica gel, toluene) and recrystallization of the product from toluene gave 0.04 g (0.7%) of pure hydrazone **29c** as orange needles; m.p. 158°C. – ^{1}H NMR: δ = 1.31 (t, J = 7.5 Hz, 3H), 2.52 (q, J = 7.5 Hz, 2H), 7.17 (ddd, J = 1.3, 7.3, and 8.2 Hz, 1H), 7.48 (ddd, J = 1.6, 7.3, and 8.8 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.81 (d, J = 8.6 Hz, 2H), 7.84 (dd, J = 1.6 and 8.1 Hz, 1H), 8.71 (dd, J = 1.2 and 8.5 Hz, 1H), 10.06 (br. s, 1H, NH). – ^{13}C NMR: δ = 9.6 (CH_3), 31.5 (CH_2), 120.31, 122.2, 123.8 (4-ClC_6H_4), 129.6 (4-ClC_6H_4), 133.3, 136.1, 137.3, 138.8, 150.7, 172.7 (C = O).

$C_{15}H_{14}ClN_3O$ Calcd. C 62.61 H 4.90 N 14.60
Found C 62.74 H 4.90 N 14.55

The fifth fraction [eluted by toluene/ethyl acetate (10:1)] gave 0.70 g (13%) of 2-(4-chlorophenyl)-2-ethylbenzimidazoline (**27**). The compound was recrystallized from hexane to give yellowish needles, m.p. 72°C. – ^{1}H NMR (CD_3OD): δ = 1.14 (t, J = 7.6 Hz, 3H, Me), 2.28 (q, J = 7.6 Hz, 2H, CH_2), 6.99 (m, 1H), 7.23 (m, 7H). – ^{13}C NMR (CD_3OD): δ = 12.8 (Me), 25.6 (CH_2), 122.1, 123.4, 128.0, 129.3, 129.4, 132.5, 146.4, 160.4.

$C_{15}H_{15}N_2Cl$ Calcd. C 69.62 H 5.84 N 10.83
Found C 69.65 H 5.91 N 10.65

The sixth fraction [eluted by toluene/ethyl acetate (10:1)] gave 0.28 g (9%) of propionanilide[54]. The seventh fraction [eluted by toluene/ethyl acetate (3:1)] gave 0.75 g (31%) of benzotriazole. The eighth fraction [eluted by toluene/ethyl acetate (3:1)] was 0.69 g (23%) of 2-ethylbenzimidazole[44] (**23**).

CAS Registry Numbers

10a: 103-84-4 / **10b**: 620-71-3 / **10c**: 1129-50-6 / **10d**: 621-06-7 / **10e**: 55679-48-6 / **10f**: 103-88-8 / **10g**: 103-89-9 / **10h**: 6876-49-9 / **14a**: 125781-61-5 / **14b**: 125781-62-6 / **14c**: 125781-63-7 / **14d**: 125781-64-8 / **14e**: 125781-65-9 / **14f**: 125781-66-0 / **14g**: 125781-67-1 / **14h**: 125781-68-2 / **15**: 125781-73-9 / **27**: 125781-72-8 / **29a**: 125781-69-3 / **29b**: 125781-70-6 / **29c**: 125781-71-7 / benzotriazole: 95-14-7 / propionic acid: 79-09-4 / aniline: 62-53-3 / *N*-methyl-*N*-Phenyloctanamide: 79779-21-8 / phenylmagnesium bromide: 100-58-3 / hexylmagnesium iodide: 89583-95-9 / 1-iodo-5-hexanone:

4367-98-0 / *N,N*-dihexylacetamide: 16423-51-1 / 4-tolylmagnesium bromide: 4294-57-9 / 4-methylpropiophenone: 5337-93-9 / 4-Chlorphenylmagnesium bromide: 873-77-8 / 2-ethylbenzimidazole: 1848-84-6 / 4-chloroaniline: 106-47-8

[1] A. R. Katritzky, *Handbook of Heterocyclic Chemistry*, p. 151, Pergamon Press Ltd., Oxford 1985.
[2] A. Ohsawa, T. Kaihoh, H. Igeta, *J. Chem. Soc., Chem. Commun.* **1985**, 1370.
[3] J. J. A. Campbell, S. J. Noyce, R. C. Storr, *J. Chem. Soc., Chem. Commun.* **1983**, 1344.
[4] D. Hunter, D. G. Neilson, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 2779.
[5] W. Dai, R. Srinivasan, J. A. Katzenellenbogen, *J. Org. Chem.* **54** (1989) 2204.
[6] L. Stamp, H. tom Dieck, *J. Organomet. Chem.* **277** (1984) 297.
[7] C. Gennari, L. Colombo, G. Bertolini, *J. Am. Chem. Soc.* **108** (1986) 6394.
[8] D. A. Evans, T. C. Britton, R. L. Dorow, J. F. Dellaria, *J. Am. Chem. Soc.* **108** (1986) 6395.
[9] L. A. Trimble, J. C. Vederas, *J. Am. Chem. Soc.* **108** (1986) 6397.
[10] T. Holm, I. Crossland, *Acta Chem. Scand., Ser. B*, **33** (1979) 421.
[11] A. R. Katritzky, S. Rachwal, B. Rachwal, *J. Org. Chem.* **54** (1989) 6022.
[12] A. R. Katritzky, C. V. Hughes, S. Rachwal, *J. Heterocycl. Chem.* **26** (1989) 1579.
[13] E. Stanoeva, M. Haimova, V. Ognyanov, *Liebigs Ann. Chem.* **1984**, 389.
[14] M. E. Kuehne, P. J. Shannon, *J. Org. Chem.* **42** (1977) 2082.
[15] Z. Najzarek, B. Prajsnar, M. Zielinski, *Zesz. Nauk. Politech. Slask., Chem.* **1969**, 90; *Chem. Abstr.* **73** (1970) 39126c.
[16] H. H. Bosshard, H. Zollinger, *Helv. Chim. Acta* **42** (1959) 1659.
[17] B. W. Hansen, E. B. Pedersen, *Liebigs Ann. Chem.* **1981**, 1485.
[18] B. W. Hansen, E. B. Pedersen, *Acta Chem. Scand., Ser. B*, **34** (1980) 369.
[19] A. R. Katritzky, S. Rachwal, B. Rachwal, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 791.
[20] A. R. Katritzky, S. Rachwal, B. Rachwal, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 799.
[21] A. R. Katritzky, K. Yannakopoulou, P. Lue, D. Rasala, L. Urogdi, *J. Chem. Soc., Perkin Trans. 1*, **1989**, 225.
[22] A. R. Katritzky, M. Drewniak, P. Lue, *J. Org. Chem.* **53** (1988) 5854.
[23] A. R. Katritzky, R. J. Offerman, P. Cabildo, M. Soleiman, *Recl. Trav. Chim. Pays-Bas* **107** (1988) 641.
[24] A. R. Katritzky, W. Kuzmierkiewicz, B. Rachwal, S. Rachwal, J. Thomson, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 811.
[25] R. Mazurkiewicz, T. Kiersznicki, *Pol. J. Chem.* **55** (1981) 547.
[26] M. R. Detty, G. P. Wood, *J. Org. Chem.* **45** (1980) 80.
[27] J. E. Mills, R. M. Cosgrove, R. D. Shah, C. A. Maryanoff, V. Paragamian, *J. Org. Chem.* **49** (1984) 546.
[28] C. Gerhardt, *Liebigs Ann. Chem.* **108** (1858) 214.
[29] P. G. Houghton, D. F. Pipe, C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 1471.
[30] T. G. Schenck, B. Bosnich, *J. Am. Chem. Soc.* **107** (1985) 2058.
[31] M. Fukuda, Y. Okamoto, H. Sakurai, *Bull. Chem. Soc. Jpn.* **50** (1977) 1895.
[32] J. R. Shroff, B. Elpern, S. Kobrin, P. Cervoni, *J. Med. Chem.* **25** (1982) 359.
[33] L. M. Litvinenko, V. A. Mikhailov, L. P. Drizhd, V. A. Savelova, E. N. Kryuchkova, *J. Org. Chem. USSR (Engl. Transl.)* **20** (1984) 1139.
[34] A. Chandler, A. F. Hegarty, M. T. McCormack, *J. Chem. Soc., Perkin Trans, 2*, **1980**, 1318.
[35] A. K. Sheinkman, I. Yu. Kozak, B. P. Zemskii, *Khim. Geterotsikl. Soedin.* **1983**, 955; *Chem. Heterocycl. Compd. (Engl. Transl.)* **1983**, 768.
[36] D. M. Malenko, L. A. Repina, A. D. Sinitsa, *J. Gen. Chem. USSR (Engl. Transl.)* **54** (1985) 1925.
[37] M. Kosugi, M. Koshiba, A. Atoh, H. Sano, T. Migita, *Bull. Chem. Soc. Jpn.* **59** (1986) 677.
[38] R. Singh, L. P. Chandrakar, R. K. Mishra, *Bull. Chem. Soc. Jpn.* **59** (1986) 1571.
[39] R. A. Abramovitch, J. Pilski, *J. Org. Chem.* **48** (1983) 4391.
[40] M. H. Palmer, R. H. Findlay, S. M. F. Kennedy, P. S. McIntyre, *J. Chem. Soc., Perkin Trans. 2*, **1975**, 1695.
[41] A. R. Katritzky, K. Yannakopoulou, W. Kuzmierkiewicz, J. M. Aurrecoechea, G. J. Palenik, E. A. Koziol, M. Szczesniak, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 2673.
[42] M. Begtrup, R. M. Claramunt, J. Elguero, *J. Chem. Soc., Perkin Trans 2*, **1987**, 99.
[43] F. J. Lalor, F. L. Scott, *J. Chem. Soc. C*, **1969**, 1034.
[44] V. A. Lopyrev, L. I. Larina, T. I. Vakulskaya, M. F. Larin, O. B. Nefedova, E. F. Shibanova, M. G. Voronkov, *Org. Magn. Reson.* **15** (1981) 219.
[45] A. A. Konstantinchenko, A. S. Morkovnik, A. F. Pozharskii, B. A. Tertov, *Khim. Geterotsikl. Soedin.* **12** (1985) 1694; *Chem. Heterocycl. Compd. (Engl. Transl.)* **12** (1985) 1398.
[46] K. Itoh, H. Ishida, H. Chikashita, *Chem. Lett.* **1982**, 1117.
[47] M. F. Belicchi, G. G. Fava, C. Pelizzi, *J. Chem. Soc., Dalton Trans.* **1983**, 65.
[48] S. M. Ramos, M. Terazi, J. D. Wuest, *J. Org. Chem.* **52** (1987) 5437.
[49] S. F. Nelsen, E. L. Clennan, L. Echegoyan, L. A. Grezzo, *J. Org. Chem.* **43** (1978) 2621.
[50] A. P. de Jonge, B. Van der Ven, W. den Hertog, *Recl. Trav. Chim. Pays-Bas* **75** (1956) 5.
[51] A. U. Rahman, M. A. Medrano, B. E. Jeanneret, *J. Org. Chem.* **27** (1962) 3315.
[52] S. S. Nigam, B. C. L. Weedon, *J. Chem. Soc.* **1957**, 3320.
[53] A. T. Balaban, A. Dinculescu, J. Elguero, R. Faure, *Magn. Reson. Chem.* **23** (1985) 553.
[54] R. E. Carter, *Acta Chem. Scand.* **21** (1967) 75.
[55] H. H. Vogt, R. Gompper, *Chem. Ber.* **114** (1981) 2884.
[56] M. Imanari, M. Kohno, M. Ohuchi, K. Ishizu, *Bull. Chem. Soc. Jpn.* **47** (1974) 708.

[17/90]