Russian Journal of Organic Chemistry, Vol. 40, No. 2, 2004, pp. 174–177. Translated from Zhurnal Organicheskoi Khimii, Vol. 40, No. 2, 2004, pp. 199–203.
Original Russian Text Copyright © 2004 by Vasil'eva, Kuz'mina, Chakhovskaya, Mysova, Terent'ev.

Addition of α-Halo-substituted Carbonitriles to and AldehydesKetones in the Presence of Iron Pentacarbonyl

T. T. Vasil'eva, N. A. Kuz'mina, O. V. Chakhovskaya, N. E. Mysova, and A. B. Terent'ev

Nesmeyanov Institute of Organoelemental Compounds, Russian Academy of Sciences, Moscow, 119991 Russia
e-mail: terent@ineos.ac.ru

Received October 2, 2002

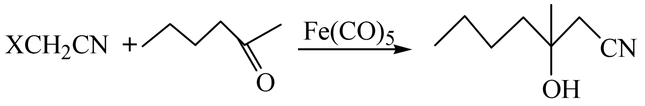
Abstract—Halo-substituted carbonitriles in the presence of iron pentacarbonyl react with aldehydes and ketones by Reformatsky reaction type. In contract to halo-substituted esters the nitriles are considerably more reactive toward ketones than aldehydes. At the same time the structure and yield of products obtained from both nitriles and esters are strongly and similarly affected by the character of the *para*-substituents in the benzaldehyde.

We showed formerly [1], that the addition of α-halo-substituted carboxylic acids esters to aldehydes and ketones by Reformatsky reaction type can be performed in good yields in homogeneous medium in the presence of iron pebtacarbonyl (heating at reflux of the reagents mixture in benzene for 2–3 h). This procedure furnished β-hydroxyacids esters or the corresponding derivatives of acrylic acids esters. Therewith the reaction with aldehydes was found to occur very efficiently, and with ketones more difficultly. It was shown besides that reactions with *para*-substituted benzaldehydes were notably affected by the polar character of the substituents: the process with *p*-chlorobenzaldehyde proceeded like that with benzaldehyde or even better to give hydroxyacids esters whereas anisaldehyde either could not be involved into the reaction or affords only unsaturated products [2] (formally arising from hydroxyesters dehydration).

In this study we used for the first time an iron pentacarbonyl to effect reactions of α-halo-substituted nitriles with aldehydes and ketones by Reformatcky reaction type planning to obtain β-hydroxynitriles and further aminoalkohols, synthons for preparation of a number of biologically active substances [3]. It turned out unexpectedly that behavior of nitriles in reactions involving $Fe(CO)_5$ was essentially unlike that of esters, in contrast to reactions of Reformatsky type carried out in the presence of cromium(II) salts [4].

We brought into the reaction of halonitriles **I** with carbonyl compounds substrates of dissimilar reactivity: acetonitriles substituted by iodine **Ia** and bromine **Ib**, dibromoacetonitrile **Ic**, and 2-bromopropionitrile **Id**. As carbonyl compounds **II** were applied 2-hexanone **IIa**, acetophenone **IIb**, cyclopentanone **IIc**, benzaldehyde **IId**, *p*-chlorobenzaldehyde **IIe**, *p*-methoxybenzaldehyde **IIf**, and pivalaldehyde **IIg.**

Nitriles **Ia, b** with ketone **IIa** afforded hydroxynitrile **III**. Therewith at the use instead of the highly reactive iodide **Ia** less active bromide **Ib** the yield of product **III** decreased from 70 to 23%. The reaction proceeds along the scheme:

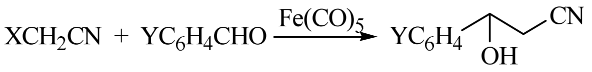


Ia, b **IIa** **III**

I, X = I (**a**), Br (**b**).

These reactions proceeded in the same manner with acetophenone **IIb** although the yield was low even with the active iodide **Ia**. As a result were obtained 3-hydroxy-3-phenylbutyronitrile **IV** and a product of acetophenone aldol condensation. The addition of benzaldehyde **IId** occurred unexpectedly inefficiently affording the corresponding hydroxynitrile **Va** in a low yield (5–8%).

The process involving aldehyde **IIe** occurred selectively and gave adduct **Vb** in a high yield whereas with anisaldehyde (**IIf**, Y = OMe) under the same conditions only the product of a formal dehydration, 3-(*p*-methoxyphenyl)acrylonitrile **VI,** was obtained in a yield as low as 12%.

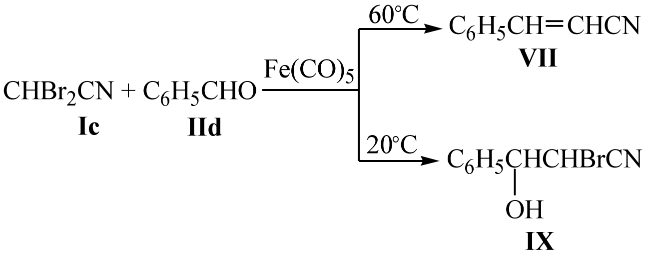


Ia, b **IId, e** **Va, b**

II, Y = H (**d**), Cl (**e**); V, Y = H (**a**), Cl (**b**).

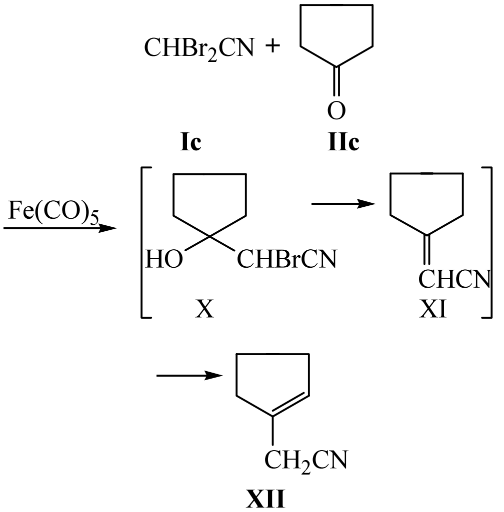
1070-4280/04/4002-0174©2004 MAIK "Nauka/Interperiodica"

The most reactive of the nitriles studied, dibromoacetonitrile **Ic,** afforded the target products in good yield both with benzaldehyde **IId** and methyl butyl ketone **IIa**, in somewhat lesser yield with cyclopentanone **IIc**. However the reactoins carried out at 60°C resulted only in unsaturated compounds (due to elimination of Br and OH). In particular, from benzaldehyde cynnamonitrle **VII**, and from ketone **IIa** 3-methyl-2-heptenylcyanide **VIII** were obtained. Only at room temperature we succeeded to prepare in plausible yield benzaldehyde adduct **IX**.



Reactions with *p*-chloro- and *p*-methoxybenzaldehyde gave rise to *p*-chloro **VIIa** and *p*-methoxy **VIIb** derivatives of nitrile **VII.**

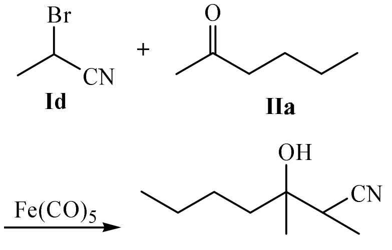
We believe that in reaction with cyclopentanone the intermediately formed adduct **X** loses BrOH and the arising cyclopentylideneacetonitrile **XI** rearranges with a double bond migration into the ring to afford unsaturated adduct **XII** whose structure is proved by the spectral data.



XII

The difference and similarity in the behavior of haloesters [1] and the corresponding halonitriles studied here is the most clearly seen by an example of reactions between 2-bromopropionitrile **Id** with aldehydes and ketones. Nitrile **Id** reacts both with ketone **IIa** providing hydroxynitrile **XIII** and with aldehyde **IId** giving adduct **XIV**, but in the former case the hydroxynitrile yield is twice as large as in the latter.

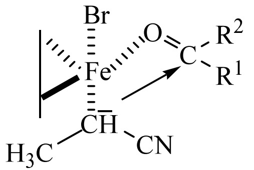
The situation in analogous reactions of methyl bromopropionate [1] is quite the opposite: the yield with benzaldehyde is considerably higher than with methyl butyl ketone.



XIII

With the sterically hindered carbonyl compounds, acetophenone **IIb** and pivalaldehyde **IIg**, both bromopropionitrile **Id** and methyl bromopropionate [1] are approximately equally reactive furnishing adducts **XV** and **XVI** in about 30% yield. A similar behavior of esters and nitriles is also observed in reactions with the *para*-substituted benzaldehydes. In reactions of haloacetonitriles **Ia, b** and of bromopropionitrile **Id** *with p*-chlorobenzaldehyde **IId** the yield of hydroxynitriles **Vb** and **XVII** attained about 60–90%, whereas with *p*-methoxybenzaldehyde **IIe** formed only the corresponding derivatives of acrylonitrile **VI** or of adduct **XVIII** in 12–30% yield.

The probable reason of the different behavior demonstrated by nitriles and esters in the reactions under study lies in the analogy with a mechanism we suggested previously [2] that involves the reaction between halonitrile and iron pentacarbonyl to form a radical followed by its reduction to carbanion; the latter in the transition state of **A** type attacks the C=O group of the electrophile.



A

Inasmuch as the cyano group is considerably stronger electron-acceptor than alkoxycarbonyl group the reaction site of nitrile is more electron-deficient and naturally should react better with the electrophile possessing higher relative electron density on its reaction site, namely, with ketone.

To the same result should lead the probable change in the reaction mechanism towards prevalence of the radical character in the intermediate species due to stabilization of radicals with a neighboring nitrile group arising in the first stage [reaction of $Fe(CO)_5$ with halogenated substrate]. In this case the side reaction involving hydrogen abstraction by radicals from the carbonyl compound that competes with radical reduction into a carbanion should occur more readily just with aldehydes.

Hence the application of the iron pentacarbonyl permits a successful performance under relatively simple homogeneous conditions (boiling of the reagents mixture in benzene for 3–4 h), without anhydrous solvents or inert gas atmosphere, of Reformatsky type reaction involving halo-substituted nitriles and furnishing in good or plausible yields the corresponding hydroxynitriles that can be easily converted into aminoalcohols [3]. Taking into account that nitriles and esters can easily be interconverted the reactions described affording hydroxy derivatives of nitriles and esters well supplement each other. The syntheses with aldehydes are more favorable with haloesters, with aliphatic ketones the reactions with halonitriles are more feasible.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were registered on spectrometer Bruker WP-200 (200 MHz) from solutions in $CDCl_3$. Chemical shifts are presented in δ scale with respect to Me_4Si. Mass spectra were measured on GC-MS instrument FINNIGAN MAT MAGNUM, column 25 long (Ultra-2), temperature programmed in the range 30–220°C at a rate 2.5 deg min^{-1}. GLC analysis was carried out on chromatograph LKhM-80 equipped with a steel column (1300×3 mm), stationary phase 15% SKTFT-50X on Chromaton-N-AW, carrier gas helium, flow rate 60 $cm^3 min^{-1}$), detector katharometer, temperature programmed in the range 50–250°C at a rate 6 deg min^{-1}. All organic reagents were purified by distillation, $Fe(CO)_5$ from FLUKA (97%) was used without additional purification.

Experimental procedure. A solution of a mixture of a halide (1 mmol), a carbonyl compound (1 mmol), $Fe(CO)_5$ (2 mmol), CCl_3Br (1–2 drops in reactions of monobromides) in benzene (2ml) was heated for 3–4 h at 80°C (in reactions with monohalides) or was left standing at room temperature for 24 h (in case of dibromoacetonitrile). Then the reaction mixture was diluted with benzene (2 ml), treated with 1 N hydrochloric acid, washed with water, and dried on $MgSO_4$. The products were isolated by preparative GLC or TLC (eluent petroleum ether–chloroform–ethyl acetate, 8 : 1 : 1). The yields were determined by GLC with respect to a reference compound.

Reaction of iodoacetonitrile with carbonyl compounds. 3-Hydroxy-3-methylenanthonitrile **III** (isolated by preparative GLC), yield 70%, n_D^{20} 1.4450, d_4^{20} 0.9349. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.56 s (1H, OH), 2.44 s (2H, CH_2CN), 1.50, 1.25 both m ($3CH_2$), 1.27 s (3H, $\underline{CH_3}C$), 0.84 t (3H, CH_3, J 3). ^{13}C NMR spectrum, δ, ppm: 118.6 (CN), 71.7 (COH), 41.9 ($\underline{CH_2}CN$), 31.8, 27.2, 26.6 ($3CH_2$), 23.6 ($\underline{CH_3}C$), 14.6 ($\underline{CH_3}CH_2$). Mass spectrum, *m/z* (I_{rel},%): 126 $[M–CH_3]^{+\cdot}$ (6), 101 $[M–CH_2CN]^+$ (23), 84 $[M–C_4H_9]^{+\cdot}$ (100), 57 $[C_4H_9]^+$ (20), 43 $[C_3H_7]^+$ (87). Found, %: C 68.20; H 10.73; N 9.91. $C_8H_{15}NO$.

Calculated, %: C 68.04; H 10.70; N 9.92.

3-Hydroxy-3-phenylpropionitrile **Va** [5], yield 8%. Mass spectrum, *m/z* (I_{rel}, %): 147 $[M]^+$ (19.0), 129 $[M–O]^+$ (65.0), 107 $[M – CH_2CN]^+$ (100.0), 77 $[C_6H_5]^+$ (85.0); cinnamonitrile (mixture of *cis-trans*-isomers). Mass spectrum, *m/z* (I_{rel}, %): 129 $[M]^+$ (100), 102 $[M – HCN]^+$.

3-Hydroxy-3-(*p*-chloropphenyl)propionitrile **Vb** (cf. [5]), yield 55%. Mass spectrum, *m/z* (I_{rel}, %): 181 $[M]^+$ (8.0), 163 $[M – H_2O]^+$ (32.0), 141 $[M–CH_2CN]^+$ (100.0), 113 $[C_6H_4Cl]^+$ (36.0).

3-(*p*-Methoxyphenyl)acrylonitrile **VI**, yield 12%. Mass spectrum, *m/z* (I_{rel}, %): 159 $[M]^+$ (100.0), 144 $[M – CH_3]^{+\cdot}$ (35.0), 129 $[C_6H_5CH{=}CHCN]^+$ (10.0).

3-Hydroxy-3-phenylbutyronitrile **IV**, yield 10%. Mass spectrum, *m/z* (I_{rel},%): 161 $[M]^+$ (**IV**), yield 10%. Mass spectrum, *m/z* (I_{rel}, %): 161 $[M]^+$ (1), 143 $[M–H_2O]^+$ (23), 121 $[M–CH_2CN]^+$, 105 $[C_6H_5CO]^+$ (30), 77 $[C_6H_5]^+$ (35), 43 $[CH_3CO]^+$ (100).

1-Oxo-1,3-diphenyl-2-butene, yield 5%. Mass spectrum, *m/z* (I_{rel}, %): 222 $[M]^{+\cdot}$ (100), 207 $[M – CH_3]^+$ (12), 145 $[M – C_6H_5]^+$(15), 117 $[C_6H_5C_3H_4]^+$ (17), 105 $[C_6H_5CO]^+$ (20), 77 $[C_6H_5]^+$ (15).

Reaction of bromoacetonitrile with carbonyl compounds. 3-Hydroxy-3-methylenanthonitrile **III**, yield 23%. 3-Hydroxy-3-phenylpropionitrile **Va**, yield 5%. 3-Hydroxy-3-(*p*-chlorophenyl)propionitrile **Vb**, yield 48%. 3-(p-methoxyphenyl)acrylonitrile **VI**, yield 12%.

Reaction of dibromoacetonitrile with carbonyl compounds. 3-Methyl-2-heptenenitrile **VIII** (mixture of *cis*- and *trans*-isomers 1:2.5), yield 78% (run at 60°C, 3 h), n_D^{20} 1.4519, d_4^{20} 0.8408. ^1H NMR spectrum, δ , ppm (*J,* Hz): 0.87, 0.90 both t (3H, $\underline{CH_3}CH_2$, *J* 6, 4), 1.25–1.48 m (4H, CH_2CH_2), 1.85, 2.00 both s (3H, CH_3C), 2.13, 2.36 both t [2H, CH_2C, *J* 8 (both)], 5.05 s (1H, CH=). ^{13}C NMR spectrum, δ, ppm: 166.4, 166.2 (CN), 117.7, 117.9 (C=), 96.1, 95.6 (CH=), 36.6, 39.0 ($\underline{CH_2}C$), 30.3, 29.8 (CH_2), 21.6, 22.8 ($\underline{CH_2}CH_3$), 22.9, 23.4 ($\underline{CH_3}C$), 14.4 ($\underline{CH_3}CH_2$). Mass spectrum, *m/z* (I_{rel}, %): 123 $[M]^+$ (12), 95 $[M–C_2H_4]^+$ (10), 81 $[M–C_3H_6]^+$ (100), 56 $[C_4H_8]^{+\cdot}$ (42). Found, %: C 77.95; H 10.43; N 11.45. $C_8H_{13}N$. Calculated, %: C 78.00; H 10.69; N 11.37. The same nitrile formed in the experiment carried out at room temperature for 24 h

Cinnamonitrile **VII** (run at 60°C, 3 h), yield 70%, mixture of *cis*- and *trans*-isomers (1:2.5). ^1H NMR spectrum, δ, ppm (*J,* Hz): (one of isomers): 5.77, 5.85 d (1H, CH=, *J* 16), 7.04, 7.10 d (1H, CH=, *J* 12). Mass spectrum, *m/z*(I_{rel}, %): 129 $[M]^+$ (100), 102 $[M – HCN]^{+\cdot}$ (37), 51 $[CHCCN]^+$ (15).

3-Hydroxy-3-phenyl-2-bromopropionitrile **IX** (room temperature, 24 h), yield 46% (isolated by TLC). Mixture of diastereomers, 1:1. ^1H NMR spectrum, δ, ppm (*J,* Hz): 3.45 br.s (1H, OH), 4.40, 4.42 d (1H, CHBr, *J* 4), 4.91, 4.94; 4.97, 4.99 both d (1H, $\underline{CH}OH$, *J* 6, 4). ^{13}C NMR spectrum, δ, ppm: 15.9, 116.2 (CN), 75.3, 75.5 (CHO), 35.0, 35.5 (CHBr). Mass spectrum, *m/z* (I_{rel}, %): 129 $[M–BrOH]^+$ (95), 107 $[C_6H_5CHOH]^+$ (100), 77 $[C_6H_5]^+$ (70).

p-Chlorocinnamonitrile **VIIa** (run at 60°C, 3 h), yield 50%, mixture of *cis*- and *trans*-isomers (1:3). ^1H NMR spectrum, δ, ppm (*J,* Hz): (one of isomers) 5.17, 5.23; 6.78, 6.85 both d (1H each, CH=, *J* 12 and 14), 7.71 m (4H, Ar). ^{13}C NMR spectrum, δ, ppm: 149.8, 97.6 (2CH=), 118.5 (CN). Mass spectrum, *m/z* (I_{rel}, %): 163, 165 $[M]^+$ (100.0, 36.6), 136 $[M–HCN]^{+\cdot}$ (12.8), 128 $[M–Cl]^{+\cdot}$ (64.4).

p-Methoxycinnamonitrile **VIIb** (run at 60°C, 3 h), yield 10%, mixture of *cis*- and *trans*-isomers (1:1.5). Mass spectrum, *m/z* (I_{rel}, %): 159 $[M]^+$ (100.0), 144 $[M– CH_3]^{+\cdot}$ (18.1), 116 $[M–H_3OC]^{+\cdot}$ (30.7), 102 $[M– OCH_3]^{+\cdot}$ (2.6), 89.

1-Cyclopentenylacetonitrile **XII**, yield 30%. ^1H NMR spectrum, δ, ppm (*J,* Hz): 1.21 s (CH_2CN, 2H), 1.74 t (2H, CH_2, *J* 2), 2.41, 2.55 both mCH_2), 5.18 t (1H, CH=, *J* 2.3). Mass spectrum, *m/z* (I_{rel}, %): 107 $[M]^+$ (28), 80 $[M – HCN]^{+\cdot}$ (15), 41 $[C_3H_5\ , CH_3CN]^+$ (100).

Reaction of 2-bromopropionitrile with carbonyl compounds. 3-Hydroxy-2,3-dimethylenanthonitrile **XIII**, yield 79% (isolated by preparative GLC). ^1H NMR spectrum, δ, ppm (*J,* Hz): 0.87 t (3H, $\underline{CH_3}CH_2$, *J* 4), 1.21, 1.26 both s (6H, $\underline{CH_3}C$, $\underline{CH_3}CH$), 1.27–1.65 m (6H, 3 CH_2), 2.02 s (OH), 2.65 m (CH). ^{13}C NMR spectrum, δ, ppm: 122.3 (CN), 73.3, 73.4 (CO), 39.8, 39.9 (CH), 37.3, 37.7 ($\underline{C}H_2C$), 26.1, 26.2, 23.6 (2 CH_2), 24.4, 24.7 ($\underline{C}H_3C$), 14.5, 14.6 ($\underline{C}H_3CH$), 13.2, 13.6 ($\underline{C}H_3CH_2$). Mass spectrum, *m/z* (I_{rel}, %): 155 $[M]^+$ (0), 140 $[M–CH_3]^{+\cdot}$ (7), 101 $[C_4H_9C(OH)CH_3]^+$ (88), 98 $[M – C_4H_9]^{+\cdot}$ (99), 85 $[C_4H_9CO]^+$ (28), 83 $[M – C_4H_9–CH_3]^+$ (36), 56 $[C_4H_8]^{+\cdot}$ (100), 43 $[CH_3CO]^+$ (92). Found, %: C 70.04; H 10.96; N 9.18. $C_9H_{17}NO$. Calculated, %: C 69.68; H 10.97; N 9.03.

3-Hydroxy-3-phenyl-2-methylpropionitrile **XIV**, yield 38% (isolated by preparative GLC). ^1H NMR spectrum, δ, ppm (*J,* Hz): 1.12, 1.13, 1.15, 1.16 d.d (3H, $\underline{CH_3}CH$, both *J* 2), 2.87 m (CHCN), 3.31 br.s (1H, OH), 4.58, 4.62, 4.66, 4.70 d.d (1H, $\underline{CH}OH$, both *J* 8), 7.2–7.4 (C_6H_5). ^{13}C NMR spectrum, δ, ppm: 127.1, 127.2 (CN), 74.8, 75.5 (CO), 34.7, 35.3 (CH), 15.4, 15.8 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 161 $[M]^+$ (1), 143 $[M – H_2O]^+$ (4), 107 $[C_6H_5CHOH]^+$ (100), 77 $[C_6H_5]^+$ (28). Found, %: C 73.50; H 6.65; N 8.23. $C_{10}H_{11}NO$. Calculated, %: C 74.50; H 6.88; N 8.69.

3-Hydroxy-3-(*p*-chlorophenyl)-2-methylpropionitrile **XVII**, yield 90%. ^1H NMR spectrum δ, ppm (*J,* Hz): 2.65, 2.68 d (2H, CH_2, *J* 6), 3.15 br.s (1H, OH), 4.93 t (1H, CH, *J* 6), 7.23–7.33 m (Ar). Mass spectrum, *m/z* (I_{rel}, %): 195 $[M]^+$ (0), 177 $[M–H_2O]^+$ (8), 141, 143 $[M–CH_3CHCN]^+$ (100), 111, 113 $[ClC_6H_4]^+$ (17), 77 $[C_6H_5]^+$ (69), 55 $[CH_3CH_2CN]^{+\cdot}$ (10).

3-Hydroxy-3-(*p*-methoxyphenyl)-2-methylbutyronitrile **XVIII**, yield 30%. Mass spectrum, *m/z* (I_{rel}, %): 191 $[M]^+$ (5), 173 $[M–H_2O]^+$ (45), 137 $[M–CH_3CHCN]^+$ (100).

3-Hydroxy-3-phenyl-2-methylbutyronitrile **XV**, yield 34%. Mass spectrum, *m/z* (I_{rel}, %): 157 $[M – H_2O]^+$ (8), 121 $[C_6H_5C(CH_3)OH]^+$ (99), 105 $[C_6H_5CO]^+$ (31), 77 $[C_6H_5]^+$ (30), 43 $[CH_3CO]^+$ (100).

3-Hydroxy-2,4,4-trimethylvaleronitrile **XVI**, yield 35% Mass spectrum, *m/z* (I_{rel}, %): 141 $[M]^+$ (0), 108 $[M – CH_3–H_2O]^{+\cdot}$ (1), 87 $[(CH_3)_3–CHOH]^+$ (23), 58 $[C_4H_{10}]^{+\cdot}$ (49), 57 $[C_4H_9]^+$ (100), 41 $[C_3H_5]^+$ (35).

REFERENCES

1. Terent'ev, A.B., Vasil'eva, T.T., Kuz'mina, N.A., Mysov, E.I., Kuznetsov, N.Yu., and Belokon', Yu.N., *Izv. Akad. Nauk, Ser. Khim.,* 1999, p. 1132.
2. Terent'ev, A.B., Vasil'eva, T.T., Kuz'mina, N.A., Mysova, N.E., and Chakhovskaya, O.V., *Zh. Org. Khim.,* 2001, vol. 37, p. 1341.
3. Huang, H-L., Liu, L.T., Chen, S-F., and Ku, H., *Tetrahedron: Asymmetry,* 1998, vol. 9, p. 1637.
4. Wessjohann, L.A. and Gabriel, T., *Synthesis*, 1999, no. 1, p. 1.
5. Inaba, Sh-I. and RiekeR.D., *Tetrahedron Lett.,* 1985, vol. 26, p. 155.