Synthesis of derivatives of prenylacetic acids by reactions of alkyl malonate, cyanoacetate, and acetoacetate with alkylating reagents in ionic liquids

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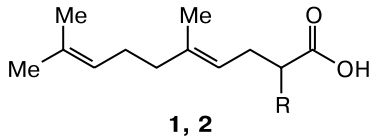
A method for the synthesis of carboxylic acid derivatives containing one or two $-CH_2CH_n(Me)CH_{n+1}CH_2-$ fragments ($n = 0, 1$) was developed. The method is based on the alkylation of (di)alkyl malonates, cyanoacetates, and acetoacetates with acyclic prenyl halides in ionic liquids, 1-butyl-3-methylimidazolium hexafluorophosphate and tetrafluoroborate. For the ambident ethyl acetoacetate anion, the reactions with prenyl halides devoid of a double bond in the allylic position relative to the halogen atom carried out in the ionic liquids give mixtures of *C*- and *O*-alkylation products, while in the case of allylic prenyl halides, only *C*-alkylation products are formed. The reactions of ethyl 2-geranylmalonate and 2-geranylacetoacetate with bromocyclohexane and 1-chloro-3-dimethylaminopropane in ionic liquids provided derivatives of pharmacologically active geranylacetic acids. The product yields are higher than those in molecular organic solvents. The ionic liquids were recovered and reused in the alkylation.

Key words: CH-acids, prenylacetic acid, prenyl halides, alkylation, ionic liquids.

Derivatives of carboxylic acids containing hydrocarbon chains composed of isoprenoid units exhibit useful types of biological activity. In the series of acyclic isoprenoid acids, insect pheromones[1] or insecticides[2] and compounds possessing wound healing,[3—5] antiulcerogenic,[6] antitumor,[7] and some other types of pharmocological activities[8] have been synthesized. Drugs based on synthetic isoprenoids usually combine valuable therapeutic properties with a moderate or low toxicity, which is, apparently, due to the structural similarity of these compounds to natural products, in particular, vitamins of groups A, E, and K.[6—8]

A common method for the synthesis of (poly)prenylacetic acids is based on alkylation of dialkyl malonates and alkyl cyanoacetates and acetoacetates with halogen derivatives of acyclic isoprenoids.[9—12] These reaction is used, in particular, in the key step of the synthesis of 2-cyclohexyl-5,9-dimethyldeca-4,8-dienoic acid (**1**), which is an active component of a wound healing formula manufactured in the USSR in 1957—1990 under the trade name Tsigerol.[3—5] Alkylation of diethyl malonate with geranyl and farnesyl chlorides[10,11] has been used to prepare amino acid derivatives of these terpenoids (for example, compound **2**), which were patented as drugs favoring healing of the postinfarction scar on the cardiac muscle.[12]



1, 2

R = *cyclo*-C_6H_{11} (**1**), $(CH_2)_3NMe_2$ (**2**)

In the known protocols for alkylation of dialkyl malonates and alkyl acetoacetates with halogen derivatives of acyclic isoprenoids, alkali metals or alkali metal alkoxides are used to generate the CH-acid anions and the reaction is carried out in an anhydrous solvent (ethanol, xylene).[9—11] These reagents and solvents are acceptable in the laboratory but they bring about engineering and environmental problems when used in industry (in particular, they are fire hazardous). An alternative approach to the synthesis of prenylacetic acid derivatives by alkylation of diethyl malonate and ethyl acetoacetate with prenyl halides in dipolar aprotic solvents (DMF, DMSO) in the presence of phase transfer catalysts has not received wide use, probably, due to difficulties associated with product isolation.[13,14]

In recent years, liquid and low-melting salts of organic cations with anions of perfluorinated acids (the so-called "ionic liquids") have attracted considerable attention as environmentally safe solvents and catalysts of

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 622—628, March, 2004.

1066-5285/04/5303-0652

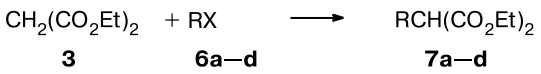
liquid-phase chemical reactions.[15—17] Many of these are stable, nonvolatile, and incombustible and can be recovered and reused.[18—20]

Recently, we have reported a method for alkylation of CH-acids with alkyl halides in an ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]).[21] The use of [bmim][PF_6] allowed us to perform this reaction under the action of a safe and easy-to-handle base (K_2CO_3) and to obtain alkylation products in comparable or higher yields than in conventional organic solvents.[21]

The aim of the present work was to study the prospects for the use of ionic liquids of the imidazole series as solvents in the reactions of diethyl malonate (**3**), ethyl cyanoacetate (**4**), and ethyl acetoacetate (**5**) with halogen derivatives of acyclic C_5 and C_{10} isoprenoids and to obtain precursors of pharmacologically active prenylacetic acids **1** and **2**.

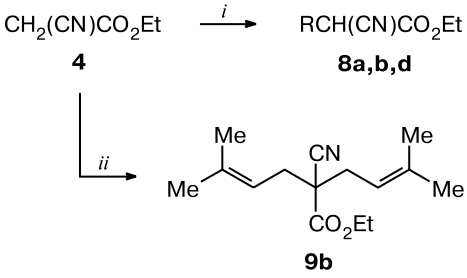
1-Bromo-3-methylbutane (**6a**), 1-chloro-3-methylbut-2-ene (**6b**, X = Cl), and 1-bromo-3-methylbut-2-ene (**6b**, X = Br) served as C_5 alkylating agents. 8-Chloro-2,6-dimethyloct-2-ene (**6c**, X = Cl), 8-bromo-2,6-dimethyloct-2-ene (**6c**, X = Br), and 1-chloroocta-3,7-dimethyl-2,6-diene (**6d**) were used as C_{10} blocks. The alkylation was carried out in the ionic liquids [bmim][PF_6][22] and [bmim][BF_4][23] with K_2CO_3 or $LiOH \cdot H_2O$ as deprotonating agents.

The reactions of diethyl malonate **3** and ethyl cyanoacetate **4** with the above-mentioned C_5- and C_{10}-prenyl halides in [bmim][PF_6] and [bmim][BF_4] resulted in the derivatives of the corresponding isoprenoid acids (**7a—d** and **8a,b,d**) in 53—70% yields (Tables 1 and 2). Changes in the base and the anion of the imidazolium salt influence only slightly the yields of the alkylation products, although reactions involving $LiOH \cdot H_2O$ proceed under milder conditions than analogous reactions in the presence of K_2CO_3. When 2.2 equivalents of prenyl bromide **6b** (X = Br) react with CH-acid **4**, a double alkylation product (**9b**) is formed.



3 **6a—d** **7a—d**

Reagents: 3 (1 equiv.), **6a—d** (1 equiv.), base (2 equiv.), [bmim][PF_6] (6 equiv.).



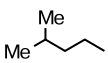
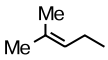
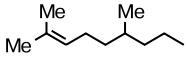
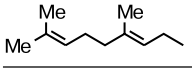
9b

Reagents: *i*. **4** (1 equiv.), **6a,b,d** (1 equiv.), base (2 equiv.), [bmim][L] (6 equiv.); *ii*. **4** (1 equiv.), **6b** (X = Br) (2 equiv.), $LiOH \cdot H_2O$ (2 equiv.), [bmim][BF_4] (6 equiv.).

The alkylation of the ambident anion of ethyl acetoacetate **5** with prenyl halides **6a** and **6c** (X = Cl, Br) containing no double bonds in allylic position relative to the halogen atom in ionic liquids, unlike similar reactions in alcohols,[27,28] affords not only the *C*-alkylation products (**10a,c**), but also the corresponding vinyl ethers (**11a,c**) (Table 3). The **10c** : **11c** ratio decreases if a less reactive alkyl halide (for example, **6c** (X = Cl)) is used instead of **6c** (X = Br). The reactions of compound **5** with allylic alkylating agents, namely, 1-chloro-3-methylbutene **6b** (X = Cl) and geranyl chloride **6d**, in the ionic liquids [bmim][PF_6] and [bmim][BF_4], like those in ethanol,[29,30] furnish only *C*-alkylation products (**10b,d**).

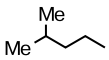
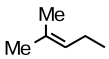
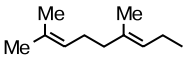
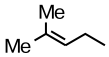
The results obtained agree with the modern views on the influence of the structure of the alkylating agent and

Table 1. Alkylation of diethyl malonate **3** with prenyl halides **6a—d** in [bmim][PF_6]

R	X	Base	τ/h	*T*/°C	Product	Yield (lit. data)*
	Br	K_2CO_3	15	110	**7a**	70 (80[a], 72[b])
	Cl	K_2CO_3	5	90	**7b**	53 (50[a], 46[c])
	Br	K_2CO_3	6	120	**7c**	54 (43[a])
	Cl	$LiOH \cdot H_2O$	2	20	**7d**	63 (52[a])

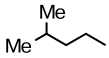
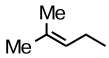
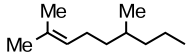
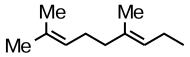
* **Reagents and conditions:** [a] **3** : **6a—d** : EtONa = 1 : 1.5 : 1.5, EtOH, 78 °C, 4—10 h.[24]
[b] **3** : **6a** : K_2CO_3 : BTEA-Cl = 1 : 1.5 : 1.5 : 0.1, DMF, 60 °C, 6 h.[13]
[c] **3** : **6b** : $NaOH_{aq}$: BTEA-Cl = 1 : 1 : 2 : 0.1, DMF, 40—45 °C, 2 h.[14]

Table 2. Alkylation of ethyl cyanoacetate **4** with prenyl halides **6a,b,d** in [bmim][L]

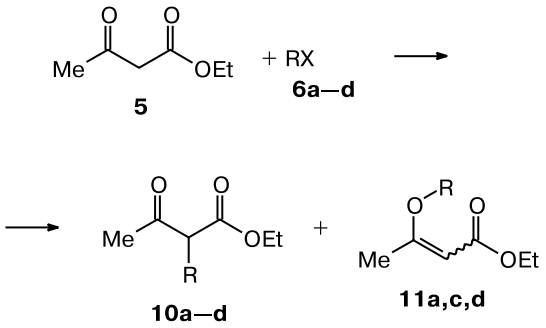
R	X	L	Base	τ/h	*T*/°C	Product	Yield (%) (lit. data)*
	Br	PF_6	K_2CO_3	15	110	**8a**	76 (76[a])
	Cl	PF_6	K_2CO_3	5	90	**8b**	53
	Br	BF_4	$LiOH \cdot H_2O$	10	20	**8b**	77(67[b])
	Cl	BF_4	$LiOH \cdot H_2O$	3	35	**8d**	54 (52[b])
	Br	BF_4	$LiOH \cdot H_2O$	5	20	**9b**	80 (38[c])

* **Reagents and conditions:** [a] **4** : **6a** : EtONa = 1 : 1.5 : 1.5, EtOH, 78 °C, 6 h (see Ref. 24).
[b] $Me_2C{=}CHCH_2OAc$: **4** : NaH : Pd(DPPE) = 1 : 2 : 1 : 0.2, THF, 65 °C, 36 h (see Ref. 24).
[c] $Me_2C{=}CH{-}CH_2SO_2Ph$: **4** : NaH : $[Mo(CO)_2(CNBu^t)_4]$ = 1 : 2 : 2 : 0.1, toluene, 110 °C, 10 h (see Ref. 26).

Table 3. Alkylation of ethyl acetoacetate **5** with prenyl halides **6a—d** in [bmim][L]

R	X	L	Base	τ/h	*T*/°C	Yield (%) and product ratio [Lit. data]*
	Br	PF_6	K_2CO_3	12	115	75, **10a** : **11a** (3 : 2) [58, **10a**][27]
	Cl	PF_6	K_2CO_3	6	90	66, **10b** [60, **10b**][29]
	Cl	PF_6	K_2CO_3	8	120	54, **10c** : **11c** (1 : 1)
	Br	PF_6	K_2CO_3	6	120	62, **10c** : **11c** (3 : 1) [54, **10c**][28]
	Cl	BF_4	K_2CO_3	6	90	56, **10d** [55, **10d**][30]
	Cl	PF_6	$LiOH \cdot H_2O$	4	20	67, **10d** [55, **10d**][30]

* EtONa (1 equiv.), EtOH, 78 °C, 2—10 h.[27—30]



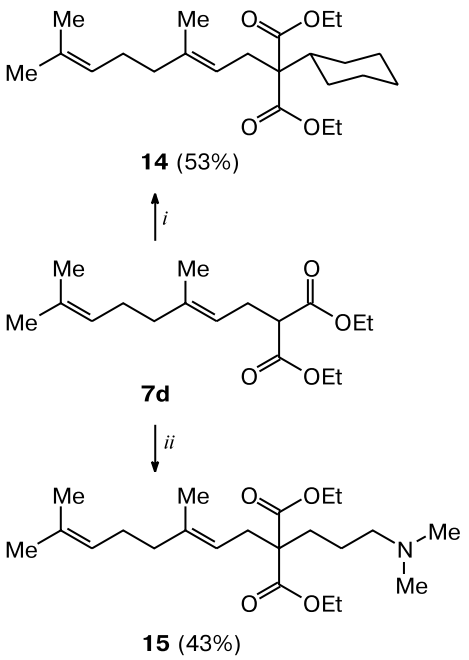
Reagents: **5** (1 equiv.), **6a—d** (1 equiv.), base (2 equiv.), [bmim][L] (6 equiv.).

the reaction conditions on the directiion of alkylation of the ambident carbanions. According to these views, the probability of alkylation at the most electronegative atom of the anion (in this case, oxygen) increases with an increase in the solvent polarity and the hardness of the leaving group of the alkylating agent (Cl > Br) and decreases if a π-bond able to interact with the electron-deficient reaction center is present in the allylic position relative to the halogen.[31—34]

The geranyl derivatives of diethyl malonate (**7d**) and ethyl acetoacetate (**10d**) were subjected to the exhaustive alkylation with bromocyclohexane (**12**) and 1-chloro-3-dimethylaminopropane (**13**) in the ionic liquids [bmim][PF_6] and [bmim][BF_4]. It was found that the introduction of the fourth substituent to the spatially crowded C(2) atom of compounds **7d** and **10d** requires rather drastic conditions, in particular, the presence of KOH as the base and a temperature of 100—120 °C. Under these conditions, ester **7d** reacts with compounds **12** and **13** to give *C*-alkylation products **14** and **15** (Scheme 1).

Ethyl 2-geranylacetoacetate (**10d**), like ethyl acetoacetate (**5**), exhibits a dual reactivity toward alkylating agents in ionic liquids. Compound **10d** reacts with bromocyclohexane (**12**) and 1-chloro-3-dimethylaminopropane (**13**) in [bmim][PF_6] or [bmim][BF_4] to give mixtures of the corresponding *C*- and *O*-alkylation products (**16**, **17** and **18**, **19**) (Scheme 2).

Scheme 1



i. **12**, KOH, [bmim][BF_4], 105 °C, 10 h; *ii*. **13**, KOH, [bmim][PF_6], 120 °C, 3 h.

The isomer pairs **16**, **17** and **18**, **19** can easily be separated into individual components by chromatography on silica gel. The proportion of the *O*-alkylation products increases with an increase in the number of hydrocarbon substituents at the α-carbon atom of the alkylating agent (steric factor). 1-Chloro-3-dimethylaminopropane (**13**) containing halogen at the terminal carbon atom reacts with compound **10d** to give a mixture of alkylation products **18** and **19** where the proportion of vinyl ether **19** does not exceed 12%, whereas the reaction of **10d** with sterically hindered cyclohexyl bromide yields a mixture of *C*- and *O*-alkylation products **16** and **17** in a 1 : 1 ratio.

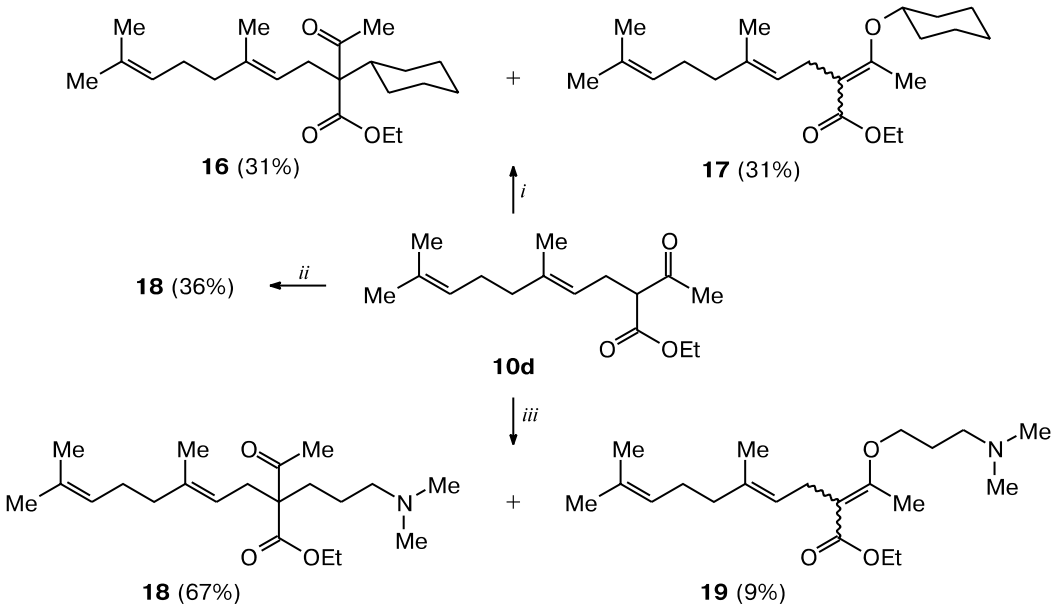
For the assessment of the influence of the medium on the yield of the *C*-alkylation product **18** in the reaction of CH-acid **10d** with alkyl halide **13**, we carried out this reaction in DMSO in the presence of a phase transfer catalyst, benzyltriethylammonium chloride (BTEA).* The reaction furnished a 4 : 1 mixture of compounds **18** and **19** in an overall yield of 45%. Thus, even with a twofold excess of the alkylating agent, the yield of compound **18** in DMSO did not exceed 36%, which is lower than in [bmim][BF_4] (67%) (see Scheme 2).

It is noteworthy that the use of [bmim][PF_6] and [bmim][BF_4] as solvents in both steps of the synthesis of compounds **14**, **15,** and **18** from CH-acids **3** and **5** (successive alkylation of **3**, **5** and **7d**, **10d**) increases the product yields based on the commercially available starting compounds **3** and **5** compared to those in reactions in common organic solvents (Table 4).

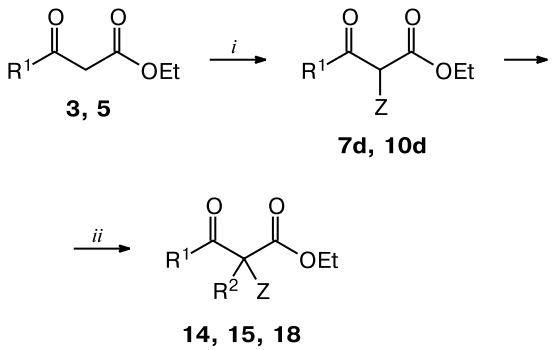
The advantages of reactions carried out in ionic liquids include the ease of isolation of products and the possibility of recovery of the ionic solvent. All the obtained compounds were isolated by extraction with ether

* The use of a phase transfer catalyst often increases the yield of the alkylation products of carbanions.[34]

Scheme 2



i. **12**, KOH, [bmim][PF_6], 100 °C, 10 h; *ii*. **13**, KOH, BTEA-Cl, DMSO, 95 °C, 2 h; *iii*. **13**, KOH, [bmim][BF_4], 120 °C, 6 h.



Reagents: *i*. **6d**, base I, solvent I; *ii*. **12** or **13**, base II, solvent II.

in which [bmim][PF_6] and [bmim][BF_4] are insoluble; the low-molecular-weight esters **7a,b**, **8a,b**, **10a,b**, and **11a** having rather low boiling points can be isolated either by extraction with ether or by direct distillation from the reaction mixture under reduced pressure. The recovery of [bmim][PF_6] and [bmim][BF_4] included separation from the insoluble inorganic salts and subsequent removal of volatile impurities under reduced pressure.[21,37] The ionic liquids recovered in this way were identical, according to ^{1}H, ^{31}P, ^{13}C, and ^{19}F NMR spectra, to freshly prepared [bmim][PF_6] and [bmim][BF_4] samples. They did not contain organic compounds in amounts detectable by ^{1}H and ^{13}C NMR spectra and were suitable for conducting reactions with the same or other CH-acids and alkylating agents without decreasing the selectivity or product yields. For example, the same sample of [bmim][PF_6] recovered after each run was used successively as the solvent in the preparation of compounds **7a**, **7b**, **7d**, **8a**, and **10a** + **11a**,

Table 4. Yields of derivatives of prenylacetic acids **14**, **15**, and **18** in ionic liquids [bmim][PF_6], [bmim][BF_4] and in conventional organic solvents

Compound	R^1	R^2	Base I (II)	Solvent I (II)	Yield[a] (%)
14	OEt	*cyclo*-C_6H_{11}	$LiOH \cdot H_2O$ (KOH)	[bmim][PF_6] ([bmim][BF_4])	33
14[b]	OEt	*cyclo*-C_6H_{11}	EtONa (Na)	EtOH ($PhCH_3$)	23
15	OEt	$(CH_2)_3NMe_2$	$LiOH \cdot H_2O$ (KOH)	[bmim][PF_6] ([bmim][PF_6])	27
15[b]	OEt	$(CH_2)_3NMe_2$	EtONa (Na)	EtOH ($PhCH_3$)	21
18	Me	$(CH_2)_3NMe_2$	$LiOH \cdot H_2O$ (KOH)	[bmim][PF_6] ([bmim][BF_4])	45
18[c]	Me	$(CH_2)_3NMe_2$	EtONa (KOH)	EtOH (DMSO)	20

[a] Based on diethyl malonate **3** and ethyl acetoacetate **5**.
[b] Refs. 22, 35, and 36.
[c] Ref. 30.

and a similar [bmim][BF_4] sample was used to prepare compounds **8b**, **9b**, **8d**, and **10d**.

Thus, we have developed a convenient method for the synthesis of prenylacetic acid derivatives based on the alkylation of diethyl malonate and ethyl cyanoacetate and ethyl acetoacetate with halogen derivatives of acyclic isoprenoids in the ionic liquids, [bmim][PF_6] and [bmim][BF_4].

Experimental

^{1}H NMR spectra were obtained on Bruker AM-300 (300.13 MHz {^{1}H}) and Bruker DRX-500 (500.13 {^{1}H}, 125.76 {^{13}C}, 470.4 {^{19}F}, 202.4 MHz {^{31}P}) instruments in $CDCl_3$ and acetone-d_6. The ^{1}H, ^{13}C, ^{19}F, and ^{31}P chemical shifts were referred to Me_4Si, acetone-d_6, $CFCl_3$, and H_3PO_4, respectively. The degree of conversion of the starting compounds and the purity of products were checked by TLC on Silufol plates using a 5% solution of ethyl acetate in benzene as the eluent and I_2 vapor for visualization.

The ratios of the *C*- and *O*-alkylation products, **10a** : **11a** and **10c** : **11c**, were determined from the ratio of the integral intensity of the ^{1}H NMR signals for the protons of the OCH_2 groups of vinyl ethers **11a**, **11c** at about δ 3.8—3.9 to the intensity of the signals for the $EtO_2C(COMe)C\underline{H}$ methine protons in 2-prenylacetoacetates **10a**, **10c** at about δ 3.3—3.4. The **16** : **17** and **18** : **19** ratios were determined from the ratio of the integral intensities of the proton signals for the OCH, COMe, and =CMe groups in the isomer mixture.

The imidazolium salts, [bmim][PF_6][22] and [bmim][BF_4],[23] were synthesized by the reported procedures. The regeneration of [bmim][PF_6] and [bmim][BF_4] was performed as described previously,[21,37] the degree of recovery being 96—98%. The parameters of the ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra of freshly prepared and recovered ionic liquids [bmim][PF_6] and [bmim][BF_4] were reported previously.[21,37]

Dimethyl sulfoxide was dried by the standard method.[38]

Reactions of compounds 3—5, 7d, and 10d with alkylating agents 6a—d, 12, and 13 in [bmim][PF_6] and [bmim][BF_4] (general procedure). CH-acid (**3—5**, **7d** or **10d**) (10 mmol) and alkylating reagent (**6a—d**, **12** or **13**) (10 mmol or, for **9b**, 20 mmol) were added successively to a stirred suspension of a base (K_2CO_3, $LiOH \cdot H_2O$ or KOH) (20 mmol) in an ionic liquid ([bmim][BF_4] or [bmim][PF_6]) (50—60 mmol). The reaction mixture was vigorously stirred under conditions indicated in Tables 1—3 and in Schemes 1 and 2. After completion of the reaction (TLC monitoring), the alkylation products were isolated by procedures *A* or *B*.

Procedure *A*. The reaction mixture was extracted with Et_2O (3×5 mL) and the combined ethereal extracts were washed with water (2×10 mL) and dried with $MgSO_4$. The solvent was removed *in vacuo* and the products **7—11** and **14—19** were distilled.

Procedure *B*. The reaction mixture was evacuated at 100 °C (1 Torr), the volatile products being condensed in an ice-cooled flask. Compounds **7a,b**, **8a,b**, **10a,b**, and **11a** were transferred into a distillation flask and distilled once again *in vacuo*.

The product yields (which were almost the same for procedures *A* and *B*) are summarized in Tables 1—3 and in Schemes 1, 2. The boiling points and the refractive indices of the obtained compounds correspond to published data.

Diethyl isopentylmalonate (7a) (see Ref. 24), b.p. 125—127 °C (10 Torr); n_D^{20} 1.4215. ^{1}H NMR ($CDCl_3$), δ: 0.82 (d, 6 H, 2 Me, J = 6.0 Hz); 1.10—1.25 (m, 2 H, CH_2); 1.20 (t, 6 H, 2 Me, J = 7.0 Hz); 1.50 (m, 1 H, CH); 1.76 (m, 2 H, CH_2); 3.35 (t, 1 H, CH, J = 7.5 Hz); 4.16 (q, 4 H, 2 CH_2, J = 7.0 Hz).

Diethyl 3-methylbut-2-enylmalonate (7b) (see Ref. 24), b.p. 120—122 °C (10 Torr); n_D^{20} 1.4410. ^{1}H NMR ($CDCl_3$), δ: 1.22 (t, 6 H, 2 Me, J = 7.0 Hz); 1.58, 1.64 (both s, 3 H each, Me); 2.55 (t, 2 H, CH_2, J = 7.5 Hz); 3.26 (t, 1 H, CH, J = 7.5 Hz); 4.14 (q, 4 H, 2 CH_2, J = 7.0 Hz); 5.02 (t, 1 H, =CH, J = 7.0 Hz).

Diethyl 3,7-dimethyloct-6-enylmalonate (7c) (see Ref. 24), b.p. 120—122 °C (0.5 Torr); n_D^{20} 1.4500. ^{1}H NMR ($CDCl_3$), δ: 0.92 (d, 3 H, Me, J = 6.0 Hz); 1.24 (t, 6 H, 2 Me, J = 7.0 Hz); 1.60, 1.66 (both s, 3 H each, Me); 1.05—1.45 (m, 7 H); 1.80—2.00 (m, 2 H); 3.24 (t, 1 H, CH, J = 7.5 Hz); 4.16 (q, 4 H, 2 CH_2, J = 7.0 Hz); 5.06 (t, 1 H, =CH, J = 7.0 Hz).

Diethyl [(2*E*)-3,7-dimethylocta-2,6-dienyl]malonate (7d) (see Ref. 24), b.p. 130—135 °C (0.8 Torr); n_D^{20} 1.4610. ^{1}H NMR ($CDCl_3$), δ: 1.26 (t, 6 H, 2 Me, J = 7.0 Hz); 1.58, 1.62, 1.68 (all s, 3 H each, Me); 2.00 (m, 4 H, 2 CH_2); 2.60 (t, 2 H, CH_2, J = 7.50 Hz); 3.32 (t, 1 H, CH, J = 7.50 Hz); 4.18 (q, 4 H, 2 CH_2, J = 7.0 Hz); 5.10 (m, 2 H, 2 CH=).

Ethyl 2-cyano-5-methylhexanoate (8a) (see Ref. 24), b.p. 106—108 °C (6 Torr); n_D^{20} 1.4310. ^{1}H NMR ($CDCl_3$), δ: 0.92 (d, 6 H, 2 Me, J = 6.0 Hz); 1.10—1.20 (m, 2 H, CH_2); 1.28 (t, 3 H, Me, J = 7.0 Hz); 1.60 (m, 1 H, CH); 1.95 (m, 2 H, CH_2); 3.48 (t, 1 H, CH, J = 7.5 Hz); 4.28 (q, 2 H, 2 CH_2, J = 7.0 Hz).

Ethyl 2-cyano-5-methylhex-4-enoate (8b) (see Ref. 25), b.p. 110—112 °C (6 Torr); n_D^{20} 1.4470. ^{1}H NMR ($CDCl_3$), δ: 1.30 (t, 3 H, Me, J = 7.0 Hz); 1.65, 1.70 (both s, 3 H each, Me); 2.60 (t, 2 H, CH_2, J = 7.5 Hz); 3.46 (t, 1 H, CH, J = 7.5 Hz); 4.22 (q, 2 H, CH_2, J = 7.0 Hz); 5.12 (t, 1 H, CH=, J = 7.0 Hz).

Ethyl 2-cyano-5,9-dimethyldeca-4,8-dienoate (8d) (see Ref. 25), b.p. 120—124 °C (0.3 Torr); n_D^{20} 1.4685. ^{1}H NMR ($CDCl_3$), δ: 1.32 (t, 3 H, Me, J = 7.0 Hz); 1.60, 1.68, 1.76 (all s, 3 H each, Me); 2.06 (m, 4 H, 2 CH_2); 2.66 (t, 2 H, CH_2, J = 7.5 Hz); 3.46 (t, 1 H, CH, J = 7.5 Hz); 4.25 (q, 2 H, CH_2, J = 7.0 Hz); 5.10—5.20 (m, 2 H, 2 CH=).

Ethyl 5-methyl-2-cyano-2-(3-methylbut-2-enyl)hex-4-enoate (9b) (see Ref. 26), b.p. 135—137 °C (6 Torr); n_D^{20} 1.4625. ^{1}H NMR ($CDCl_3$), δ: 1.28 (t, 3 H, Me, J = 7.0 Hz); 1.62, 1.70 (both s, 6 H each, 2 Me); 2.50 (m, 4 H, 2 CH_2); 4.20 (q, 2 H, CH_2, J = 7.0 Hz); 5.18 (t, 2 H, 2 CH=, J = 7.0 Hz).

A mixture of ethyl 2-acetyl-5-methylhexanoate (10a) and ethyl 3-isopentyloxybut-2-enoate (11a) (see Ref. 27), b.p. 122—125 °C (10 Torr); n_D^{20} 1.4350. ^{1}H NMR ($CDCl_3$), δ: 0.88 (m, 6 H, 2 Me); 1.15—1.25 (m, 2 H, CH_2); 1.28 (t, 3 H, Me, J = 7.0 Hz); 1.55 (m, 1 H, CH); 1.85 (m, CH_2); 2.20 (s, COMe (**10a**)); 2.28 (s, =CMe (**11a**)); 3.35 (t, CH (**10a**), J = 7.5 Hz); 3.76 (t, OCH_2 (**11a**), J = 7.5 Hz); 4.15 (m, 2 H, CH_2); 5.00 (s, =CH (**10a**)).

Ethyl 2-acetyl-5-methylhex-4-enoate (10b) (see Ref. 29), b.p. 114—116 °C (12 Torr); n_D^{20} 1.4462. ^{1}H NMR ($CDCl_3$), δ: 1.22 (t, 3 H, Me, J = 7.0 Hz); 1.58, 1.64, 2.20 (all s, 3 H each, Me); 2.50 (t, 2 H, CH_2, J = 7.5 Hz); 3.38 (t, 1 H, CH, J = 7.5 Hz); 4.14 (q, 4 H, 2 CH_2, J = 7.0 Hz); 5.00 (t, 1 H, =CH, J = 7.0 Hz).

A mixture of ethyl 2-acetyl-5,9-dimethyldec-8-enoate (10c) and 3-[(3,7-dimethyloct-6-enyl)oxy]but-2-enoate (11c) (see Ref. 28), b.p. 120—122 °C (0.5 Torr); n_D^{20} 1.4500. ^{1}H NMR ($CDCl_3$), δ: 0.82 (m, 3 H, Me); 1.00—1.90 (m, CH_2, CH); 1.22 (t, 3 H, Me, J = 7.0 Hz); 1.55, 1.63 (both s, 3 H each, Me); 2.18 (s, COMe (**10c**)); 2.24 (s, =CMe (**11c**)); 3.30 (t, CH (**10c**), J = 7.5 Hz); 3.74 (t, OCH_2 (**11c**), J = 7.5 Hz); 4.16 (m, 2 H, CH_2); 4.96 (s, =CH (**11c**)); 5.04 (t, 1 H, =CH, J = 7.0 Hz).

Ethyl 2-acetyl-5,9-dimethyldeca-4,8-dienoate (10d) (see Ref. 30), b.p. 120—125 °C (0.2 Torr); n_D^{20} 1.4675. ^{1}H NMR ($CDCl_3$), δ: 1.28 (t, 3 H, Me, J = 7.0 Hz); 1.58, 1.62, 1.68 (all s, 3 H each, Me); 2.00 (m, 4 H, 2 CH_2); 2.22 (s, 3 H, Me); 2.55 (t, 2 H, CH_2, J = 7.5 Hz); 3.42 (t, 1 H, CH, J = 7.5 Hz); 4.18 (q, 4 H, 2 CH_2, J = 7.0 Hz); 5.04 (m, 2 H, 2 CH=).

Diethyl [(2*E*)-3,7-dimethylocta-2,6-dienyl](cyclohexyl)malonate (14) (see Refs. 4, 5), b.p. 150—155 °C (0.2 Torr); n_D^{20} 1.4645. ^{1}H NMR ($CDCl_3$), δ: 0.85—1.00 (m, 4 H, 2 CH_2); 1.25 (t, 6 H, 2 Me, J = 7.0 Hz); 1.30—1.40 (m, 2 H, CH_2); 1.55—1.75 (m, 4 H, 2 CH_2); 1.60, 1.62, 1.68 (all s, 3 H, Me); 1.90—2.10 (m, 6 H, 3 CH_2); 2.65 (m, 1 H, CH); 4.12 (q, 4 H, 2 CH_2, J = 7.0 Hz); 5.10 (m, 2 H, 2 CH=).

Diethyl [3-(dimethylamino)propyl][(2*E*)-3,7-dimethylocta-2,6-dienyl]malonate (15) (see Refs. 10, 11), b.p. 145—148 °C (0.2 Torr); n_D^{20} 1.4660. ^{1}H NMR ($CDCl_3$), δ: 1.29 (t, 6 H, 2 Me, J = 7.0 Hz); 1.25—1.35 (m, 2 H, CH_2); 1.54, 1.57, 1.63 (all s, 3 H each, Me); 1.75—1.85, 1.90—2.05 (both m, 8 H, 4 CH_2); 2.58 (m, 2 H, CH_2); 4.12 (q, 4 H, 2 CH_2, J = 7.0 Hz); 5.00 (m, 2 H, 2 CH=).

A mixture of ethyl (4*E*)-2-acetyl-2-cyclohexyl-5,9-dimethyldeca-4,8-dienoate (16) and ethyl (4*E*)-2-[1-(cyclohexyloxy)ethylidene]-5,9-dimethyldeca-4,8-dienoate (17), b.p. 147—150 °C (0.2 Torr); n_D^{20} 1.4680. Found (%): C, 75.64; H, 10.33. $C_{22}H_{36}O_3$. Calculated (%): C, 75.82; H, 10.41. A mixture of isomers **16** and **17** was separated into components on a column with SiO_2 using a light petroleum—benzene mixture as the eluent (5% PhH for **17**, 10% PhH for **16**) to give (in the order of elution): (1) compound **17**, colorless oil, ^{1}H NMR ($CDCl_3$), δ: 0.85—0.95 (m, 4 H, 2 CH_2); 1.28 (t, 3 H, Me, J = 7.0 Hz); 1.30—1.40 (m, 2 H, CH_2); 1.55—1.75 (m, 4 H, 2 CH_2); 1.62, 1.65, 1.70 (all s, 3 H each, Me); 1.90—2.10 (m, 6 H, 3 CH_2); 2.35 (d, 3 H, =CMe, J = 1.5 Hz); 3.65 (m, 1 H, OCH); 4.16 (q, 2 H, CH_2, J = 7.0 Hz); 5.10 (m, 2 H, 2 CH=); (2) compound **16**, colorless oil, ^{1}H NMR ($CDCl_3$), δ: 0.85—0.95 (m, 4 H, 2 CH_2); 1.28 (t, 3 H, Me, J = 7.0 Hz); 1.30—1.40 (m, 2 H, CH_2); 1.55—1.75 (m, 4 H, 2 CH_2); 1.62, 1.65, 1.70 (all s, 3 H each, Me); 1.90—2.10 (m, 7 H, 3 CH_2, CH); 2.08 (s, COMe); 4.16 (q, 2 H, CH_2, J = 7.0 Hz); 5.10 (m, 2 H, 2 CH=).

A mixture of ethyl (4*E*)-2-acetyl-2-[3-(dimethylamino)propyl]-5,9-dimethyldeca-4,8-dienoate (18) and (4*E*)-2-{1-[3-(dimethylamino)propoxy]ethylidene}-5,9-dimethyldeca-4,8-dienoate (19) (see Ref. 39), b.p. 158—162 °C (0.1 Torr); n_D^{20} 1.4760. A mixture of isomers **18** and **19** was separated into components on a column with SiO_2 using a $CHCl_3$—MeOH mixture as the eluent (2% MeOH for **19**, 5% MeOH for **18**) to give (in the order of elution) (1) compound **19**, pale yellow oil, ^{1}H NMR ($CDCl_3$) δ: 1.28 (t, 3 H, Me, J = 7.0 Hz); 1.58, 1.62, 1.68 (all s, 3 H each, Me); 1.80—1.90, 1.90—2.10 (both m, 4 H each, 2 CH_2); 2.20 (s, 6 H, 2 Me); 2.26 (s, =CMe); 2.60 (m, 2 H, CH_2); 3.95 (t, OCH_2, J = 7.5 Hz); 4.18 (q, 2 H, CH_2, J = 7.0 Hz); 4.90 (m, 1 H, CH=); 5.10 (m, 1 H, CH=); (2) compound **18**, pale yellow oil, ^{1}H NMR ($CDCl_3$), δ: 1.28 (t, 3 H, Me, J = 7.0 Hz); 1.58, 1.62, 1.68 (all s, 3 H each, Me); 1.70—1.80, 1.85—2.00 (both m, 4 H each, 2 CH_2); 2.12 (s, COMe); 2.20 (s, 6 H, 2 Me); 2.20—2.25, 2.50 (both m, 2 H each, CH_2); 4.18 (q, 2 H, CH_2, J = 7.0 Hz); 4.90, 5.10 (both m, CH=).

Reaction of 2-geranylacetoacetate (10d) with 1-chloro-3-dimethylaminopropane (13) in dimethyl sulfoxide. A mixture of 2-geranylacetoacetate (**10d**) (13.3 g, 50 mmol) and 1-chloro-3-dimethylaminopropane (**13**) (12.1 g, 100 mmol) was added dropwise at 90—95 °C with vigorous stirring to a slurry of finely ground KOH (5.70 g, 100 mmol) and benzyltriethylammonium chloride (0.50 g, 3.0 mmol) in anhydrous DMSO (30 mL). The reaction mixture was stirred for 2 h at the same temperature, cooled, and treated with 15% HCl (50 mL). The acidic solution was washed with ether (2×10 mL) to remove impurities and saturated with K_2CO_3. The organic layer formed was extracted with CH_2Cl_2 (4×20 mL) and dried with $MgSO_4$. The solvent was removed and the residue was distilled *in vacuo* to give 7.60 g (45%) of a mixture of compounds **18** and **19** (4 : 1 according to ^{1}H NMR). The boiling point and ^{1}H NMR spectral parameters of the resulting mixture coincided with the corresponding characteristics of isomers **18** and **19** obtained in [bmim][BF_4].

This work was financially supported by the Russian Foundation for Basic Research (Project No. 03-03-32659) and by the Russian Academy of Sciences (Fundamental Research Program of the Presidium of the Russian Academy of Sciences).

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Received January 30, 2004;
in revised form March 9, 2004