A New Reaction of 1,2-Di- and 1,2,3-Trialkyldiaziridines: Ring Expansion under the Action of Diethyl Acetylenedicarboxylate in Ionic Liquids

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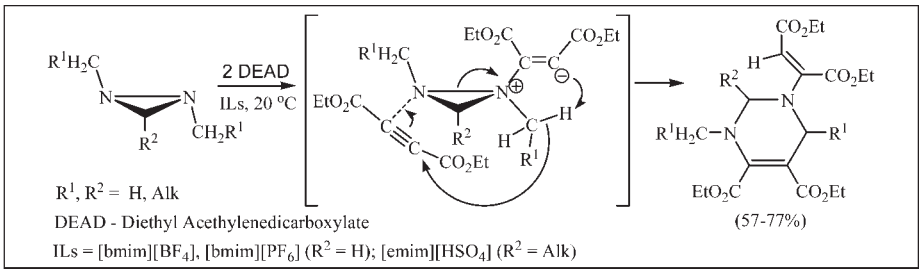

New reaction of diaziridine ring expansion resulting in diethyl 1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate derivatives was discovered under the action of diethyl acetylenedicarboxylate on 1,2-di- and 1,2,3-trialkyldiaziridines in ionic liquids.

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INTRODUCTION

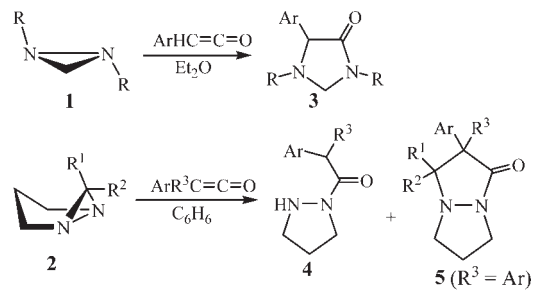
Over a few last years, new simple approaches to the construction of different nitrogen-containing heterocyclic systems have been developed in our laboratory. These are based on the strained diaziridine ring transformation in readily available [1,2] 1,2-dialkyldiaziridines **1** and 1,5-diazabicyclo[3.1.0]hexanes **2** under the action of electrophilic reagents, in particular, dipolarophiles. Herein, the diaziridine ring is capable of opening on the C—N or N—N bonds to generate dipolar intermediates prone to cycloaddition reactions (so-called ring expansion reactions) resulting in other heterocyclic structures [3–10].

Arylketenes [3–6], aroyliso- and aroylisothiocyanates [7,8], carbon disulfide [9,10], and activated nitriles [10,11] were investigated as dipolarophiles. Thus, the reaction of arylketenes with 1,2-dialkyldiaziridines **1** resulted in 5-aryl-1,3-dialkylimidazolidin-4-ones **3** and with 1,5-diazabicyclo[3.1.0]hexanes **2**—in heterocyclic compounds of two kinds—1-(arylacetyl)pyrazolidines **4** and 1,5-diazabicyclo[3.3.0]octan-2-ones **5** (Scheme 1).

However, these researches showed that new heterocyclic systems in common organic solvents could only be achieved in reactions with highly reactive reagents—arylketenes [3–6] and aroylisocyanates [7]. A reaction between diaziridines **1** and **2** and the other foresaid reagents was also performed successfully though only with ionic liquids (ILs) used as a reaction medium [8–11]. Moreover, absolutely unexpected heterocyclic structures were built in those solvents in some cases. For example, derivatives of earlier unknown infused 1,2,4,6-tetrazepan-5-thione were obtained in one preparative step by an interaction of 1,2-dialkyldiaziridines **1** with benzoylisothiocyanate in 1-butyl-3-methylimidazilium tetrafluoroborate ([bmim][BF_4]) or hexafluorophosphate ([bmim][PF_6]) [8].

We continued examining ring expansion reactions of monocyclic 1,2-dialkyldiaziridines **1** with dipolarophiles in ionic liquids within this research effort. As a dipolarophile dialkyl esters of acetylenedicarboxylic acid were selected. The reaction between 1,2-dialkyldiaziridine derivatives and dimethyl acetylenedicarboxylate in benzene had been described in literature [12]. The authors of this study have found out that the interaction of these compounds resulted in only linear products **7** and **8** and the diaziridine ring opening occurred on the N—N bond. The research on this reaction mechanism was assisted by labeled atoms (D). On the basis of the obtained compounds structure authors of the work [12] assumed that the first reaction step was the formation of dipolar intermediates **9**. Where one of the substituents at nitrogen atoms of initial diaziridine **1a** was benzyl, intermediate **9a** was stabilized by a proton split-off from the CH_2 group of the benzyl fragment followed by the generation of enamine **7**. If one of the substituents at nitrogen atoms was Ph (**1b**), intermediate **9b** was stabilized by proton breaking from the C(3)-carbon atom of the

Scheme 1



diaziridine ring with further generation of product **8** (Scheme 2) [12].

Originating from the data obtained in [8–11] we hoped that ILs as a reaction medium would change the stabilization pathways of intermediates **9** and result in heterocyclic structures **10** or **11** depending on C—N- or N—N-positioned opening of the diaziridine ring in the interaction of 1,2-dialkyldiaziridines **1** with dialkyl esters of acetylenedicarboxylic acid (Scheme 3).

Ionic liquids have been widely used over the past years as a potential replacement of conventional solvents for a variety of chemical processes [13,14]. ILs have considerable advantages over available organic solvents—they are fire-resistant and have limited vapor pressure thus allowing efficient recovery of organic products. In addition, they are recyclable and can be used several times in the same reactions. Moreover, many reactions gain acceleration in ILs due to stabilization of charged intermediates or ions [15–17]. The realization of different reactions in ILs pertains to a new prospective field of organic chemistry—''green chemistry.''

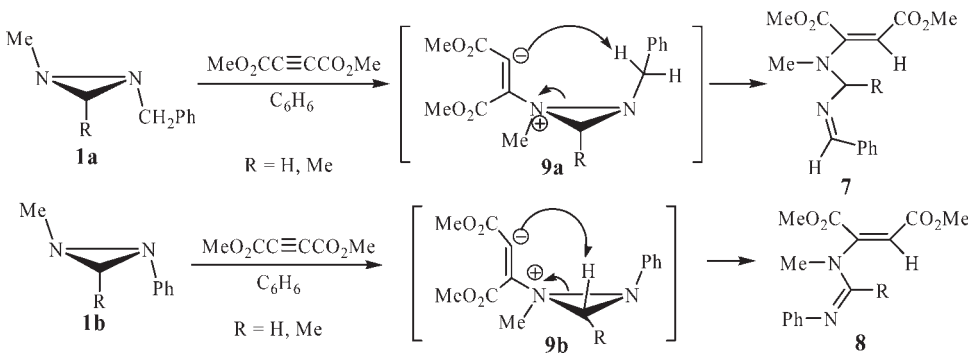
RESULTS AND DISCUSSION

1,2-Dibutyl-(**1c**), 1,2-dipropyl-(**1d**), 1,2-diethyl-(**1e**), 1,2-dimethyl-(**1f**), 1,2,3-triethyl-(**1g**), 1,2-diethyl-3-methyl-(**1h**), 1,2-dipropyl-3-ethyl-(**1i**), and 3-benzyl-1,2-di(2-phenylethyl)- (**1j**) diaziridines were examined as initial dialkyldiaziridines **1** and diethyl acetylenedicarboxylate **12** as a dipolarophyle. From a large number of ILs we picked 1-butyl-3-methylimidazolium tetrafluoroborate or hexafluorophosphate ([bmim][BF_4] or [bmim][PF_6]). These ionic liquids relate to room temperature ionic liquids group (RTIL) and are one of the most accessible ones. Note that during the reaction the reaction mixture is colored orange at first and then red at reaction end.

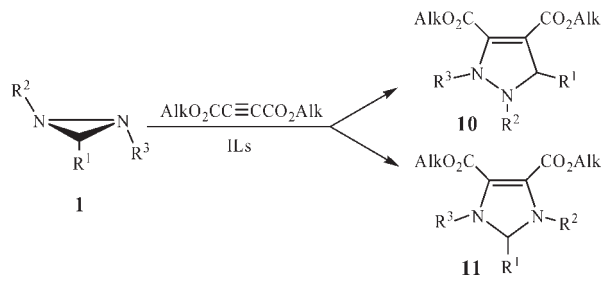
The investigations were started with 1,2-dibutyldiaziridine **1c** in [bmim][BF_4]. At first, the equimolar quantity of the reagents was added to the reaction. In about 30 min at 20°C, the reaction was completed (as shown by TLC) and a new compound, diethyl 1-[3-ethoxy-1-(ethoxycarbonyl)-3-oxoprop-1-enyl]-3-buthyl-6-propyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **13c,** was obtained in 37% yield. According to mass spectra this contained one molecule of diaziridine **1c** and two molecules of diethyl acetylenedicarboxylate **12**. After adding one mole of diaziridine **1c** and two moles of dipolarophile **12** to the reaction, the yield of **13c** became higher −69%. This reaction was found to have a general character—compounds **13d–f** were synthesized from diaziridines **1d–f** and dipolarophile **12** in close yields. The reaction ran in ionic liquid [bmim][PF_6] as well as in [bmim][BF_4]. Reaction rate depended on solubility of initial diaziridines **1c–f** in Ils—the shorter alkyl substituents at nitrogen atoms the higher their solubility and rate of reaction.

Further on, it was found that, apart from 1,2-dialkyldiaziridines **1c–f**, 1,2,3-trialkyldiaziridines **1g–i** were also capable of entering the reaction with diethyl acetylenedicarboxylate **12** to produce corresponding tetrahydropyrimidine derivatives **13g–i**. However, the latter are formed only at the replacement of ionic liquids [bmim][BF_4] or [bmim][PF_6] with [emim][HSO_4] being herein both a reaction medium and an acidic catalyst. Yields of compounds **13g–i** were also increased as affected by lengthening of the alkyl substituents both at N and at C(3) atoms of initial diaziridines **1g–i**.

Scheme 2



Scheme 3



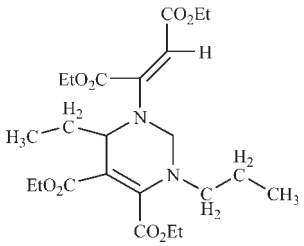


Figure 1. The molecule **13d** structure.

The structures of compounds **13c–i** were established by aggregating elemental analysis data and spectral characteristics (mass-spectra, IR-, NMR ^{1}H, ^{13}C, ^{15}N-spectra with use of COSY, NOESY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, and ^{1}H-^{15}N HMBC methods). The proof of compounds **13** structure was demonstrated on example of compound **13d**. ^{13}C APT spectrum revealed 6 CH_3 groups, 8 CH_2 groups, 2 CH groups, and 7 quaternary carbon atoms, four of them were in the region of carboxylic carbon resonance. ^{1}H spectrum was assigned with COSY, NOESY, and HSQC 2D spectra. The investigation of these spectra showed that molecule contained four carboethoxy, one *N*-propyl-, one 1-substituted *N*-propyl group, one CH_2 group which had no interactions with other protons, and one sp^2-CH group. ^{1}H-^{13}C HMBC 2D spectral correlations allowed us to approve the structure of these fragments and interconnections between them, as well as positions of quaternary carbon atoms. The proposed molecular structure was tetrahydropyrimidine ring with substituents (Fig. 1)

The ^{1}H-^{13}C HMBC correlations of the compound **13d** are shown in Figure 2.

The ^{1}H-^{15}N HMBC spectrum revealed two sp^3 N-atoms with chemical shifts of −295.1 and −291.9 ppm (with an external reference CH_3NO_2, $\delta = 0.0$ ppm) and connectivity between both N-atoms and protons, which is shown in Figure 3.

The most important NOE interactions in the molecule **13d** revealed in NOESY experiment (Fig. 4)

Cis-configuration of two carboethoxy groups near double bond at N-1 was proved by NOE interactions H-8/H-2 and H-6/H-12 in NOESY spectrum. Another important NOE correlation was between H-2 and H-9 also proved the structure of this molecule.

Initial 1,2-dialkyldiaziridines **1c–i** are chiral compounds but they were introduced to the reaction with diethyl acetylenedicarboxylate **12** in a racemic form.

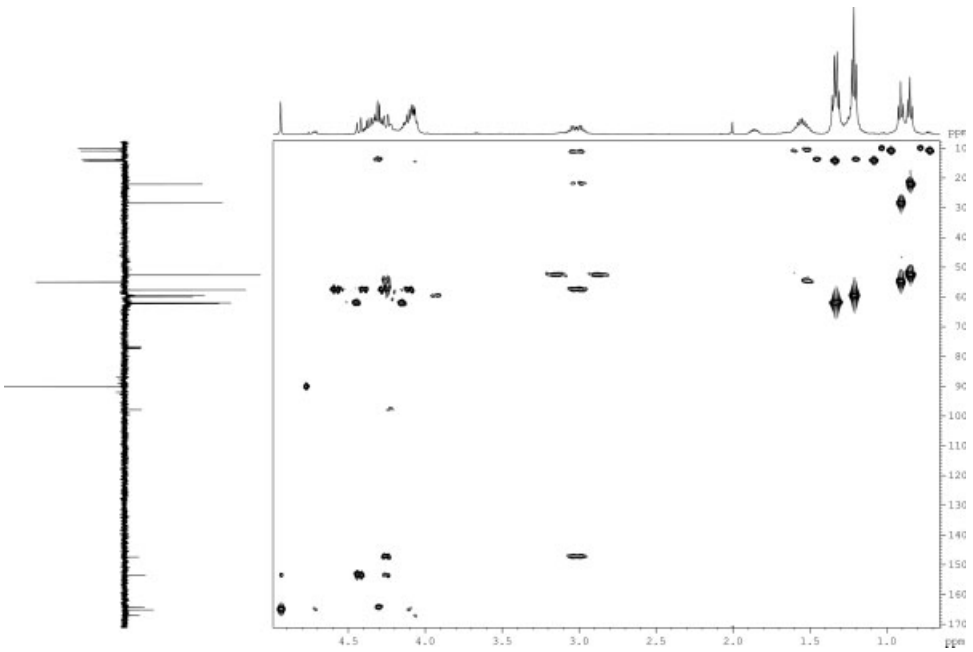


Figure 2. ^{1}H-^{13}C HMBC correlations of the compound **13d**.

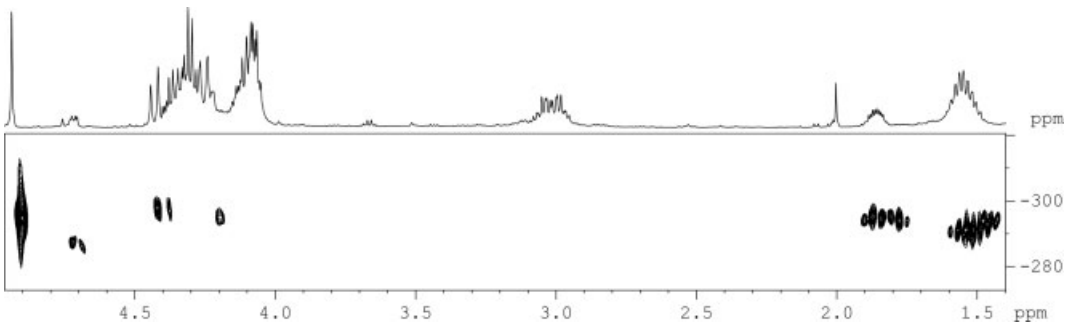


Figure 3. ^{1}H-^{15}N HMBC correlations of the compound **13d**.

And the reaction evidently proceeds not stereoselectively. The synthesized compounds (**13c–i**) contain chiral carbon atoms (C(6) in **13c–f** and C(2) and C(6) in **13g–i**), however, **13c–f** are racemates and, as seen from the spectral characteristics, no diastereomers were fixed in **13g–i** prepared from 1,2,3-trialkyldiaziridines **1g–i**.

The chemical shifts of signals NMR ^{1}H, ^{13}C, ^{15}N spectra by the example of compounds **13c**, **13d**, **13h** are presented in Table 1. The atom numeration is shown on Figure 5.

This result is in agreement with the assumed mechanism of the reaction. The first step (as in ref. [12]) is the formation of dipolar intermediate **9**, however, its life time evidently increases in ionic liquids able to solvate both positively and negatively charged particles or molecule moieties [15–17]. Therefore, the second molecule of diethyl acetylenedicarboxylate **12** has time to enter a reaction with intermediate **9,** generating the second intermediate **14,** which is transformed to final compound **13**. Generally, the formation of compounds **13** can be presented as two-step condensation of one molecule of initial diaziridine **1** and two molecules of compound **12** according to Scheme 4. Unlike the transformation of intermediate **9** in benzene (Scheme 2), the anion of intermediate **9** in ILs evidently attacks the proton of the CH_2 group bound to same nitrogen atom to generate a new anion, which in turn attacks the second molecule of diethyl acetylenedicarboxylate **12** (Scheme 4).

The expected five-member heterocyclic compound, *i.e*., diethyl 5-benzyl-1,2-bis(2-phenylethyl)-2,5-dihydro-1*H*-pyrazole-3,4-dicarboxylate **15**, was obtained only in one case by the interaction of 1,2-di(2-phenylethyl)-3-phenylmethyldiaziridine **1j** with diethyl acetylenedicarboxylate **12** in ionic liquid [emim][HSO_4] (Scheme 5). Evidently, here, the attack of the second molecule of dipolarophile **12** on intermediate **9j** was sterically hindered.

Thus a new unexpected transformation of 1,2-dialkyldiaziridines **1** under the action of diethyl acetylenedicarboxylate **12** in ionic liquids resulting in tetrahydropyrimidine derivatives **13** was discovered. The reaction is a new method for preparing tetrahydropyrimidine derivatives and is a valuable supplement to the known synthetic methods for such kind of compounds. Pyrimidines and their analogs represent an important class of nitrogen heterocycles, which are components both of various biologically active natural compounds and of diverse drugs [18(a)]. They display antiviral [18(b)], antibacterial [18(b,c)], anti-inflammatory [18(a,b)], and anti-HIV (HIV Integrase inhibitors) activities [18(d)] and are useful as inflammatory mediators in Parkinson's disease therapy [18(e)].

EXPERIMENTAL

Elemental analysis was performed by the CHN Analyzer Perkin–Elmer 2400. The IR spectra (ν, cm^{-1}) were measured using a SPECORD-M82 spectrometer. Mass spectra were measured using a Finnigan MAT INCOS-50 instrument. The NMR spectra of compound **15** were recorded using a Bruker AM-300 spectrometer at 300 MHz for ^{1}H and 75.47 MHz for ^{13}C Spectra in $CDCl_3$. The NMR spectra of all compounds **13c–i** were measured on Bruker AV-600 instrument with the frequencies 600.13, 150.90, and 60.81 MHz for ^{1}H, ^{13}C, and ^{15}N, correspondingly. The chemical shifts of the signals of $CDCl_3$ residual proton (7.27 ppm) and carbon (77.0 ppm) were used as the internal standard. The ^{15}N spectra were measured with CH_3NO_2 ($\delta_{^{15}N} = 0.0$ ppm) as the external standard. All 2D-spectra were recorded using standard Bruker methods with Z-gradient. The spectra were measured at 30°C. Analytical thin-layer chromatography (TLC) was conducted on silica gel plates (Silufol UV-254). New compounds were purified by flash-chromatography (column chromatography for **15**) on

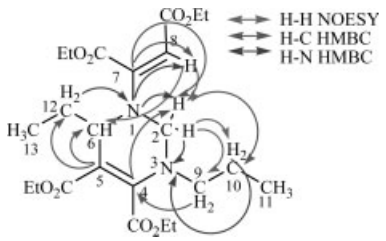


Figure 4. The most important NOE interactions in the molecule revealed in NOESY experiment.

Table 1

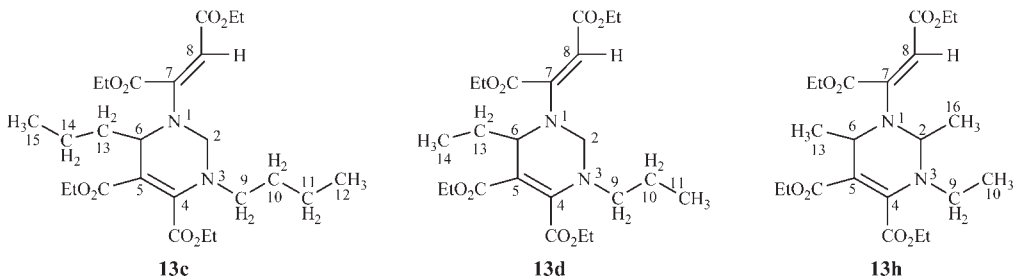
Chemical shifts of **13c**, **13d**, **13h** NMR ^{1}H, ^{13}C, ^{15}N spectra.

Atom numbers (Fig. 5)	Compounds					
	13c		**13d**		**13h**	
	^{1}H	$^{13}C/^{15}N$	^{1}H	$^{13}C/^{15}N$	^{1}H	$^{13}C/^{15}N$
1	–	−292.2	–	−291.9	–	–
2	4.24; 4.45	59.1	4.25; 4.43	57.6	4.48	67.5
3	–	−293.8	–	−295.2	–	–
4	–	148.8	–	147.5	–	146.0
5	–	99.3	–	97.9	–	106.3
6	4.33	53.4	4.22	55.0	4.22	47.1
7	–	154.9	–	153.6	–	150.1
8	4.94	91.8	4.94	90.2	4.99	91.0
9	3.03; 3.07	52.3	2.98; 3.04	52.7	3.03; 3.19	45.6
10	1.52	32.4	1.55	22.1	1.18	14.4
11	1.26	21.3	0.85	10.9	–	–
12	0.89	15.2	–	–	–	–
13	1.51; 1.76	39.3	1.51; 1.85	28.6	1.42	20.0
14	1.34; 1.41	20.2	0.91	10.1	–	–
15	0.89	15.2	–	–	–	–
16	–	–	–	–	1.36	16.9
4-COOEt	–	168.5	–	167.0	–	167.2
	4.06	61.1	4.07	59.5	4.09	59.6
	1.23	15.3	1.22	13.7	1.25	14.2
5-COOEt	–	165.7	–	164.2	–	164.5
	4.31	63.4	4.30	61.9	4.32	61.9
	1.35	15.3	1.32	13.7	1.33	14.3
7-COOEt	–	166.6	–	165.1	–	164.7
	4.14	61.3	4.12	59.8	4.17	60.2
	1.22	15.7	1.22	14.2	1.27	14.4
8-COOEt	–	166.6	–	165.1	–	165.5
	4.36	63.7	4.36	62.2	4.43	62.1
	1.33	15.7	1.35	14.2	1.39	14.2

Silicagel, 0.060–0.200 mm, 60 A (ACROS). R_f of all compounds **13** and **15** was measured with the usage of eluent [*n*-hexane-ethyl acetate, 2:1 (v/v)].

General procedure for the synthesis of substituted 1,2,3,6-tetrahydropyrimidines by the reaction of 1,2-di- and 1,2,3-trialkyldiaziridines 1c-i with diethyl acetylenedicarboxylate 12 in ionic liquid. To a stirred mixture (20°C) of diaziridine **1c–i** (1.0 mmol) and ionic liquid ([bmim][BF_4] or [bmim][PF_6] for 1,2-dialkyldiaziridines **1c–f** and [emim][HSO_4] for 1,2,3-trialkyldiaziridines **1g–i**) (0.4 g), diethyl acetylenedicarboxylate **12** (2.0 mmol) was added dropwise for about 1 min and the reaction mixture was stirred for an additional 30 min to the full conversion of initial compounds (TLC-control), the reaction mixture color was changed through the time from orange to red. After that the resulting substituted 1,2,3,6-tetrahydropyrimidine **13** was extracted from ionic liquid by mixture of solvents hexane and ethyl acetate (5:1, 4–5 times by 7 mL), then the solvent was evaporated. Final substituted 1,2,3,6-tetrahydropyrimidine **13** was purified by the method of flash-chromatography on Silicagel with the solvent of *n*-hexane and ethyl acetate (2:1).

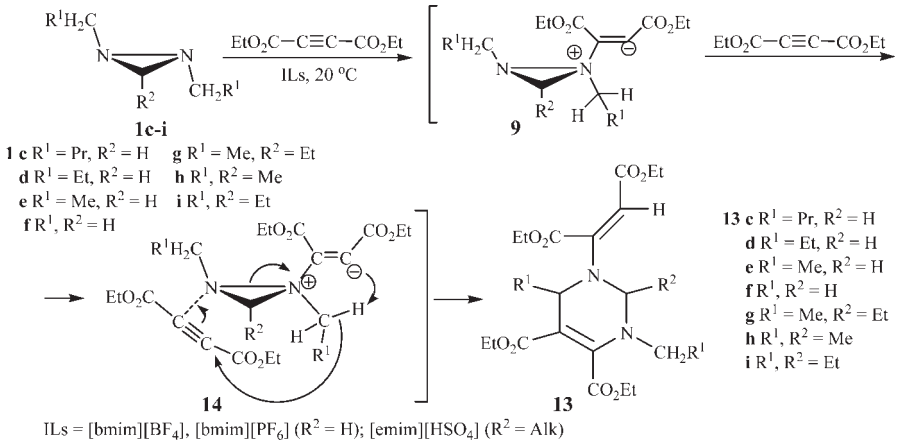
Synthesis of diethyl 5-benzyl-1,2-bis(2-phenylethyl)-2,5-dihydro-1*H*-pyrazole-3,4-dicarboxylate (15). To a stirred mixture (20°C) of diaziridine **1j** (1.0 mmol) and ionic liquid ([bmim][BF_4] or [bmim][PF_6]) (0.4 g), diethyl acetylenedicarboxylate **12** (1.0 mmol) was added dropwise for about 1 min



13c **13d** **13h**

Figure 5. Atom numeration of compounds **13c**, **13d**, and **13h**.

Scheme 4



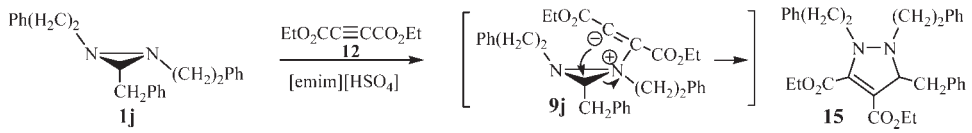
and the reaction mixture was stirred for an additional 48 h to the full conversion of initial compounds (TLC-control), the reaction mixture color was changed through the time from orange to red. After that the resulting compound **15** was extracted from ionic liquid by mixture of solvents hexane and ethyl acetate (5:1, 6 times by 7 mL), then the solvent was evaporated. Final compound **15** was purified by the method of column chromatography on Silicagel with the solvent of *n*-hexane and ethyl acetate (3:1).

The physical and spectral data of compounds **13c–i** and **15** are as follows.

Diethyl 1-[3-ethoxy-1-(ethoxycarbonyl)-3-oxoprop-1-enyl]-3-buthyl-6-propyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (13c). This compound was obtained as yellow nondistilled oil, 69% yield, R_f 0.37; IR: 668, 772, 864, 924, 1024, 1044, 1096, 1152, 1172, 1220, 1248, 1372, 1444, 1456, 1580, 1652, 1700, 1740, 2876, 2936, 2960, 2970 cm^{-1}; ^1H NMR: δ 0.89 (t, 6H, C*H*$_3$(CH$_2$)$_3$N + C*H*$_3$(CH$_2$)$_2$N, ^3J = 7.1 Hz), 1.22 (t, 3H, C*H*$_3$CH$_2$OOCC$_{chain}$N, ^3J = 7.2 Hz), 1.23 (t, 3H, C*H*$_3$CH$_2$OOCC$^4_{ring}$, ^3J = 7.2 Hz), 1.26 (m, 2H, CH$_3$C*H*$_2$(CH$_2$)$_2$N, ^3J = 7.2), 1.33 (t, 3H, C*H*$_3$CH$_2$OOCC$_{chain}$H, ^3J = 7.2 Hz), 1.34, 1.41 (2m, 2H, CH$_3$C*H*$_2$CH$_2$C$^6_{ring}$), 1.35 (t, 3H, C*H*$_3$CH$_2$OOCC$^5_{ring}$, ^3J = 7.2 Hz), 1.51, 1.76 (2m, 2H, CH$_3$CH$_2$C*H*$_2$C$^6_{ring}$), 1.52 (m, 2H, CH$_3$CH$_2$C*H*$_2$CH$_2$N), 3.03, 3.07 (2m, 2H, CH$_3$(CH$_2$)$_2$C*H*$_2$N), 4.06 (m, 2H, CH$_3$C*H*$_2$OOCC$^4_{ring}$, ^3J = 7.2 Hz), 4.14 (m, 2H, CH$_3$C*H*$_2$OOCC$_{chain}$N, ^3J = 7.2 Hz), 4.24, 4.45 (dd, 2H, C$^2_{ring}$*H*$_2$), 4.31 (m, 2H, CH$_3$C*H*$_2$OOCC$^5_{ring}$, ^3J = 7.2 Hz), 4.33 (m, 2H, C$^6_{ring}$*H*), 4.36 (m, 2H, CH$_3$C*H*$_2$OOCC$_{chain}$H, ^3J = 7.2 Hz), 4.94 ppm (s, 1H, EtOOCC$_{chain}$*H*); ^{13}C NMR: 15.25 (*C*H$_3$(CH$_2$)$_3$N and *C*H$_3$(CH$_2$)$_2$C$^6_{ring}$), 15.26 (*C*H$_3$CH$_2$OOCC$^4_{ring}$), 15.29 (*C*H$_3$CH$_2$OOCC$^5_{ring}$), 15.68 (*C*H$_3$CH$_2$OOCC$_{chain}$N), 15.74 (*C*H$_3$CH$_2$OOCC$_{chain}$H), 20.24 (CH$_3$*C*H$_2$CH$_2$C$^6_{ring}$), 21.27 (CH$_3$*C*H$_2$CH$_2$CH$_2$N), 32.39 (CH$_3$CH$_2$*C*H$_2$CH$_2$N), 39.32 (C$^6_{ring}$*C*H$_2$), 52.27 (CH$_3$CH$_2$CH$_2$*C*H$_2$N), 53.36 (*C*$^6_{ring}$H), 59.11 (*C*$^2_{ring}$H$_2$), 61.08 (CH$_3$*C*H$_2$OOCC$^4_{ring}$), 61.28 (CH$_3$*C*H$_2$OOCC$_{chain}$N), 63.44 (CH$_3$*C*H$_2$OOCC$^5_{ring}$), 63.73 (CH$_3$*C*H$_2$OOCC$_{chain}$H), 91.79 (EtOOC*C*$_{chain}$H), 99.26 (EtOOC*C*$^5_{ring}$), 148.85 (EtOOC*C*$^4_{ring}$), 154.90 (EtOC*C*$_{chain}$N), 165.72 (EtO*C*OC$^5_{ring}$), 166.58 (EtO*C*OC$_{chain}$H), 166.61 (EtO*C*OC$_{chain}$N), 168.51 ppm (EtO*C*OC$^4_{ring}$); ^{15}N NMR: δ −292.2 ppm (*N*^{1}), −293.8 (*N*^{3}); ms: *m*/*z* (I, %) 496 (3, M), 467 (23, M – C_2H_5), 451 (5, M – C_3H_7 – 2H), 438 (4, M – 2C_2H_5), 323 (13, M – $CO_2C_2H_5$), 350 (6, M – 2$CO_2C_2H_5$), 168 (15, diethyl acetilenedicarboxylate – 2H), 155 (71, 1,2-dibutyl diaziridine – H), 43 (100, C_3H_7). Anal. Calcd for $C_{25}H_{40}N_2O_8$ (496.59): C, 60.47; H, 8.12; N, 5.64. Found: C, 60.44; H, 8.15; N, 5.63.

Diethyl 1-[3-ethoxy-1-(ethoxycarbonyl)-3-oxoprop-1-enyl]-3-propyl-6-ethyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (13d). This compound was obtained as yellow nondistilled oil, 77% yield, R_f 0.37; IR: 666, 748, 774, 864, 1024, 1046, 1098, 1154, 1222, 1246, 1372, 1446, 1462, 1580, 1700, 1738, 2876, 2922, 2950, 2984 cm^{-1}; ^1H NMR: δ 0.85 (t, 3H, C*H*$_3$(CH$_2$)$_2$N, ^3J = 7.2 Hz), 0.91 (t, 3H, C*H*$_3$CH$_2$C$^6_{ring}$H, ^3J = 7.3 Hz), 1.22 (t, 6H, C*H*$_3$CH$_2$OOCC$^4_{ring}$ + C*H*$_3$CH$_2$OOCC$_{chain}$N, ^3J = 7.2 Hz), 1.32 (t, 3H, C*H*$_3$CH$_2$OOCC$^5_{ring}$, ^3J = 7.2 Hz), 1.35 (t, 3H, C*H*$_3$CH$_2$OOCC$_{chain}$H, ^3J = 7.2 Hz), 1.51, 1.85 (2m, 2H, CH$_3$C*H*$_2$C$^6_{ring}$), 1.55 (m, 2H, CH$_3$C*H*$_2$CH$_2$N), 2.98, 3.04 (2m, 2H, CH$_3$CH$_2$C*H*$_2$N), 4.07 (m, 2H, CH$_3$C*H*$_2$OOCC$^4_{ring}$, ^3J = 7.2 Hz), 4.12 (m, 2H, CH$_3$C*H*$_2$OOCC$_{chain}$N, ^3J = 7.2 Hz), 4.22 (m, 2H, C$^6_{ring}$*H*), 4.25, 4.43 (dd, 2H, C$^2_{ring}$*H*$_2$), 4.30 (m, 2H, CH$_3$C*H*$_2$OOCC$^6_{ring}$, ^3J = 7.2 Hz), 4.36 (m, 2H, CH$_3$C*H*$_2$OOCC$_{chain}$H, ^3J = 7.2 Hz), 4.94 ppm (s, 1H, EtOOCC$_{chain}$*H*); ^{13}C NMR: δ 10.12 (*C*H$_3$CH$_2$C$^6_{ring}$), 10.86 (*C*H$_3$CH$_2$CH$_2$N), 13.72 (*C*H$_3$CH$_2$OOCC$^4_{ring}$), 13.76 (*C*H$_3$CH$_2$OOCC$^5_{ring}$), 14.18 (*C*H$_3$CH$_2$OOCC$_{chain}$N), 14.23 (*C*H$_3$CH$_2$OOCC$_{chain}$H), 22.09 (CH$_3$*C*H$_2$CH$_2$N), 28.56 (C$^6_{ring}$*C*H$_2$CH$_3$), 52.67 (CH$_3$CH$_2$*C*H$_2$N), 55.02 (*C*$^6_{ring}$H), 57.55 (*C*$^2_{ring}$H$_2$), 59.51 (CH$_3$*C*H$_2$OOCC$^4_{ring}$), 59.77 (CH$_3$*C*H$_2$OOCC$_{chain}$N), 61.93 (CH$_3$*C*H$_2$OOCC$^5_{ring}$),

Scheme 5



62.16 ($CH_3CH_2OOCC_{chain}H$), 90.23 ($EtOOCC_{chain}H$), 97.90 ($EtOOCC^5_{ring}$), 147.46 ($EtOOCC^4_{ring}$), 153.60 ($EtOOCC_{chain}N$), 164.17 ($EtOOCC^5_{ring}$), 165.10 ($EtOOCC_{chain}N$ and $EtOOC$-$C_{chain}H$), 167.01 ppm ($EtOOCC^4_{ring}N$); ^{15}N NMR: δ −291.9 ppm (N^1), −295.2 (N^3); ms: *m*/*z* (I, %) 468 (5, M), 439 (30, M – C_2H_5), 423 (4, M – C_3H_7 – 2H), 410 (3, M – $2C_2H_5$), 395 (7, M – $CO_2C_2H_5$), 322 (3, M – $2CO_2C_2H_5$), 168 (17, diethyl acetilenedicarboxylate – 2H), 126 (60, 1,2-dipropyl diaziridine – 2H), 43 (100, C_3H_7). Anal. Calcd for $C_{23}H_{36}N_2O_8$ (468.54): C, 58.96; H, 7.74; N, 5.98. Found: C, 59.00; H, 8.11; N, 5.96.

Diethyl 1-[3-ethoxy-1-(ethoxycarbonyl)-3-oxoprop-1-enyl]-3-ethyl-6-methyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (13e). This compound was obtained as yellow nondistilled oil, 65% yield, R_f 0.36; IR: 664, 752, 776, 804, 864, 1024, 1048, 1100, 1156, 1224, 1244, 1300, 1372, 1384, 1448, 1468, 1580, 1700, 1736, 2876, 2908, 2940, 2984 cm^{-1}; ^1H NMR: δ 1.06 (t, 3H, CH_3CH_2N, ^3J = 7.3 Hz), 1.13 (t, 3H, $CH_3C^6_{ring}$, ^3J = 7.5 Hz), 1.21 (t, 6H, $CH_3CH_2OOCC_{chain}H$ + $CH_3CH_2OOCC^4_{ring}$, ^3J = 7.3 Hz), 1.34 (t, 6H, CH_3CH_2OOC-C^5_{ring} + $CH_3CH_2OOCC_{chain}N$, ^3J = 7.3 Hz), 3.15, 3.25 (2m, 2H, CH_3CH_2N), 4.06 (m, 2H, $CH_3CH_2OOCC^4_{ring}$, ^3J = 7.3 Hz), 4.11 (m, 2H, $CH_3CH_2OOCC_{chain}H$, ^3J = 7.3 Hz), 4.28 (m, 2H, $CH_3CH_2OOCC^5_{ring}$, ^3J = 7.3 Hz), 4.35, 4.46 (dd, 2H, $C^2_{ring}H_2$), 4.36 (m, 2H, $CH_3CH_2OOCC_{chain}N$, ^3J = 7.3 Hz), 4.82 (m, 2H, $C^6_{ring}H$Me), 4.83 ppm (s, 1H, $EtOOCC_{chain}H$); ^{13}C NMR: 10.33 (CH_3CH_2N), 13.65 ($CH_3CH_2OOCC^5_{ring}$ and CH_3CH_2OOC-$C_{chain}N$), 13.92 ($CH_3CH_2OOCC_{chain}H$ and $CH_3CH_2OOCC^4_{ring}$), 16.02 ($C^6_{ring}CH_3$), 41.22 (CH_3CH_2N), 48.97 ($C^6_{ring}H$), 59.41 ($CH_3CH_2OOCC^4_{ring}$), 59.55 ($CH_3CH_2OOCC_{chain}H$), 61.32 ($CH_3CH_2OOCC^5_{ring}$), 62.31 ($CH_3CH_2OOCC_{chain}N$), 63.98 ($C^2_{ring}H_2$), 88.45 ($EtOOCC_{chain}H$), 112.33 ($EtOOCC^5_{ring}$), 149.43 ($EtOOCC^4_{ring}N$), 151.95 ($EtOOCC_{chain}N$), 163.65 ($EtOOCC$-$_{chain}H$), 165.16 ($EtOOCC_{chain}N$), 166.78 ($EtOOCC^4_{ring}N$), 167.01 ppm ($EtOOCC^5_{ring}$); ^{15}N NMR: δ −280.3 (N^1), −288.0 ppm (N^3). Anal. Calcd for $C_{21}H_{32}N_2O_8$ (440.49): C, 57.26; H, 7.32; N, 6.36. Found: C, 57.30; H, 7.29; N, 6.33.

Diethyl 1-[3-ethoxy-1-(ethoxycarbonyl)-3-oxoprop-1-enyl]-3-methyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (13f). This compound was obtained as yellow nondistilled oil, 34% yield, R_f 0.36; IR: 664, 756, 860, 1028, 1096, 1144, 1252, 1372, 1448, 1560, 1696, 1736, 2872, 2940, 2984 cm^{-1}; ^1H NMR: δ 1.06 (t, 3H, CH_3CH_2N, ^3J = 7.34 Hz), 1.13 (t, 3H, $CH_3C_{ring}HN$, ^3J = 6.61 Hz), 1.21 (t, 6H, CH_3CH_2OOC-$C_{chain}H$, $CH_3CH_2OOCC_{ring}NEt$, ^3J = 5.14 Hz), 1.34 (t, 6H, $CH_3CH_2OOCC_{ring}CHMe$, $CH_3CH_2OOCC_{chain}N$, ^3J = 5.87 Hz), 3.15, 3.25 (2m, 2H, CH_3CH_2N), 4.06 (m, 2H, $CH_3CH_2OOCC_{ring}NEt$), 4.11 (m, 2H, $CH_3CH_2OOCC_{chain}H$), 4.28 (m, 2H, $CH_3CH_2OOCC_{ring}CHMe$), 4.35, 4.46 (dd, 2H, $C^2_{ring}H_2$, ^2J = 5.87 Hz), 4.36 (m, 2H, $CH_3CH_2OOCC_{chain}N$), 4.82 (m, 1H, C*H*Me), 4.83 ppm (s, 1H, $CH_3CH_2OOCC_{chain}H$); ^{13}C NMR: 13.77 (CH_3 in $EtOOCC_{ring}CHMe$ and $EtOOCC$-$_{chain}N$), 14.23 (CH_3 in $EtOOCC_{chain}H$ and $EtOOCC_{ring}N$), 16.02 ($NC_{ring}HCH_3$), 41.22 (CH_3CH_2N), 48.97 ($NC_{ring}HMe$), 59.41 (CH_2 in $EtOOCC_{ring}N$), 59.55 (CH_2 in $EtOOCC_{chain}H$), 61.32 (CH_2 in $EtOOCC_{ring}CHN$), 62.31 (CH_2 in $EtOOCC$-$_{chain}N$), 63.98 (NCH_2N), 88.45 ($EtOOCC_{chain}H$), 112.33 ($EtOOCC_{ring}CHN$), 149.43 ($EtOOCC_{ring}N$), 151.95 ($EtOOCC$-$_{chain}N$), 163.65 ($EtOOCC_{chain}H$), 165.16 ($EtOOCC_{chain}N$), 166.78 ($EtOOCC_{ring}N$), 167.01 ppm ($EtOOCC_{ring}CHN$). Anal. Calcd for $C_{19}H_{28}N_2O_8$ (412.43): C, 55.33; H, 6.84; N, 6.79. Found: C, 55.35; H, 6.84; N, 6.76.

Diethyl 1-[3-ethoxy-1-(ethoxycarbonyl)-3-oxoprop-1-enyl]-2,3-diethyl-6-methyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (13g). This compound was obtained as yellow nondistilled oil, 57% yield, R_f 0.38; IR: 664, 748, 782, 810, 866, 974, 1042, 1110, 1160, 1234, 1282, 1366, 1442, 1588, 1710, 1738, 2868, 2910, 2940, 2974, 2986 cm^{-1}; ^1H NMR: δ 0.82 (t, 3H, $CH_3CH_2C^2_{ring}$, ^3J = 6.35 Hz), 1.20, 1.28 (2t, 12H, CH_3CH_2COO, ^3J = 7.33 Hz), 1.49 (m, 3H, NCH_2CH_3, ^3J = 6.84 Hz), 1.59, 1.97 (2m, 3H, $CH_3C^6_{ring}$, ^3J = 5.86 Hz), 1.86, 2.22 (2m, 2H, $CH_3CH_2C^2_{ring}$, ^3J = 5.37 Hz), 3.01, 3.22 (2m, 2H, NCH_2CH_3, ^3J = 6.83 Hz), 4.11, 4.26 (2m, 10H, $C^6_{ring}H$, $C^2_{ring}H$, 4 CH_3CH_2OOC), 4.79 ppm (s, 1H, $EtOOCC_{chain}H$); ^{13}C NMR: δ 10.36 ($CH_3CH_2C^2_{ring}$), 13.91, 14.27 (CH_3CH_2COO), 14.73 (NCH_2CH_3), 20.24 ($C^6_{ring}CH_3$), 24.63 ($CH_3CH_2C^2_{ring}$), 47.34 (NCH_2CH_3), 63.03 ($C^2_{ring}H$), 59.70, 60.36, 61.99, 62.22 (CH_3CH_2COO), 73.57 ($C^6_{ring}H$), 91.10 ($EtOOCC_{chain}H$), 108.28 ($EtOOCC_{chain}N$), 145.55 ($EtOOCC^4_{ring}$), 150.67 ($EtOOCC^5_{ring}$), 164.78, 164.86, 165.61, 167.15 ppm (*C*OOEt). Anal. Calcd for $C_{23}H_{36}N_2O_8$ (468.54): C, 58.96; H, 7.74; N, 5.98. Found: C, 58.96; H, 7.77; N, 5.98.

Diethyl 1-[3-ethoxy-1-(ethoxycarbonyl)-3-oxoprop-1-enyl]-3-ethyl-2,6-dimethyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (13h). This compound was obtained as yellow nondistilled oil, 35% yield, R_f 0.39; IR: 668, 756, 864, 1032, 1040, 1040, 1152, 1296, 1368, 1444, 1464, 1588, 1736, 2880, 2940, 2984 cm^{-1}; ^1H NMR: δ 1.18 (t, 3H, CH_3CH_2N, ^3J = 5.37 Hz), 1.25 (t, 3H, $CH_3CH_2OOCC^4_{ring}$, ^3J = 6.35 Hz), 1.27 (t, 3H, $CH_3CH_2OOCC_{chain}N$, ^3J = 6.35 Hz), 1.33 (t, 3H, $CH_3CH_2OOCC^5_{ring}$, ^3J = 6.35 Hz), 1.36 (t, 3H, $CH_3C^2_{ring}$, ^3J = 5.86 Hz), 1.39 (t, 3H, $CH_3CH_2OOCC_{chain}H$, ^3J = 6.35 Hz), 1.42 (d, 3H, $CH_3C^6_{ring}$, ^3J = 4.88 Hz), 3.03, 3.19 (2m, 2H, CH_3CH_2N, ^3J = 6.84 Hz), 4.09 (qv, 2H, $CH_3CH_2OOCC^4_{ring}$, ^3J = 6.35 Hz), 4.17 (qv, 2H, $CH_3CH_2OOCC_{chain}N$, ^3J = 6.35 Hz), 4.22 (qv, 1H, $C^6_{ring}H$, ^3J = 4.88 Hz), 4.32 (m, 2H, $CH_3CH_2OOCC^5_{ring}$, ^3J = 6.35 Hz), 4.43 (m, 2H, $CH_3CH_2OOCC_{chain}H$, ^3J = 6.35 Hz), 4.48 (qv, 1H, $C^2_{ring}H$, ^3J = 5.86 Hz), 4.99 ppm (s, 1H, $EtOOCC_{chain}H$); ^{13}C NMR: δ 14.18 ($CH_3CH_2OOCC^4_{ring}$), 14.22 ($CH_3CH_2OOCC_{chain}H$), 14.30 ($CH_3CH_2OOCC^5_{ring}$), 14.38 ($CH_3CH_2OOCC_{chain}N$), 14.39 (CH_3CH_2N), 16.94 (CH_3C^2), 19.98 ($CH_3C^6_{ring}$), 45.64 (NCH_2CH_3), 47.10 ($C^6_{ring}H$), 59.57 ($CH_3CH_2OOCC^4_{ring}$), 60.16 ($CH_3CH_2OOCC_{chain}N$), 61.91 ($CH_3CH_2OOCC^5_{ring}$), 62.13 ($CH_3CH_2OOCC_{chain}H$), 67.50 ($C^2_{ring}H$), 91.03 ($EtOOCC_{chain}H$), 106.32 ($EtOOCC^5_{ring}$), 145.99 ($EtOOCC^4_{ring}$), 150.11 ($EtOOCC_{chain}N$), 164.52 ($EtOOCC^5_{ring}$), 164.75 ($EtOOCC_{chain}N$), 165.53 ($EtOOCC_{chain}H$), 167.17 ppm ($EtOOCC^4_{ring}$); ms: *m*/*z* (I, %) 423 (3, M – OC_2H_5 – 2H), 381 (7, M – $CO_2C_2H_5$), 366 (3, M – OC_2H_5 – C_2H_5 – 2 CH_3), 243 (36, M – 2 $CO_2C_2H_5$ – 2 C – CH – CH_3), 168 (100, pyrimidine + 2 CO_2), 138 (23, pyrimidine + 2 H +2 CH_3) + C_2H_5), 94 (37, pyrimidine + H + CH_3), 45 (46, C_2H_5). Anal. Calcd for $C_{22}H_{34}N_2O_8$ (454.51): C, 58.14; H, 7.54; N, 6.16. Found: C, 58.17; H, 7.53; N, 6.16.

Diethyl 1-[3-ethoxy-1-(ethoxycarbonyl)-3-oxoprop-1-enyl]-3-propyl-2,6-diethyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (13i). This compound was obtained as yellow nondistilled oil, 62% yield, R_f 0.38; IR: 668, 748, 780, 808, 864, 976, 1048, 1100, 1156, 1232, 1280, 1368, 1448, 1584, 1700, 1736, 2876, 2908, 2936, 2980 cm^{-1}; ^1H NMR: δ 0.64 (t, 3H, $CH_3CH_2C^2_{ring}$, ^3J = 6.84 Hz), 0.77 (t, 3H, $CH_3CH_2CH_2N$), 0.79 (t, 3H, $CH_3CH_2C^6_{ring}H$), 1.16, 1.28 (2t, 12H, CH_3CH_2COO, ^3J = 6.35 Hz), 1.44 (m, 2H, $NCH_2CH_2CH_3$, ^3J = 6.84 Hz), 1.51,

1.86 (2m, 2H, $CH_3CH_2C^6_{ring}H$, ^3J = 7.32 Hz), 1.62, 2.09 (2m, 2H, $CH_3CH_2C^2_{ring}$, ^3J = 7.33 Hz), 2.81, 3.07 (2m, 2H, NCH_2CH_2, ^3J = 6.35 Hz), 4.11 (m, 1H, $C^6_{ring}H$), 4.24, 4.32 (2m, 8H, CH_3CH_2OOC, ^3J = 6.35 Hz), 4.27 (m, 1H, $C^2_{ring}H$), 4.82 ppm (s, 1H, $EtOOCC_{chain}H$); ^{13}C NMR: δ 7.45 ($CH_3CH_2C^2_{ring}$), 10.38 ($CH_3CH_2C^6_{ring}$), 11.46 ($CH_3CH_2CH_2N$), 14.18, 14.63 (CH_3CH_2COO), 22.18 ($CH_3CH_2C^2_{ring}$), 23.12 ($NCH_2CH_2CH_3$), 24.22 ($CH_3CH_2C^6_{ring}$), 51.44 ($C^2_{ring}H$), 54.46 ($NCH_2CH_2CH_3$), 59.32, 59.78, 61.94, 62.36 (CH_3CH_2COO), 73.94 ($C^6_{ring}H$), 92.16 ($EtOOCC_{chain}H$), 102.96 ($EtOOCC_{chain}N$), 147.94 ($EtOOCC^4_{ring}$), 150.08 ($EtOOCC^5_{ring}$), 164.56, 167.22 ($EtOOCC^4_{ring}$, $EtOOCC^5_{ring}$, $EtOOCC_{chain}N$), 165.28 ppm ($EtOOCC_{chain}H$). Anal. Calcd for $C_{25}H_{40}N_2O_8$ (496.59): C, 60.47; H, 8.12; N, 5.64. Found: C, 60.46; H, 8.14; N, 5.62.

Diethyl 5-benzyl-1,2-bis(2-phenylethyl)-2,5-dihydro-1*H*-pyrazole-3,4-dicarboxylate (15). This compound was obtained as yellow nondistilled oil, 47% yield, R_f 0.41; IR: 700, 752, 860, 1028, 1096, 1180, 1240, 1372, 1456, 1500, 1604, 1740, 2876, 2940, 2984, 3028, 3064 cm^{-1}; ^1H NMR: δ 1.31 (t, 6H, 2 CH_3CH_2OOC, ^3J = 6.33 Hz), 2.92 (m, 6H, 3 $C_6H_5CH_2$, ^3J = 7.34 Hz), 4.24 (m, 5H, $C^5_{ring}H$, 2 NCH_2, ^3J = 6.61 Hz), 4.30 (qv, 4H, 2 CH_3CH_2OOC, ^3J = 6.35 Hz), 7.27 ppm (m, 15H, H in C_6H_5); ^{13}C NMR: δ 14.06 (CH_3CH_2OOC), 33.17, 35.13, 36.04 ($C_6H_5CH_2$), 54.44, 63.02 (NCH_2), 60.44, 61.84 (CH_3CH_2OOC), 66.30 ($C^5_{ring}H$), 126.62, 127.74, 128.02, 128.13, 128.39, 128.48, 128.66, 128.83 (*o*-, *m*-, *p*-*C* in C_6H_5), 137.56, 139.65, 139.82 ppm (*ipso*- *C* in C_6H_5); ms: *m*/*z* 481 (5, M – CH_2CH_3 – 2H), 445 (6, M – CH_3CH_2OO – 2H), 346 (8, M – $2C_6H_5$ – CH_2), 329 (10, M – $2C_6H_5CH_2$), 301 (16, M – $2C_6H_5CH_2CH_2$), 226 (14, M – $3C_6H_5$ – $2CH_2CH_2$), 105 (100, $C_6H_5CH_2CH_2$), 91 (88, $C_6H_5CH_2$), 77 (64, C_6H_5), 65 (35, pyrazole), 43 (36, NCH_2CH_2 + H). Anal. Calcd for $C_{19}H_{28}N_2O_8$ (512.43): C, 74.97; H, 7.08; N, 5.46. Found: C, 74.95; H, 7.10; N, 5.48.

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REFERENCES AND NOTES

[1] Makhova, N. N.; Petukhova, V. Y.; Kuznetsov, V. V. ARKIVOC 2008, i, 128.

[2] Kuznetsov, V. V.; Syroeshkina, Y. S.; Moskvin, D. I.; Struchkova, M. I.; Makhova, N. N.; Zharov, A. A. J Heterocycl Chem 2008, 45, 497.

[3] Shevtsov, A. V.; Petukhova, V. Y.; Strelenko, Y. A.; Lyssenko, K. A.; Fedyanin, I. V.; Makhova, N. N. Mendeleev Commun 2003, 221.

[4] Shevtsov, A. V.; Petukhova, V. Y.; Strelenko, Y. A. Mendeleev Commun 2005, 29.

[5] Shevtsov, A. V.; Petukhova, V. Y.; Strelenko, Y. A.; Lyssenko, K. A.; Makhova, N. N.; Tartakovski, V. A. Izv Acad Nauk Ser Khim 2005, 997 (Russ Chem Bull Int Ed 2005, 54, 1021).

[6] Shevtsov, A. V.; Kuznetsov, V. V.; Kislukhin, A. A.; Petukhova, V. Y.; Strelenko, Y. A.; Makhova, N. N. J Heterocycl Chem 2006, 43, 881.

[7] Shevtsov, A. V.; Kuznetsov, V. V.; Molotov, S. I.; Lyssenko, K. A.; Makhova, N. N. Izv Acad Nauk Ser Khim 2006, 534 (Russ Chem Bull Int Ed 2006, 55, 554).

[8] Shevtsov, A. V.; Kuznetsov, V. V.; Kislukhin, A. A.; Petukhova, V. Y.; Strelenko, Y. A.; Makhova, N. N. Mendeleev Commun 2006, 218.

[9] Syroeshkina, Y. S.; Kuznetsov, V. V.; Lyssenko, K. A.; Makhova, N. N. Mendeleev Commun 2008, 18, 42.

[10] Syroeshkina, Y. S.; Kuznetsov, V. V.; Lyssenko, K. A.; Makhova, N. N. Izv Acad Nauk Ser Khim 2009, 534 (Russ Chem Bull Int Ed 2009, 58, 554).

[11] Syroeshkina, Y. S.; Kuznetsov, V. V.; Struchkova, M. I.; Epishina, M. A.; Makhova, N. N. Mendeleev Commun 2008, 18, 207.

[12] Carbony, B.; Toupet, L.; Carrie, R. Tetrahedron 1987, 43, 2293.

[13] Welton, T. Chem Rev 1999, 99, 2071.

[14] Wasserscheid, P.; Kein, W. Angew Chem Int Ed Engl 2000, 39, 3772.

[15] Wasserscheid, P.; Welton, T. Ionic Liquids in Synthesis; Wiley-VCH: New York, 2003; p 380.

[16] D'Anna, F.; Noto, R. Tetrahedron 2007, 63, 11681.

[17] Astolfi, D. L.; Mayville, F. C., Jr. Tetrahedron Lett 2003, 44, 9223.

[18] (a) Niedballa, U.; Vorbruggen, H. J Org Chem 1974, 39, 3660; (b) Zhang, M.; Jiang, H.; Liu, H.; Zhu, Q. Org Lett 2007, 9, 4111; (c) Weston Hurst, E.; Hull, R. J Med Pharm Chem 1961, 3, 215; (d) Nair, V.; Chi, G.; Ptak, R.; Neamati, N. J Med Chem 2006, 49, 445; (e) Pattarini, R.; Smeyne, R. J.; Morgan, J. I. Neuroscience 2007, 145, 654.