HETEROCYCLES, Vol. 89, No. 3, 2014, pp. 641 - 651. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 10th December, 2013, Accepted, 16th January, 2014, Published online, 24th January, 2014
DOI: 10.3987/COM-13-12910

SYNTHESIS OF PYRAZOLES BASED ON FUNCTIONALIZED ALLENOATES

Ilshat M. Sakhautdinov,[a]* Aynur M. Gumerov,[a] Ilnur R. Batyrshin,[a] Akhnaf A. Fatykhov,[a] Kyrill Yu. Suponitsky,[b] and Marat S. Yunusov[a]

[a] Institute of Organic Chemistry, Ufa Research Centre, Russian Academy of Sciences, Prospect Oktyabrya, 71,450054, Ufa, Russian Federation; e-mail: aygumer@mail.ru

[b] N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilov str., Moscow 119991, Russian Federation

Abstract – Regiospecific synthesis of pyrazole-3-carboxylate derivatives by 1,3-dipolar cycloaddition of diazomethane with allenoates in presence of triethylamine is demonstrated. Reaction of allenoates with stearic acid moiety containing diazoketone is explored under ultrasonic conditions. Novel derivatives of pyrazole were achieved in excellent yields.

INTRODUCTION

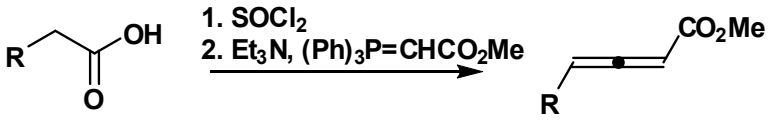
Among compounds containing nitrogen heterocyclic frameworks, pyrazole is one of most useful building blocks for various biologically active molecules. The biological activities of these compounds have been widely used as antidiabetic, antiviral, antimicrobial, antibacterial, anticancer agents. In addition to their biological importance, pyrazoles play important role as catalysts, molecular magnetic devices and sensors.[1-3] 1,3-Dipolar cycloaddition reactions of diazo compounds to double and triple bonds are well known and documented.[4] In contrast, studies including this methodology with regard to allenes have received much less attention.[5] In consideration of biological activity of compounds bearing the pyrazole moiety we planned the synthesis of series of pyrazole derivatives from functionalized allenoates.

RESULTS AND DISCUSSION

Allenoates **2a-f** were obtained from *N*-phthalyl amino acids **1a-c** and fatty acids **1d-f**. Thionyl chloride was used to convert acids **1a-f** to their corresponding acid chlorides. The reaction of acid chlorides with

triethylamine produced ketenes, followed by treatment with methyl (triphenylphosphoranylidene)acetate afforded allenoates **2a-f**[6] (Table 1).

Table 1. Synthesis of allenoates **2a-f**

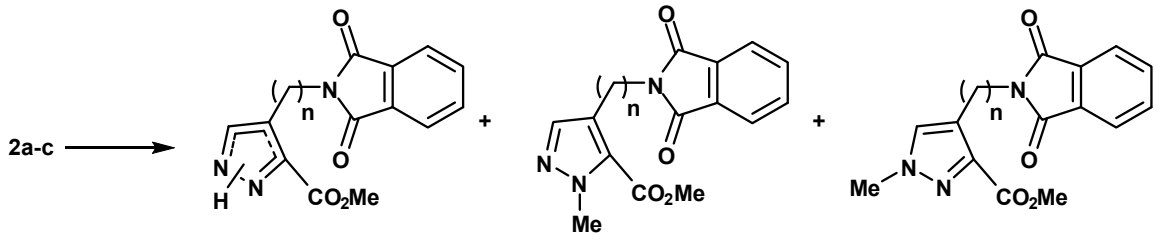


1 2

Entry	R	Isolated yields (%)
a	*N*-Phth	63
b	*N*-MePhth	75
c	*N*-EtPhth	87
d	$Me(CH_2)_{15}$	77
e	$Me(CH_2)_{13}$	85
f	$Me(CH_2)_4$	66

The allenoates **2a-c** were treated by excess diazomethane in the presence of equimolar quantity of triethylamine, what lead to formation of isomeric *N*-methylpyrazoles **4a-c**, **5a-c** (Table 2). Formation of *N*-methylpyrazoles observed even in a small excess of diazomethane but the best results were achieved in a six-fold excess.

Table 2. 1,3-Dipolar cycloaddition reaction of diazomethane with allenoates **2a-c**



3 4 5

Entry	n	Reagents	Isolated yields (%)		
			3	**4**	**5**
a	1	CH_2N_2, Et_3N	20	5	3
	1	6×CH_2N_2, Et_3N	-	33	40
b	2	CH_2N_2, Et_3N	-	10	5
	2	6×CH_2N_2, Et_3N	-	51	24
c	3	CH_2N_2, Et_3N	-	5	5
	3	6×CH_2N_2, Et_3N	-	27	21

When the reaction of allene **2a** with diazomethane was carried out in equimolar quantities, we obtained **3a** in 20% yield. The structure of pyrazole **3a** was confirmed by X-ray crystallographic analysis (Figure 1). Molecular structure of **3a** has some similarities and differences to **4a** that we characterized recently.[7]

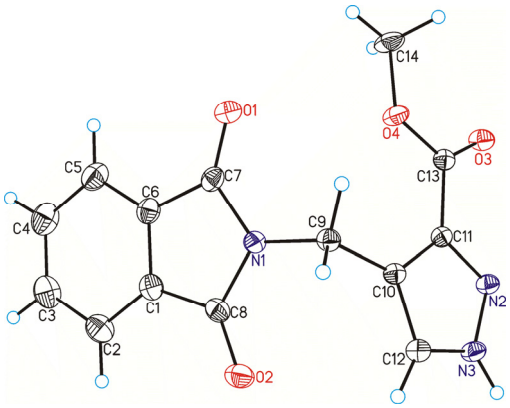
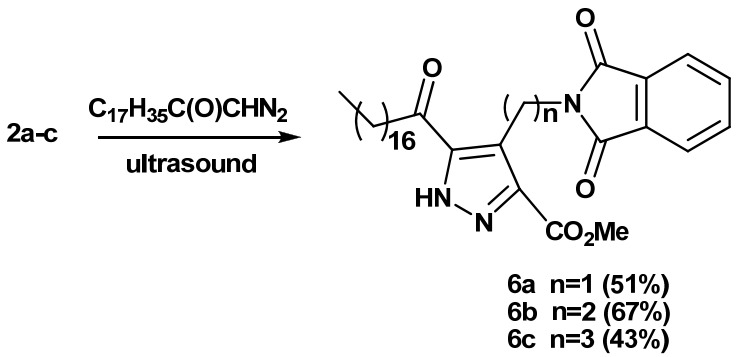


Figure 1. X-Ray crystal structure of **3a**

Regioisomeric compounds **4a-c** and **5a-c** were individually isolated by column chromatography on silica gel. The structure of **4a** was determined by X-ray crystallography, and the structure of compound **5a** was elucidated by a comparative analysis of the NMR spectra of compounds **4a** and **5a** using homo- and heteronuclear 2D correlations COSY, NOESY, HSQC, HMBC and ^{1}H-^{15}N-HMBC.[7]

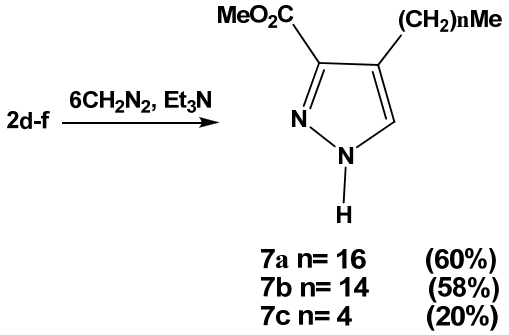
1,3-Dipolar cycloaddition reaction of diazoketone, obtained from stearic acid, with allenoates **2a-c** was carried out under ultrasonic irradiation in benzene at 65 °C during 20 h. The reaction proceeded regioselectively to provide pyrazole derivatives **6a-c** (Scheme 1).



Scheme 1. Ultrasonic irradiation assisted regioselective synthesis of pyrazoles **6a-c**

However, without ultrasonic treatment in benzene at reflux for 40 h, reaction did not proceed at all. Formation of the N-H insertion products were not observed when obtained pyrazoles **6a-c** were treated with excess of diazomethane or diazoketone from stearic acid, that is evidenced by the lack of consumption of

the starting materials. It was found that the pyrazoles **7a-c**, obtained from allenes **2d-f** including stearic, palmitic and caproic acids moieties, behave similarly (Scheme 2).



Scheme 2. Synthesis of pyrazoles **7a-c** including fatty acids moieties

1,3-Dipolar cycloaddition reaction of diazomethane with allenoates in the presence of triethylamine lead to regiospecific formation of pyrazoles, in case of absence of triethylamine we got the mixture of products that we couldn't isolate and identify. Apparently triethylamine forms complex with diazomethane,[8] which regioselectively attacks electrophilic sp-hybridized central carbon atom with the closure into cycle by the nucleophilic carbon that is in α-position to an ester group. The mechanism is shown in Figure 2.

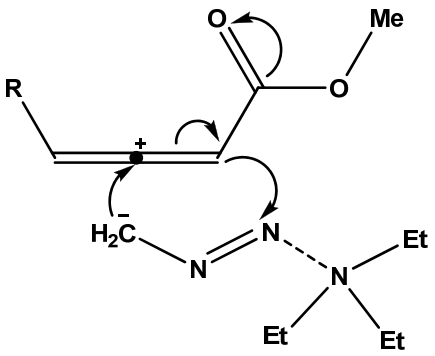


Figure 2. Mechanism of pyrazole synthesis

Formation of two *N*-methylpyrazoles from allenoates **2a-c** is explained by the isomerization of pyrazoline into pyrazole derivative that can exist in two tautomeric forms.[9,10] Due to formation of hydrogen bond similar to carboxylic acids[11] pyrazoles produce dimers, which tend to prototropic tautomerism (Figure 3).

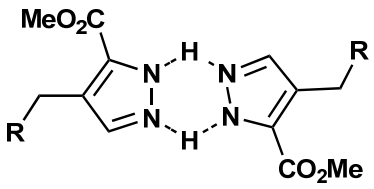


Figure 3

Polarization of N←H^+ bond, in the presence of electron acceptor group next to nitrogen atom, promotes N-H insertion of diazomethane similar to known reaction of the O-H insertion of diazomethane in carboxylic acids. In case of stearic, palmitic and caproic acids moieties containing pyrazoles **7a-c**, formation of *N*-methyl derivatives hindered due to steric factor and, on the other hand, being electron donor substituents, fatty acid moieties reduce N←H^+ polarization.

In conclusion, we have demonstrated that the treatment of 1,2-dienoates with diazomethane in the presence of triethylamine gives pyrazole-3-carboxylate derivatives with good regioselectivity. We have succeeded in developing the 1, 3-dipolar cycloaddition reaction of stearic acid moiety containing diazoketone with allenoates under ultrasonic condition, and a series of novel derivatives of pyrazole were obtained.

EXPERIMENTAL

The IR spectra were measured on a Spekord M-80 spectrometer from thin films or suspensions in mineral oil. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-500 spectrometer at 500.13 and 125.76 MHz, respectively, using tetramethylsilane as internal standard. Correct assignment of signals in the NMR spectra of compounds was achieved using homo- and heteronuclear 2-D correlation techniques: COSY, NOESY, HSQC, HMBC, ^{1}H-^{15}N-HMBC. The progress of reactions was monitored by thin-layer chromatography on Sorbfil PTSKh-AF-A plates; spots were detected by UV irradiation, treatment with iodine vapor, or spraying with a solution of ninhydrin or *p*-methoxybenzaldehyde with subsequent heating to 100–120 °C. The mass spectra were obtained on a Shimadzu LCMS-2010EV instrument. Elemental analysis was carried out using a EURO EA-3000 CHN element analyzer. Ultrasound was generated using a UZDN-2T setup with an operating frequency of 22 kHz. X-Ray diffraction measurements were carried out with Bruker APEX-II CCD diffractometer at 100K. Melting points were measured with a Buetius apparatus. The products were isolated by column chromatography on silica gel (40–100 and 100–160 μm; Chemapol).

General procedure for the synthesis of the allenoates 2a-f by Wittig reaction 1 g of an acid was dispersed in 10 mL of anhydrous benzene, five-fold excess of thionyl chloride was added, and the mixture was heated for 3 h under reflux. The solvent and excess thionyl chloride was distilled off on a rotary evaporator, and the residue (phthalimidoacetyl chloride) was used without additional purification. An equimolar amount of triethylamine was added to a solution of methyl (triphenyl-λ5-phosphanylidene)acetate in THF, the mixture was cooled to -10 °C, and a cold solution of phthalimidoacetyl chloride was slowly added dropwise. The mixture was stirred for 0.5 h and kept at 0 °C for 6 h, the precipitate was filtered off, the solvent was distilled off from the filtrate, and the residue was subjected to column chromatography on silica gel using petroleum ether–EtOAc (4 : 1) as eluent.

Methyl 4-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)buta-2,3-dienoate (2a). Yield 0.75 g (63%), white crystals, mp 95–97 °C. IR spectrum, ν cm^{-1}: 1782, 1763. ^{1}H NMR spectrum ($CDCl_3$), δ ppm: 3.72 s (3H,

CH_3), 6.21 d (1H, CH, J = 5.1 Hz), 7.25 d (1H, CH, J = 5.1 Hz), 7.74–7.83 m (4H, C_6H_4). ^{13}C NMR spectrum ($CDCl_3$), δ ppm: 52.62 (CH_3), 91.77 (CH), 96.71 (CH), 123.77 (CH_{arom}), 131.76 (C_{arom}), 134.67 (CH_{arom}), 164.49 (C=O), 164.74 (C=O), 210.03 (=C=); MS: *m/z* 244 $[MH]^+$, 243 $[M]^-$. Anal. Calcd for $C_{13}H_9NO_4$ (243.21): C 64.20; H 3.73; N 5.76; O 26.31. Found: C 64.21; H 3.74; N 5.73.

Methyl 5-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)penta-2,3-dienoate (2b). Yield 0.88 g (75%), white crystals, mp 87-88 °C. IR spectrum, ν cm^{-1}: 1709, 1771, 1964. ^1H NMR ($CDCl_3$), δ ppm: 3.63 s (3H, CH_3); 4.36 m. (2H, CH_2), 5.64 d.d. (1H, CH, J = 6.2, 2.9, 2.6 Hz), 5.74 m (1H, CH), 7.66-7.81 m (4H, C_6H_4). ^{13}C NMR ($CDCl_3$), δ ppm: 35.09 (CH_2), 52.11 (CH_3), 90.43 ($CH_{allene.}$), 91.40 ($CH_{allene.}$), 123.39 ($CH_{arom.}$), 131.91 ($C_{arom.}$), 134.15 ($CH_{arom.}$), 165.36 (C=O), 167.39 (C=O), 212.37 (=C=). MS: *m/z* 258 $[MH]^+$, 257 $[M]^-$. Anal. Calcd for $C_{14}H_{11}NO_4$ (257.07): C 65.37; H 4.31; N 5.44; O 24.88. Found: C 65.35; H 4.29; N 5.44.

Methyl 6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)hexa-2,3-dienoate (2c). Yield 1.01 g (87%), white crystals, mp 102-104 °C. IR, ν cm^{-1}: 1701, 1765, 1952. ^1H NMR ($CDCl_3$), δ ppm: 2.59 m (2H, CH_2), 3.54 s (3H, CH_3); 3.87 t (2H, CH_2, J = 7 Hz), 5.52 m (1H, CH), 5.65 m (1H, CH), 7.68-7.83 m (4H, C_6H_4). ^{13}C NMR ($CDCl_3$), δ ppm: 26.70 (CH_2), 36.77 (CH_2), 51.76 (CH_3), 88.39 ($CH_{allene.}$), 91.69 ($CH_{allene.}$), 123.21 ($CH_{arom.}$), 131.97 ($C_{arom.}$), 133.93 ($CH_{arom.}$), 165.96 (C=O), 168.11 (C=O), 212.44 (=C=). MS: *m/z* 272 $[MH]^+$, 271 $[M]^-$. Anal. Calcd for $C_{15}H_{13}NO_4$ (271.27): C 66.41; H 4.83; N 5.16; O 23.59. Found: C 66.39; H 4.81; N 5.16.

Methyl icosa-2,3-dienoate (2d). Yield 0.88 g (77%), yellow oil. IR, ν cm^{-1}: 1724, 1961, 2852, 2922. ^1H NMR ($CDCl_3$), δ ppm: 0.88 t (3H, CH_3, J = 7.2); 1.25 m (26H, $13CH_2$), 1.63 m (2H, CH_2), 3.73 s (3H, CH_3), 4.45 m (2H, CH_2), 5.57 m (1H, =CH, J = 7.0), 5.63 d (1H, =CH, J = 7.0). ^{13}C NMR ($CDCl_3$), δ ppm: 14.07 (CH_3), 22.66 (CH_2), 27.43 (CH_2), 28.7 (CH_2), 28.95 (CH_2), 29.33 (CH_2), 29.67 ($9CH_2$), 31.91 (CH_2), 51.83 (CH_3), 87.7 ($=CH_{allene}$), 95.44 ($=CH_{allene}$), 167.2 (C=O), 212.41 (=C=). MS: *m/z* 323 $[MH]^+$, 322 $[M]^-$. Anal. Calcd for $C_{21}H_{38}O_2$ (322.53): C 78.2; H 11.88; O 9.92. Found: C 78.2; H 11.88.

Methyl octadeca-2,3-dienoate (2e). Yield 0.98 g (85%), yellow oil. IR, ν cm^{-1}: 1961, 61. ^1H NMR ($CDCl_3$), δ ppm: 0.85 t (3H, CH_3, J = 6.7); 1.14-1.23 m (22H, $2CH_2$), 1.38-1.46 m (2H, CH_2), 2.08-2.14 m (2H, CH_2), 3.59 s (3H, CH_3), 5.53 s (1H, =CH), 5.58 s (1H, =CH). ^{13}C NMR ($CDCl_3$), δ ppm: 14.8 (CH_3), 22.62 (CH_2), 25.74 (CH_2), 28,64 (CH_2), 28,79 (CH_2), 28,91 (CH_2), 29.09 (CH_2), 29.3 (CH_2), 29.48 ($5CH_2$), 31.88 (CH_2), 51,8 (OCH_3), 87.85 ($=CH_{alk}$), 95.45 (CH), 166.58 (C=O), 212.32 (=C=). MS: *m/z* 295 $[MH]^+$, 294 $[M]^-$. Anal. Calcd for $C_{19}H_{34}O_2$ (294.47): C 77.5; H 11.64; O 10.87. Found: C 77.51; H 11.65; O 10.84.

Methyl octa-2,3-dienoate (2f). Yield 0.88 g (66%), yellow oil. IR, ν cm^{-1}: 1961, 61. ^1H NMR ($CDCl_3$), δ ppm: 0.87 t (3H, CH_3, J = 6,5); 1.21-1.48 m (4H, $2CH_2$), 2.15 m (2H, CH_2), 3.74 s (3H, CH_3), 5.64 s (1H, =CH), 6.55 s (1H, =CH). ^{13}C NMR ($CDCl_3$), δ ppm: 13.64 (CH_3), 21.82 (CH_2), 25.74 (CH_2), 30.67 (CH_2),

51.86 (OCH_3), 87.78 (=CH_{alk}), 95.36 (CH), 167.8 (C=O), 211.8 (=C=). MS: *m/z* 155 $[MH]^+$, 154 $[M]^-$. Anal. Calcd for $C_9H_{14}O_2$ (154,21): C 70.10; H 9.15; O 20.75. Found: C 70.12; H 9.15.

General procedure for the synthesis of the pyrazoles 3a, 4a-c, 5a-c, 7a-c from allenoates 2a-f A cold solution (0 °C) of 0.5 g of allenoates **2a-f** in 20 mL of CH_2Cl_2 was combined with an equimolar amount of triethylamine, and a six-fold excess of a freshly prepared solution of diazomethane in CH_2Cl_2 was added dropwise. The reaction mixture was stirred on a magnetic stirrer for 6 h at room temperature. The precipitate formed was separated by filtration, the solvent was removed, and the reaction products were separated by column chromatography on silica gel (eluent: petroleum ether/EtOAc 4/1).

Methyl 4-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-1*H*-pyrazole-3-carboxylate (3a). Yield 0.12 g (20%), mp 196-198 °C. IR, ν cm^{-1}: 1107, 1362, 1377, 1457, 1694. ^{1}H NMR (d_6-DMSO), δ ppm: 3.86 s (3H, CH_3O); 4.90 s (2H, CH_2), 7.87 s (1H, =CHN), 7.85-7.89 m (2H, C_6H_2), 7.91-7.94 m (2H, C_6H_2), 13.43 s (1H, NH). ^{13}C NMR ($CDCl_3$), δ ppm: 33.24 (CH_2), 51.92 (CH_3O), 119.75 (C), 123.57 ($CH_{arom.}$), 129.69 (=CHN), 132.27 ($C_{arom.}$), 134.80 ($CH_{arom.}$), 139.41(C=N), 163.35 (O=CO), 168.05 (O=CN). ^{15}N NMR ($CDCl_3$), δ ppm: 121 (N), 164 (NC=O), 213 (NH). MS: *m/z* 286 $[MH]^+$, 285 $[M]^-$. Anal. Calcd for $C_{14}H_{11}N_3O_4$ (285.25): C 58.95; H 3.89; N 14.73; O 22.44. Found: C 58.95; H 3.89; N 14.73.

X-Ray diffraction data of 3a. Monoclinic, space group $P2_1/c$: a = 12.9491(13)Å, b = 12.6702(13)Å, c = 7.9024(8)Å, β = 90.524(2)°, V = 1296.5(2)Å^3, Z = 4, M = 285.26, d_{calc} = 1.461 g cm^{-3}, $wR2$ = 0.1087 calculated on F^2_{hkl} for all 3435 independent reflections with 2θ<58°, (*GOF* = 1.019 R = 0.0427 calculated on F_{hkl} for 2711 reflections with $I>2\sigma(I)$). Crystallographic data (excluding structure factors) for the structure have been deposited at the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication No. CCDC 858681.

Methyl 4-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-methyl-1*H*-pyrazole-5-carboxylate (4b). Yield 0.31 g (51%), mp 110-112 °C. IR, ν cm^{-1}: 1125, 1286, 1396, 1466, 1713. ^{1}H NMR ($CDCl_3$), δ ppm: 3.02 t (2H, CH_2, J = 7.6, 7.4 Hz), 3.85 t (2H, CH_2N, J = 7.6, 7.4 Hz), 3.91 s (3H, CH_3O), 4.08 s (3H, CH_3N), 7.29 s (1H, CH=N), 7.71-7.75 m (2H, C_6H_2), 7.76-7.79 m (2H, C_6H_2). ^{13}C NMR ($CDCl_3$), δ ppm: 24.40 (CH_2), 38.22 (CH_2N), 40.29 (CH_3N), 51.89 (CH_3O), 122.83 (C), 123.16 ($CH_{arom.}$), 129.76 (=CN), 131.97 ($C_{arom.}$), 133.92 ($CH_{arom.}$), 138.62 (CH=N), 160.60 (O=CO), 168.10 (O=CN). ^{15}N NMR ($CDCl_3$), δ ppm: 19 (N), 163 ($N_{phtalyl.}$), 207 (NCH_3). MS: *m/z* 314 $[MH]^+$, 213 $[M]^-$. Anal. Calcd for $C_{16}H_{15}N_3O_4$ (313.31): C 61.34; H 4.83; N 13.41; O 20.43. Found: C 61. 33; H 4.83; N 13.41.

Methyl 4-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-methyl-1*H*-pyrazole-3-carboxylate (5b). Yield 0.15 g (24%), mp 153-154 °C. IR, ν cm^{-1}: 1119, 1273, 1385, 1466, 1705. ^{1}H NMR ($CDCl_3$), δ ppm: 3.14 t (2H, CH_2, J = 7.6, 7.1 Hz), 3.89 s (3H, CH_3O); 3.91 s (3H, CH_3N), 3.95 t (2H, CH_2N, J = 7.6, 7.1 Hz), 7.33 s (1H, CHN), 7.70-7.73 m (2H, C_6H_2), 7.75-7.78 m (2H, C_6H_2). ^{13}C NMR ($CDCl_3$), δ ppm:

23.38 (CH_2), 38.10 (CH_2N), 39.64 (CH_3N), 51.77 (CH_3O), 121.71 (C), 123.17 ($CH_{arom.}$), 131.00 (CHN), 131.85 ($C_{arom.}$), 133.88 (CH_{arom}), 140.47 (C=N), 162.81 (O=CO), 168.16 (O=CN). ^{15}N NMR ($CDCl_3$), δ ppm: 18 (N), 163 ($N_{phtalyl.}$), 205 (NCH_3). MS: *m*/*z* 314 $[MH]^+$, 213 $[M]^-$. Anal. Calcd for $C_{16}H_{15}N_3O_4$ (313.31): C 61.34; H 4.83; N 13.41; O 20.43. Found: C 61. 34; H 4.83; N 13.41.

Methyl 4-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-1-methyl-1*H*-pyrazole-5-carboxylate (4c). Yield 0.16 g (27%), mp 74-75 °C. IR, ν cm^{-1}: 1119, 1293, 1614, 1721, 1765. ^{1}H NMR ($CDCl_3$), δ ppm: 1.95-1.97 m (2H, CH_2), 2.73 t (2H, CH_2, *J* = 8.0, 7.3 Hz), 3.73 t (2H, CH_2, *J* = 6.6, 4.7 Hz), 3.85 s (3H, CH_3O); 4.09 s (3H, CH_3N), 7.37 s (1H, CHN), 7.70-7.72 m (2H, C_6H_2), 7.83-7.85 m (2H, C_6H_2). ^{13}C NMR ($CDCl_3$), δ ppm: 22.63 (CH_2), 29.10 (CH_2), 37.73 (CH_2N), 40.27 (CH_3N), 51.66 (CH_3O), 123.16 ($CH_{arom.}$), 127.31 (C), 132.09 ($C_{arom.}$), 133.15 (=CN), 133.97 ($CH_{arom.}$), 138.02 (CHN), 160.82 (O=CO), 168.33 (O=CN). MS: *m*/*z* 328 $[MH]^+$, 227 $[M]^-$. Anal. Calcd for $C_{17}H_{17}N_3O_4$ (327.33): C 62.38; H 5.23; N 12.84; O 19.55. Found: C 62.39; H 5.20; N 12.81.

Methyl 4-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-1-methyl-1*H*-pyrazole-3-carboxylate (5c). Yield 0.13 g (21%), white powder, mp 87-88 °C. IR, ν cm^{-1}: 1125, 1279, 1655, 1726, 1765. ^{1}H NMR ($CDCl_3$), δ ppm: 2.12-2.14 m (2H, CH_2), 3.22 t (2H, CH_2, *J* = 7.6, 7.3 Hz), 3.96 s (3H, CH_3O), 4.02 s (3H, CH_3N), 4.07 t (2H, CH_2, *J* = 6.4, 3.9 Hz), 7.69-7.72 m (2H, C_6H_2), 7.76 s (1H, CHN), 7.81-7.83 m (2H, C_6H_2). ^{13}C NMR ($CDCl_3$), δ ppm: 29.69 (CH_2), 33.23 (CH_2), 39.24 (CH_3N), 39.73 (CH_2N), 53.09 (CH_3O), 123.29 ($CH_{arom.}$), 124.24 (C), 132.06 ($C_{arom.}$), 134.07 (CHN), 134.09 ($CH_{arom.}$), 139.13 (C=N), 160.56 (O=CO), 168.09 (O=CN). MS: *m*/*z* 328 $[MH]^+$, 227 $[M]^-$. Anal. Calcd for $C_{17}H_{17}N_3O_4$ (327.33): C 62.38; H 5.23; N 12.84; O 19.55. Found: C 62.40; H 5.22; N 12.84.

Methyl 4-heptadecyl-1*H*-pyrazole-3-carboxylate (7a). Yield 0.34 g (60%), white oil. IR, ν cm^{-1}: 1697.36, 2868, 2936, 3238. ^{1}H NMR ($CDCl_3$), δ ppm: 0.9 t (3H, CH_3, *J* = 6,7); 1.27-1.38 m (28H, $14CH_2$), 1.61 m (2H, CH_2), 2.77 m (2H,CH_2), 3.97 s (3H, CH_3), 7.59 s (1H, =CH), 12.87 s (1H, = N H). ^{13}C NMR ($CDCl_3$), δ ppm: 14.11 (CH_3), 22.69 (CH_2), 24,44 (CH_2), 29.36 (CH_2), 29.43 (CH_2), 29.47 (CH_2), 29.65 (CH_2), 29.69 ($8CH_2$), 30.42 (CH_2), 31.92 (CH_2), 51.65 (OCH_3), 125.43 (=CH_{alk}), 130.5 (=CH), 133.26 (C= N), 162.73 (C=O). MS: *m*/*z* 365 $[MH]^+$, 364 $[M]^-$. Anal. Calcd for $C_{22}H_{40}N_2O_2$ (364.57): C 72.48; H 11.06; N 7.68; O 8.78. Found: C 72.46; H 10.05; N 7.65.

Methyl 4-pentadecyl-1*H*-pyrazole-3-carboxylate (7b). Yield 0.33 g (58%), white oil. IR, ν cm^{-1}: 1697, 2868, 2936, 3238. ^{1}H NMR ($CDCl_3$), δ ppm: 0.7 t (3H, CH_3, *J* = 7.2); 1.25-1.31 m (24H, $12CH_2$), 1.60 m (2H, CH_2), 2.75 m (2H, CH_2), 3.97 s (3H, OCH_3), 7.55 s (1H, =CH), 12.85 s (1H, N H). ^{13}C NMR ($CDCl_3$), δ ppm: 14.11 (CH_3), 22.69 (CH_2), 24.05 (CH_2), 29.35 (CH_2), 29.42 (CH_2), 29.60 (CH_2), 29.65 (CH_2), 29.68 (CH_2.), 30.26 (CH_2), 31.92 (CH_2), 51.93 (OCH_3), 125 (=CH_{alk}), 129.88 (=CH), 133.61 (C= N), 162.073 (C=O). MS: *m*/*z* 337 $[MH]^+$, 336 $[M]^-$. Anal. Calcd for $C_{20}H_{36}N_2O_2$ (336.51): C 71.38; H 10.78; N 8.32 O

9.51. Found: C 71.38; H 10.75; N 8.32.

Methyl 4-pentyl-1*H*-pyrazole-3-carboxylate (7c). Yield 0.13 g (20%), yellow oil. IR, ν cm^{-1}: 1961, 61. ^{1}H NMR ($CDCl_3$), δ ppm: 0.93 t (3H, CH_3, J = 7.5); 1.46 m (4H, $2CH_2$), 1.63 m (2H, CH_2), 2.77 m (2H, CH_2), 3.18 s (3H, OCH_3), 7.57 s (1H, =CH), 9.02 s (1H, NH). ^{13}C NMR ($CDCl_3$), δ ppm: 14.01 (CH_3), 22.42 (CH_2), 24.07 (CH_2), 29.9967 (CH_2), 31.52 (CH_2), 51.78 (OCH_3), 125.1 (=CH_{alk}), 133.85 (=CH), 135.77 (C=N), 162.1 (C=O). MS: *m*/*z* 197 $[MH]^+$, 196 $[M]^-$ Anal. Calcd for $C_{10}H_{16}N_2O_2$ (196.25): C 61.20; H 8.22; N 14.27; O 16.31. Found: C 61.22; H 8.21; N 14.23.

1-Diazononadecan-2-one. 1 g (3.5 mmol) of stearic acid , was dispersed in 10 mL of anhydrous benzene, five-fold excess of thionyl chloride was added, and the mixture was heated for 3 h under reflux. The solvent and excess thionyl chloride were removed under vacuum. The stearoyl chloride was dissolved in THF (15 mL), solution was stirred at 0 °C and diazomethane, obtained from nitrosomethylurea (26 mmol) in CH_2Cl_2 (26 mL), was slowly added dropwise. The mixture was stirred until gas no longer evolved. The solvent was removed under vacuum. The resulting crude products were purified by column chromatography using CH_2Cl_2 as eluent. Yield 0.89 g (82%), mp 52–53 °C. IR, ν cm^{-1}: 1620, 2122, 2849, 2918, 2955. ^{1}H NMR ($CDCl_3$), δ ppm: 0.88 t (3H, CH_3, ^3J = 5.7 Hz), 1.15-1.41 m (28H, $14CH_2$), 1.59-1.74 m (2H, CH_2), 2.25-2.42 m (2H, CH_2), 5.23 s (1H, CHN_2). ^{13}C NMR ($CDCl_3$), δ ppm: 14.06 (CH_3), 22.65 (CH_2), 25.19 (CH_2), 29.20 (CH_2), 29.33 (CH_2), 29.43 (CH_2), 29.65 (CH_2), 31.90 (CH_2), 41.10 (CH_2), 54.07 (CHN_2), 195.23 (C=O). Anal. Calcd for $C_{19}H_{36}N_2O$: C 73.97; H 11.76; N 9.08. Found: C 74.15; H 11.71; N 9.12.

General procedure for the synthesis of the pyrazoles 6a-c from allenoates 2a-c. Dry 50 ml flask was charged with allene (1mmol), 1-diazononadecan-2-one (1 mmol) and benzene (10 mL). The mixture was sonicated at 68 °C for 20 h (monitored by TLC). After completion of the reaction, the solvent was removed under vacuum. The resulting crude products were purified by column chromatography using petroleum ether – EtOAc (7:3) as eluent.

Methyl 4-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-5-stearoyl-1*H*-pyrazole-3-carboxylate (6a). Yield 0.28 g (51%), mp 98-99 °C, IR, ν, cm^{-1}: 1686, 1709, 2918. ^{1}H NMR ($CDCl_3$), δ ppm: 0.92 t (3H, CH_3, ^3J = 6.9 Hz), 1.19-1.40 m (28H, $14CH_2$), 1.71-1.79 m (2H, CH_2), 3.09 t (2H, CH_2, ^3J = 7.7 Hz), 3.90 c (3H, CH_3), 5.40 s (2H, CH_2N), 7.73-7.74 m (2H, C_6H_2), 7.83-7.85 m (2H, C_6H_2), 11.82 s (1H, NH). ^{13}C NMR ($CDCl_3$), δ ppm: 14.13 (CH_3), 22.69 (CH_2), 23.59 (CH_2), 29.29 (CH_2), 29.36 (CH_2), 29.50 (CH_2), 29.52 (CH_2), 29.66 (CH_2), 31.70 (CH_2), 31.92 (CH_2), 39.88 (CH_2), 52.63 (CH_2N), 120.05 ($\underline{C}CH_2$), 123.17 ($CH_{arom.}$), 132.01 ($C_{arom.}$), 132.02 ($\underline{C}COOCH_3$), 133.83 ($CH_{arom.}$), 149.56 ($\underline{C}$-C=O), 159.61 (O=CO), 167.84(O=CN), 197.43 (C=O). MS: *m*/*z* 552 $[MH]^+$, 551 $[M]^-$. Anal. Calcd for $C_{32}H_{45}N_3O_5$ (551.72): C 69.66; H 8.22; N 7.62; O 14.50. Found: C 69.68; H 8.20; N 7.62.

Methyl 4-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-5-stearoyl-1*H*-pyrazole-3-carboxylate

(6b). Yield 0.38 g (67%), mp 66-67 °C. IR, ν, cm^{-1}: 1672, 1715, 2851. ^1H NMR ($CDCl_3$), δ ppm: 0.86 t (3H, CH_3, ^3J = 6.5 Hz), 1.12-1.32 m (28H, 14CH_2), 1.53-1.61 m (2H, CH_2), 2.96 t (2H, CH_2, ^3J = 7.5 Hz), 3.44 t (2H, CH_2, ^3J = 7.5 Hz), 3.74 s (3H, CH_3), 4.00 t (2H, CH_2N, ^3J = 6.5 Hz), 7.64-7.66 m (2H, C_6H_2), 7.71-7.73 m (2H, C_6H_2), 11.78 s (1H, NH). ^{13}C NMR ($CDCl_3$), δ ppm: 14.12 (CH_3), 22.68 (CH_2), 22.90 (CH_2), 23.88 (CH_2), 29.28 (CH_2), 29.35 (CH_2), 29.52 (CH_2), 29.69 (CH_2), 31.90 (CH_2), 35.12 (CH_2), 37.82 (CH_2N), 39.58 ($\underline{C}H_2CO$), 52.25 (CH_3), 123.04 ($CH_{arom.}$), 124.06 ($\underline{C}CH_2$), 132.03 ($C_{arom.}$), 132.95 ($\underline{C}COOCH_3$), 133.73 ($CH_{arom.}$), 148.85 ($\underline{C}C{=}O$), 160.03 (O=CO), 168.19 (O=CN), 197.49 (C=O). MS: *m*/*z* 566 $[MH]^+$ 565 $[M]^-$. Anal. Calcd for $C_{33}H_{47}N_3O_5$ (565.74): C 70.06; H 8.37; N 7.43; O 14.14. Found: C 69.98; H 8.35; N 7.42.

Methyl 4-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-5-stearoyl-1*H*-pyrazole-3-carboxylate (6c). Yield 0.25 g (43%), mp 60-61 °C. IR, ν cm^{-1}: 1689, 1724, 2925. ^1H NMR ($CDCl_3$), δ ppm: 0.90 t (3H, CH_3, ^3J = 6.9 Hz), 1.18-1.40 m (28H, 14CH_2), 1.68-1.74 m (2H, CH_2), 2.01-2.03 m (2H, CH_2), 3.04 t (2H, CH_2, ^3J = 7.5 Hz), 3.16 t (2H, CH_2, ^3J = 7.7 Hz), 3.81 t (2H, CH_2, ^3J = 7.0 Hz), 3.89 s (3H, CH_3), 7.74-7.76 m (2H, C_6H_2), 7.88-7.89 m (2H, C_6H_2), 11.77 s (1H, NH). ^{13}C NMR ($CDCl_3$), δ ppm: 14.13 (CH_3), 21.02 (CH_2), 22.70 (CH_2), 23.91 (CH_2), 28.99 (CH_2), 29.31 (CH_2), 29.36 (CH_2), 29.54 (CH_2), 29.71 (CH_2), 31.92 (CH_2), 37.83 (CH_2N), 39.67 ($\underline{C}H_2CO$), 52.25 (CH_3), 123.17 ($CH_{arom.}$), 123.21 ($C_{arom.}$), 123.54 ($\underline{C}COOCH_3$), 127.05 ($\underline{C}CH_2$), 133.80 ($CH_{arom.}$), 148.43 ($\underline{C}C{=}O$), 160.14 (O=CO), 168.46 (O=CN), 197.09 (C=O). MS: *m*/*z* 580 $[MH]^+$ 579 $[M]^-$. Anal. Calcd for $C_{33}H_{47}N_3O_5$ (579.77): C 70.44; H 8.52; N 7.25; O 13.80. Found: C 70.42; H 8.55; N 7.25.

ACKNOWLEDGEMENTS

This study was performed under financial support by the President of the Russian Federation (program for support of leading scientific schools, project no. NSh-7014.2012.3) and by the Russian Foundation for Basic Research Competition «a» 14-03-00180.

REFERENCES

1. J. Elguero, P. Goya, N. Jagerovic, and A. M. S. Silva, *Targets in Heterocyclic Systems*, ed. by O. A. Attanasi and D. Spinelli, Italian Society of Chemistry, Rome, 2002, **6**, 52.
2. A. A. Bekhit, H. M. Ashour, and A. A. Guemei, *Arch. Pharm.,* 2005, **338**, 167.
3. A. Ramadan, A. Eltaib, and U. Kamal, *Tetrahedron,* 2012, **68**, 1637.
4. (a) G. Maas, In Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products; Wiley: Hoboken, NJ, 2003; (b) M. Kissane, S. E. Lawrence, and A. R. Maguire, *Org. Biomol. Chem*., 2010, **8**, 2735; (c) J. L. Ruano, M. T. Peromingo, M. Alonso, A. Fraile, M. R.

Martin, and A. Tito, *J. Org. Chem.*, 2005, **70**, 8942; (d) M. Yu. Ovchinnikov, T. A. Yangirov, A. N. Lobov, R. M. Sultanova, and S. L. Khursan, *Int. J. of Chem. Kinet*., 2013, **45**, 499.

5. N. Krause and A. S. K. Hashmi, Modern Allene Chemistry, WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004, 675.
6. (a) R. W. Lang and H. J. Hansen, *Helv. Chim. Acta*, 1979, **62**, 1025; (b) R. W. Lang and H. J. Hansen, *Helv. Chim. Acta*, 1980, **63**, 438; (c) R. W. Lang and H. J. Hansen, *Org. Synth.*, 1984, **62**, 202.
7. I. M. Sakhautdinov, I. R. Batyrshin, A. A. Fatykhov, V. M. Yumabaeva, K. Yu. Suponitsky, M. Yu. Antipin, and M. S. Yunusov, *J. Struct. Chem.*, 2013, **54**, 383.
8. R. K. Palakodety, R. S. Empati, and M. Florence, *Tetrahedron Lett*., 2008, **49**, 6768.
9. E. Consuelo, B. Mercedes, M. Rosa, S. Dionisia, and E. José, *The Open Org. Chem. J.,* 2008, **2***,* 10.
10. G. Bekker, An Introduction to the Electronic Theory of Organic Reactions, Moscow, 1977, 164.
11. J. Steed and J. Atwood, Supramolecular Chemistry, J. Wiley & Sons: Chichester, 2009, 29.