

A NEW APPROACH TO SYNTHESIS OF FUNCTIONALIZED SPIRO[5,5]UNDEC-2-EN-2-CARBOXYLATES

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Abstract. As a result of the studies, a new multicomponent condensation of dime-done, aromatic aldehydes, acetoacetic ester and allylamine in amolar ratio of 1: 2: 1: 1, respectively, was revealed. These reactions lead to the formation of ethyl-3-(allylamino)-9,9-dimethyl-7,11-dioxo-1,5-diarylspro[5.5]undec-2-en-2-carboxylates. Thus, new possibilities of multicomponent reactions involving 1,3-dicarbonyl compounds proceeding via the cascade carbocyclization mechanism are shown. Structure of all synthesized compounds confirmed by modern physical methods of analysis. By the method of XRD analysis the stereo orientation of substituents in the spirocyclic framework is established.

Keywords: multicomponent condensation, dimedone, 1,3-dicarbonyl compounds, allylamine, spiro[5.5]undec-2-en-2-carboxylates.

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Received: 25 October 2019; **Accepted:** 03 December 2019; **Published:** 15 December 2019.

1. Introduction

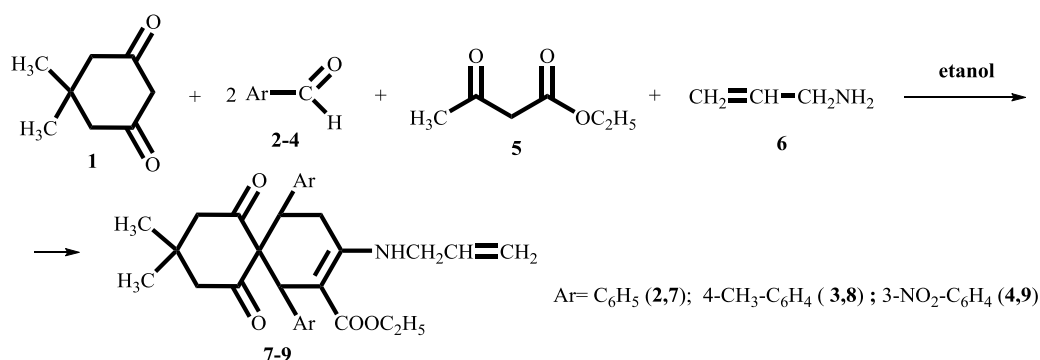
One of the urgent problems of modern organic chemistry is the creation of the structurally complex organic compounds from simple substrates. The synthetic procedures used for that purpose must correspond to criteria of ecology, safety, atomic (Trost, 2002) and stage (Wender *et al.*, 2005) efficiency. It is considered that multicomponent reactions correspond well to the indicated requirements and approach close to the "ideal synthesis". However, in recent time, together with such generally known advantages of multicomponent reactions, as one-pottedness, simplicity of automation, availability of starting materials, low consumption of solvents, one more argument comes to the fore, namely the possibility of increasing the variety of the compounds synthesized (Ruijter *et al.*, 2011; Biggs-Houck, 2010). This is linked with the fact that multicomponent reactions occur not as singly acting synchronous processes but as tandem processes consisting of sequential two-component interactions. It is significant that on interaction of the same starting reactants, several tandem cascades are possible, and the final products in each case may differ somewhat in their structure. For example, three-component reaction of substrates A, B, and C may take place by several routes: (A+B)+C, (B+C)+A, (A+C)+B etc. All this, in particular, leads to the fact that such factors as the stoichiometric ratio of reactants (Sha *et al.* 2009) or the sequence of adding them (Suzuki *et al.* 2009; Chebanov *et al.*, 2012) show a significant influence on the selectivity of multicomponent reactions.

Expanding preparative abilities of multicomponent reactions by using novel functional reagents is one of most important fields of organic synthesis. From this viewpoint multicomponent reactions of 1,3-dicarbonyl compounds, in particular dimedone, are particularly attractive, since the variation of the reagent structure in these

reactions leads to the formation of complex carbo- and heterocyclic compounds (Kozlov *et al.*, 2008; Kefayati *et al.*, 2012; Bazgir *et al.*, 2007; Azzam *et al.*, 2012; Quiroga, 2005; Nasri *et al.* 2018; Kour *et al.*, 2017; Puligoundla *et al.*, 2013; Abiyeva, *et al.* 2018). Multicomponent condensation of dimedone, acetoacetic acid derivatives, aromatic aldehydes and ammonium (amines) is usually performed with equimolar amounts of these reagents and results in polyhydroquinoline derivatives having a wide range of biological properties (Evans *et al.*, 2009).

2. Results and discussion

As a result of studies of multicomponent reactions involving dimedone, we found that the condensation of dimedone (**1**), arylaldehydes (**2-4**), acetoacetic acid ester (**5**) and allylamine (**6**), in a molar ratio of 1:2:1:1, respectively, proceeds in a direction not described in the literature and leads to new compounds with a spirocyclic framework (**7-9**) (Scheme 1):



Scheme 1.

The structure of ethyl-3-(allylamino)-9,9-dimethyl-7,11-dioxo-1,5-diarylspro[5.5]undec-2-en-2-carboxylates (**7-9**) is confirmed by the IR-, NMR and mass spectrometry and elemental analysis, as well as the XRD analysis of compound (**7**) (Magerramov *et al.*, 2014).

The prospective view of the molecule of (**7**) with the numbering of non-hydrogen atoms is shown in Fig.1.

The C₃₁H₃₅NO₄ crystals are monoclinic: $a = 10.5761(6)$ Å, $b = 13.5860(8)$ Å, $c = 18.412(1)$ Å, $\beta = 92.563(1)^\circ$, $V = 2642.9(3)$ Å³, space group $P2_1/n$, $Z = 4$.

The structure was solved by direct method and refined by the least squares technique against F^2 in the anisotropic approximation for non-hydrogen atoms. The non-hydrogen atoms of disordered moieties of the molecule (ethyl and vinyl groups) were refined in the isotropic approximation. The position of the H atom involved in the formation of the intramolecular hydrogen bond is found from the electron density difference map and refined in the isotropic approximation. Coordinates of other H atoms were calculated geometrically and refined in the riding model. The final values of the divergence factors are: $R_1 = 0.0542$ and $wR_2 = 0.1417$ (for 4391 diffraction reflections with $I > 2\sigma(I)$), $R_1 = 0.0732$ and $wR_2 = 0.1615$ over the whole set of independent diffraction reflections. All calculations were carried out using the SHELXTL program package.

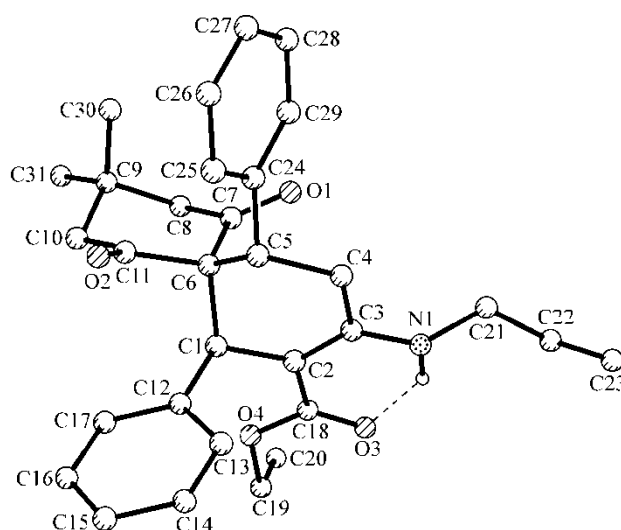


Figure 1. Prospective view of the molecule of (7) with the numbering of non-hydrogen atoms

The CIF-file containing full information on the studied structure of **7** has been deposited with CCDC under No.914117 and can be received free of charge on request at the following site: www.ccdc.cam.ac.uk/data_request/cif.

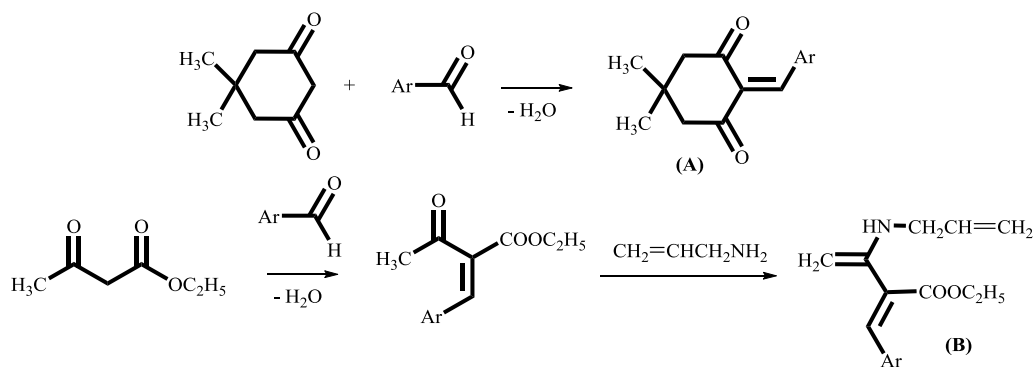
The molecule of (**7**) contains a spirocyclic moiety consisting of two six-membered aunctionally substituted carbocycles: $C_1-C_2-C_3-C_4-C_5-C_6$ (**A**) and $C_6-C_7-C_8-C_9-C_{10}-C_{11}$ (**B**). The cycle (**A**) has an *envelope* conformation (semi-boat): C_1 , C_2 , C_3 , C_4 and C_5 atoms lie in one plane (the average deviation of the mentioned atoms from the plane is $0.010(3)$ Å at a maximum deviation of $0.013(3)$ Å), whereas the C_6 atom deviates from the mentioned plane by $0.743(3)$ Å. The cycle (**B**) has a slightly flattened *chair* conformation: C_7 , C_8 , C_{10} and C_{11} atoms lie in one plane (the average deviation of the mentioned atoms from the plane is $0.001(3)$ Å at a maximum deviation of $0.003(3)$ Å), whereas the C_6 and C_9 atoms deviate from the mentioned plane to different sides by $-0.454(3)$ Å and $0.704(3)$ Å respectively.

The molecule of (**7**) has the intramolecular $N_1-H_1 \dots O_3$ hydrogen bond (Fig. 1) whose geometric characteristics are given in Table 1.

Table 1. Geometric characteristics of intramolecular $N_1-H_1 \dots O_3$ hydrogen bonds

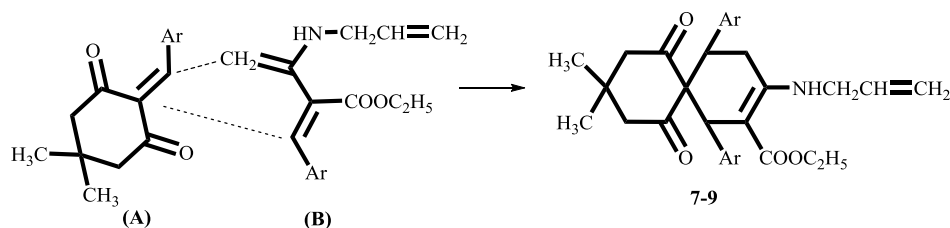
D—H...A bond	$d(D-H)$	$d(H...A)$	$d(D...A)$	D—H—A angle, deg
$N_1-H_1 \dots O_3$	0,89(2)	1,88(2)	2,620(3)	140(2)

The proposed reaction mechanism involves the initial formation of enamine (**A**) and Knoevenagel product (**B**) (Scheme 2):



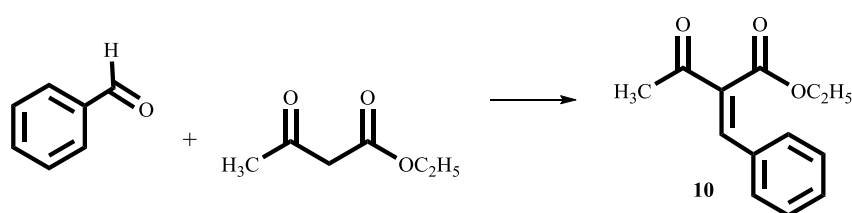
Scheme 2.

In our opinion, these two intermediates eventually form the Diels-Alder reaction products (7-9) (scheme 3):



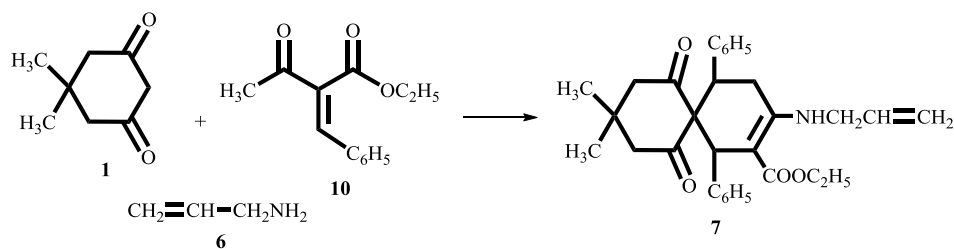
Scheme 3.

Earlier, we reported about the structure of (Z)-ethyl 2-benzylidene-3-oxobutanoate (10) (Fig.2), obtained by the reaction of benzaldehyde with acetoacetic ether in the presence of a piperidine as catalyst (scheme 4) (Ismiyev, 2011)

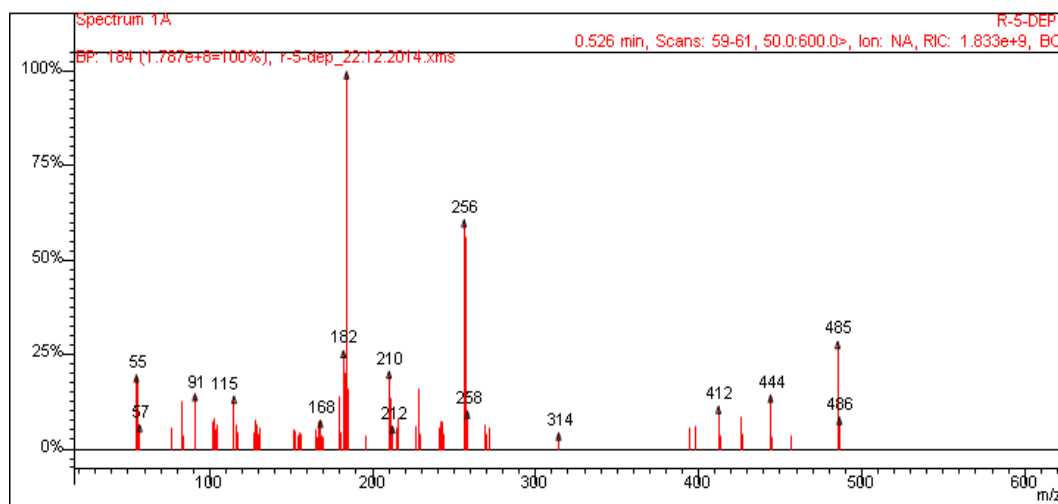


Scheme 4.

Investigating the three-component reaction of compound (10) with dimedone and allylamine, we found that the previously synthesized compound (7) is formed as the only reaction product in a yield of 76% (scheme 4)



The structure of synthesized compound (7) was also established by mass spectrometry (**Fig. 2**).



3. Experimental part

All commercially available chemicals were obtained from Merc and Sigma-Aldrich companies without further purification. The IR spectra were run on a Varian 3600 FT-IR Excalibur Series FTIR spectrometer in KBr pellets. The ^1H and ^{13}C NMR spectra were measured on a Bruker Avance-300 MHz spectrometer at 300 and 75 MHz, respectively. Elemental analysis for C, H, and N was performed on a Carlo Erba 1106 analyzer. The melting points were measured on a Kofler hot stage. The purity of the synthesized compounds was checked by TLC on Silufol UV-254 plates, eluent acetone–hexane (1 : 1), development in iodine vapor, UV detector. The crystal for XRD was obtained by double crystallization of compound (7) from ethanol. The XRD analysis of compound (7) was performed at room temperature on a Bruker SMART APEX II CCD diffractometer (MoK $_{\alpha}$ radiation, graphite monochromator, φ - and ω -scanning). In total, 25248 diffraction reflections were measured, $\theta_{\text{max}} = 26^\circ$. Intensities of symmetrically equivalent reflections were averaged. As a result of the averaging we obtained 5190 independent diffraction reflections with $R(\text{int}) = 0.0265$ which were used to solve and refine the crystal structure.

Ethyl-3-(allylamino)-9,9-dimethyl-7,11-dioxo-1,5-diarylspiro[5.5]undec-2-en-2-carboxylates (7-9)

A mixture consisting of 0.01 mol of dimeone, 0.01 mol of acetoacetic ester, 0.02 mol of aromatic aldehyde and 0.01 mol of allylamine in 15 ml of ethanol was stirred at room temperature for 6 hours, after which the reaction mixture was kept under the same conditions for 72 hours. The precipitated powder is filtered, recrystallized from a mixture of ethanol-dimethyl sulfoxide (1:1).

Ethyl-3-(allylamino)-9,9-dimethyl-7,11-dioxo-1,5-diphenylspiro[5.5]undec-2-en-2-carboxylate (7), yield 72 %, colorless crystals, m.p.198°C.

IR spectrum, ν , cm^{-1} : 1750 (COO), 1690 (C=O), 1250 (C-O)

$^1\text{H-NMR}$ spectrum (300 MHz, $(\text{CD}_3)_2\text{SO}$), δ , ppm: 0.23 (s, 3H, CH_3); 0.89-0.93 (t, 3H, CH_3); 1.1(s, 3H, CH_3); 2.02-2.05 (d, 1H, CH); 2.23–2.26 (d, 1H, CH); 2.93-3.00 (dd, 1H, CH_2); 3.12-3.16 (d, 1H, CH_2); 3.21-3.24 (d, 2H, CH_2); 4.64 (s, 1H, $\text{CH-C}_6\text{H}_5$); 3.69-3.74 (t, 1H, $\text{CH-C}_6\text{H}_4$); 3.86-3.95 (m, 4H, O- CH_2 , N- CH_2); 5.18-5.28 (m, 2H, $\text{CH}_2=$); 5.9–5.99 (m, 1H, CH=); 7.08–7.30 (m, 10H, C_6H_5); 9.22 (s, 1H, NH)

$^{13}\text{C-NMR}$ spectrum (75 MHz, $(\text{CD}_3)_2\text{SO}$), δ , ppm: 14.0; 25.0; 30.0; 32.0; 37.0; 43.0; 47.0; 51.0; 52.0; 58.0; 70.0; 88.0; 115.0; 126.42; 129.0; 131.0; 135.0; 141.0; 142.0; 161.0, 168.0, 206.0, 209.0

Found, %: C 76.72; H 7.30; N 2.92. $\text{C}_{31}\text{H}_{35}\text{NO}_4$. Calculated, %: C 76.67; H 7.26; N 2.88

Ethyl-3-(allylamino)-9,9-dimethyl-7,11-dioxo-1,5-di(4-metilphenyl)spiro[5.5]undec-2-en-2-carboxylate (8), yield 67 %, colorless crystals, m.p.219°C.

IR spectrum, ν , cm^{-1} : 1750 (COO), 1690 (C=O), 1250 (C-O)

$^1\text{H-NMR}$ spectrum (300 MHz, $(\text{CD}_3)_2\text{SO}$), δ , ppm: 0.23 (s, 3H, CH_3); 0.89-0.93 (t, 3H, CH_3); 1.1(s, 3H, CH_3); 2.02-2.05 (d, 1H, CH); 2.18 (s, 3H, CH_3); 2.23–2.26 (d, 1H, CH); 2.27(s, 3H, CH_3); 2.93-3.00 (dd, 1H, CH_2); 3.12-3.16 (d, 1H, CH_2); 3.21-3.24(d, 2H, CH_2); 4.64 (s, 1H, $\text{CH-C}_6\text{H}_5$); 3.69-3.74 (t, 1H, CH); 3.86-3.95 (m, 4H, O- CH_2 , N- CH_2); 5.18-5.28 (m, 2H, $\text{CH}_2=$); 5.9–5.99 (m, 1H, CH=); 7.08–7.30 (m, 10H, C_6H_5); 9.22 (s, 1H, NH)

$^{13}\text{C-NMR}$ spectrum (75 MHz, $(\text{CD}_3)_2\text{SO}$), δ , ppm: 14.0; 22.0; 23.0; 25.0; 30.0; 32.0; 37.0; 43.0; 47.0; 51.0; 52.0; 58.0; 70.0; 88.0; 115.0; 126.42; 129.0; 131.0; 135.0; 139.0; 140.0; 141.0; 142.0; 161.0, 168.0, 206.0, 209.0

Found, %: C 77.25; H 7.72; N 2.79. $\text{C}_{33}\text{H}_{39}\text{NO}_4$. Calculated, %: C 77.16; H 7.65; N 2.73

Ethyl-3-(allylamino)-9,9-dimethyl-7,11-dioxo-1,5-di(3-nitrophenyl)spiro[5.5]undec-2-en-2-carboxylate (9), yield 75 %, yellow crystals, m.p.121°C.

IR spectrum, ν , cm^{-1} : 1750 (COO), 1690 (C=O), 1560(N=O), 1250 (C-O)

$^1\text{H-NMR}$ spectrum (300 MHz, $(\text{CD}_3)_2\text{SO}$), δ , ppm: 0.20 (s, 3H, CH_3); 0.89-0.93 (t, 3H, CH_3); 1.06(s, 3H, CH_3); 2.05-2.07 (d, 1H, CH_2); 2.27-2.31 (d, 1H, CH_2); 3.07-3.14 (dd, 1H, CH_2); 3.12-3.16 (d, 1H, CH_2); 3.21-3.24 (d, 2H, CH_2); 3.69-3.74 (t, 1H, CH); 4.64 (s, 1H, $\text{CH-C}_6\text{H}_5$); 3.86-3.95 (m, 4H, O- CH_2 , N- CH_2); 5.18-5.28 (m, 2H, $\text{CH}_2=$); 5.9–5.99 (m, 1H, CH=); 7.47–8.50 (m, 8H, CH_{arom}); 9.22 (s, 1H, NH)

$^{13}\text{C-NMR}$ spectrum (75 MHz, $(\text{CD}_3)_2\text{SO}$), δ , ppm: 14.0; 25.0; 30.0; 32.0; 37.0; 43.0; 47.0; 51.0; 52.0; 58.0; 70.0; 88.0; 115.0; 126.42; 129.0; 131.0; 135.0; 141.0; 142.0; 147.0; 148.0; 161.0, 168.0, 206.0, 209.0

Found, %: C 64.73; H 5.82; N 7.39. $C_{24}H_{29}N_3O_6$. Calculated, %: C 64.69; H 5.78; N 7.30

4. Conclusion

Thus, in the multicomponent condensation of dimedone, aromatic aldehydes, acetoacetic ester, and allylamine in the 1:2:1:1 molar ratio a new direction in the condensation of these reagents is found, which results in the formation of the spirocyclic system: ethyl-3(allylamino)-9,9-dimethyl-7,11-dioxo-1,5-diarylspiro[5.5]undec-2-en-2-carboxylates.

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