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REACTION OF NITROMETHANE WITH CINNAMOYL DERIVATIVES OF CYCLIC β-DICARBONYL COMPOUNDS. APPLICATION TO THE SYNTHESIS OF 2(3)-(4-ARYL-PYRROLIDIN-2-YLIDENE)-1,3(2,4)-DIONES*

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We have shown that reaction of nitromethane with cinnamoyl derivatives of five- and six-membered carbo- and heterocylic β-dicarbonyl compounds in the presence of 1,1,3,3-tetramethylguanidine proceeds according to the mechanism of 1,4-conjugate addition to the enone fragment of cinnamoyl moiety to give 2(3)-(3-aryl-4-nitrobutanoyl)-substituted cyclic 1,3- or 2,4-diones in good to excellent yields. Chemoselective reduction of nitro function of the latter leads to synthetically useful and biologically interesting 2(3)-(4-arylpyrrolidin-2-ylidene) derivatives.

Keywords: 2(3)-(4-arylpyrrolidin-2-ylidene)-1,3(2,4)-diones, cyclic β-tricarbonyl compounds, enones, nitromethane, chemoselectivity, Michael addition, reduction.

The cyclic β-tricarbonyl functionality is an essential structural unit of a great diversity of natural products. Components of extracts from different plants (leptospermone, humulones, hulupones, filicines, etc.), various fungal metabolites and antibiotics (chelocardin, dutomicin, usnic acid), pheromones, and the kairomones of some *Lepidoptera* species, as well as many others, are cyclic β-triketones [1-3]. Many of these bioactive compounds exhibit a broad spectrum of useful therapeutic properties and are applied in traditional as well as in modern medicine. Synthetic benzoyl triketones based on the leptospermone structure template are currently used as effective agrochemicals (mesotrione, sulcotrione, tembotrione) and therapeutic agents for the treatment of hereditary tyrosinaemia type I disease (nitisinone, also known as NTBC) [4, 5]. Moreover, carbo-, as well as heterocyclic β-tricarbonyl compounds, are valuable multifunctional precursors for the synthesis of natural products and biologically active heterocycles [2, 6-8].

Among cyclic β-tricarbonyls, the compounds in which the keto function of the cinnamoyl substituent is involved in the β-tricarbonyl fragment are of special interest. Naturally occurring cinnamoyl derivatives of five- (linderone, lucidone [9], coruscanone B [10]) and six-membered cyclic β-dicarbonyl compounds (champanones [11], schefflerichalcone [12], saffloquinosides [13], and others) along with their synthetic congeners [14-17],

*Dedicated to Academician G. Duburs on the occasion of his 80th birthday.

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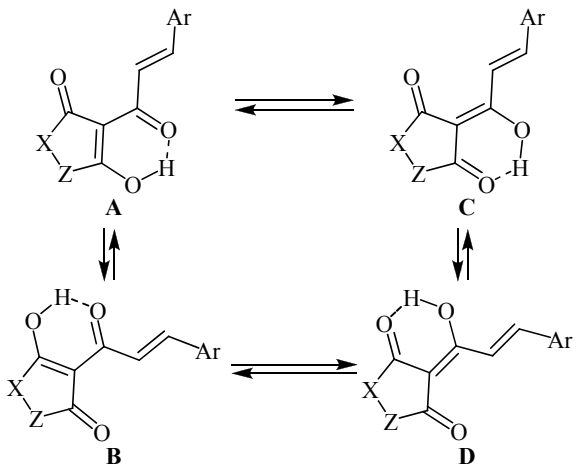
possess high antibiotic, antifungal, anthelmintic, antimalarial, antiplasmodial, antiparasitic, antidiabetic, anticancer, anticoagulant, and HIV-1 integrase inhibition activities. Due to the presence of polyunsaturated system in the structure of cinnamoyl derivatives of cyclic β-dicarbonyl compounds and their acidic character (vinylogous acids) they are considered to be perspective polarity-sensitive fluorescent probes and acidichromic colorants [5, 18, 19]. From a synthetic point of view, α,β-unsaturated functionality in the side chain of these compounds provides additional possibilities for selective chemical reactions at their enone fragment. Thus, methods for selective reduction of the enone moiety in cinnamoyl substituent of cyclic β-dicarbonyl compounds developed by us [20, 21] were applied in the synthesis of interphenylene prostanoids and their precursors [22, 23]. The reactivity of different binucleophiles towards the enone system of cinnamoyl derivatives of 6-methyl-3*H*-pyran-2,4-dione, 4-hydroxycoumarin, and 4-hydroxy-2-quinolone has been extensively used to synthesize numerous heterocycles (2-pyrazolines [6, 24, 25], pyridines [26], pyrimidines [27], 1,4-diazepines [28], 1,5-benzodiazepines [29], 1,5-benzothiazepines and 1,4-benzothiazines [30]).

Among mononucleophiles, nitroalkanes are of special value. Their conjugate addition to Michael acceptors is widely used for carbon–carbon bond formation [31]. The ability of the nitro derivatives thus formed to transform into organic compounds of different classes, including heterocycles [32, 33], promoted their application as key precursors for the synthesis of dyes, medicines, and agrochemicals. In spite of the fact that conjugate addition of nitroalkanes to chalcones, substituted cinnamic aldehydes, and cinnamic acid esters has been extensively studied, a literature survey revealed that nothing was known about reactions of nitroalkanes with cinnamoyl derivatives of cyclic β-dicarbonyl compounds.

In the present paper, we describe our experimental results that demonstrate 1,4-conjugate Michael addition of nitromethane to the enone moiety of cinnamoyl derivatives of five- and six-membered carbo- and heterocyclic β-dicarbonyl compounds for the first time. We also demonstrate the application of the Michael adducts thus formed in the preparation of new synthetically and biologically useful heterocycles – 2(3)-(4-aryl-pyrrolidin-2-ylidene)-1,3(2,4)-diones.

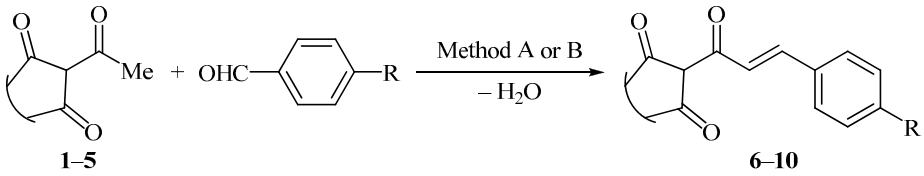
Cinnamoyl derivatives of carbo- and heterocyclic β-dicarbonyl compounds **6**-**10** were obtained by Claisen–Schmidt condensation of the readily available 2-acetylcyclopentane-1,3-dione (**1**), 3-acetyltetronic acid (**2**), 2-acetyldimedone (**3**), dehydroacetic acid (**4**), and 3-acetyl-1-(4-methoxyphenyl)-6-methylpyridine-2,4(1*H*,3*H*)-dione (**5**) with aromatic aldehydes [22, 34, 35] (Table 1).

The reaction of five- (compounds **6**, **7**) and six-membered (compounds **8**-**10**) cyclic β-tricarbonyl compounds with nitromethane was investigated at room temperature. In the reaction, nitromethane served both as reagent and solvent. Since the compounds **6**-**10** are vinylogous acids, more than one equivalent of basic catalyst is necessary. 1,1,3,3-Tetramethylguanidine (TMG) (1.5 equiv.) was applied as the base because its vinylogous salts were readily soluble in nitromethane, and thus the reaction took place as a homogenous process.

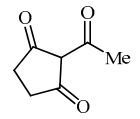
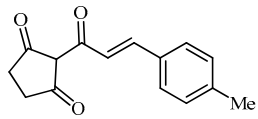
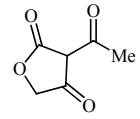
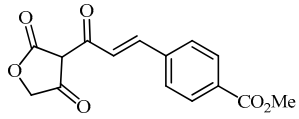
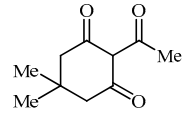
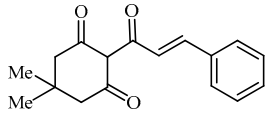
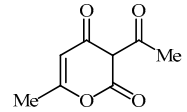
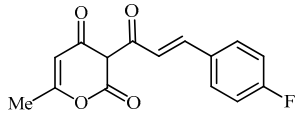
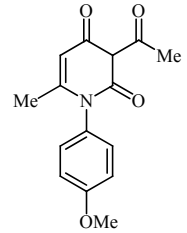
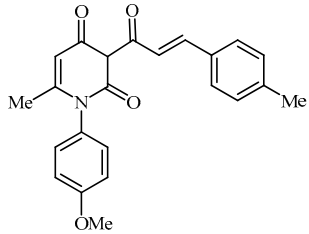


It is important to note that, unlike chalcones and cinnamic acid esters, cyclic β-tricarbonyl compounds exist as equilibrium mixture of *endo*- (**A**, **B**) and *exo*-cylic (**C**, **D**) enol forms, the structure of the main tautomer being dependent to a great extent on the character of the β-tricarbonyl functionality, the physical state of these compounds, nature of the solvent used, etc. [5, 36]. Conversion of *endo*-cyclic tautomers **A**, **B** into the *exo*-cyclic ones **C**, **D** transforms the enone system of the side chain into the diene moiety which makes the Michael reaction at this fragment problematic. As in the case of the precursors **1-5**, cyclic β-tricarbonyl system of the compounds **6-10** exists in solution in the enol form (**B** or **D**), which is confirmed by their NMR spectra and literature data [17, 22, 28, 34].

TABLE 1. Synthesis of β-Diketone Cinnamoyl derivatives **6-10**

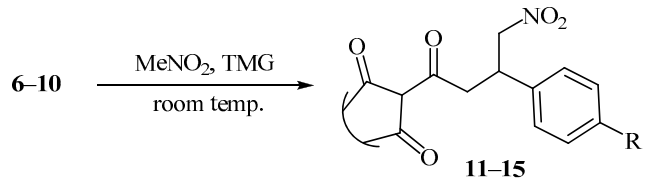


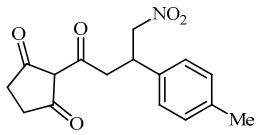
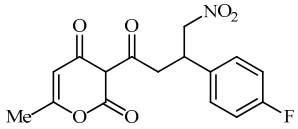
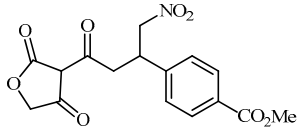
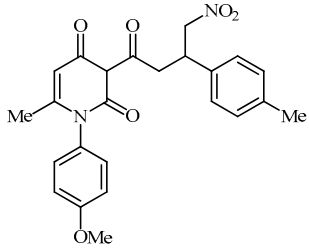
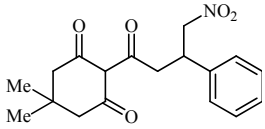
1–5 **6–10**

Starting tricarbonyl compound	R	Method*	Reaction product	Mp, °C	Yield, %
1 	Me	A	**6** 	143-144 (acetone)	73
2 	CO_2Me	A	**7** 	171-172 (EtOAc) (171-172 (EtOAc) [22])	75
3 	H	A	**8** 	92-93 (EtOAc–petroleum ether, 1:1) (92-93 (EtOAc–petroleum ether, 1:1) [34])	73
4 	F	B	**9** 	138-139 (2-PrOH) (140-145 (2-PrOH) [28])	58
5 	Me	A	**10** 	185-189 (EtOAc–petroleum ether, 1:1)	83

*Method A: compounds **1-3**, **5** (1.0 equiv.), aldehyde (0.9 equiv.), piperidine (1.5 equiv.) in PhH (2 ml/mmol), reflux [22, 34]. Method B: compound **4** (1.0 equiv.), aldehyde (1.0 equiv.) in Py (0.8 ml/mmol), 5 drops of piperidine and glacial AcOH, 45 min at 45-50°C, then 15 min at 100°C [35].

TABLE 2. 1,4-Conjugate Addition of Nitromethane to the Enone Moiety of β-Diketone Cinnamoyl Derivatives **6-10**



Michael adduct	Time, h	Yield, %	Michael adduct	Time, h	Yield, %
11 	72	52	**14** 	24	62
12 	24	47*	**15** 	24	92
13 	24	89			

*Yield of the crude product.

However, under the described conditions nitromethane reacted with compounds **6-10** according to the scheme of 1,4-conjugate addition to the enone fragment of cinnamoyl moiety to give nitromethyl derivatives **11-15** in 47-92% yield (Table 2). In most cases, the reaction time did not exceed 24 h. The structure of the obtained compounds was unambiguously assigned on the basis of the spectral data. Compounds **11**, **13-15** are stable, while tetronic acid derivative **12** decomposes during chromatographic purification.

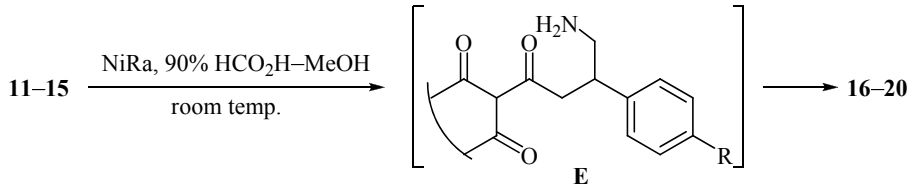
Thus, the described method is a simple general tool for construction of 2(3)-(3-aryl-4-nitrobutanoyl)-substituted carbo- and heterocylic β-dicarbonyl compounds, which can serve as multifunctional precursors for new synthetically useful and bioactive derivatives.

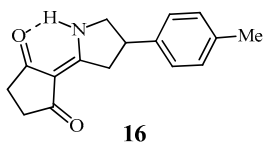
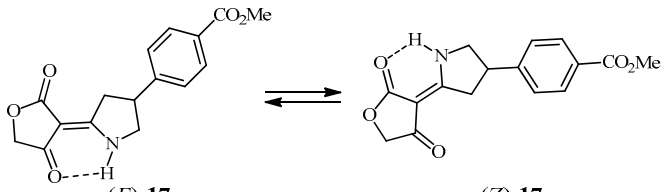
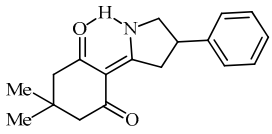
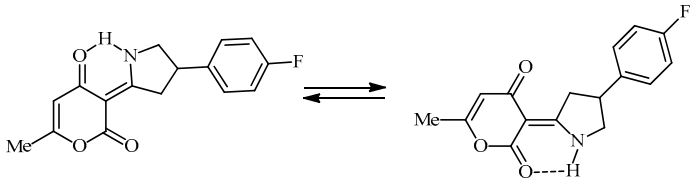
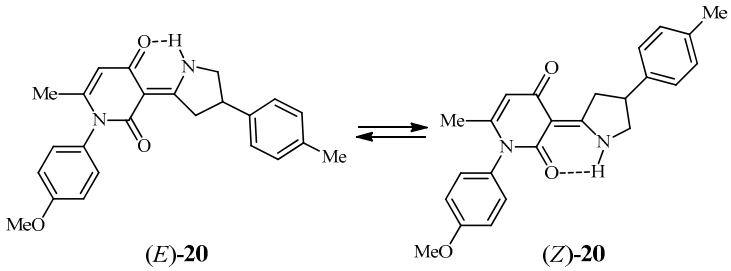
As an example, we applied the Michael adducts **11-15** for the preparation of 4-arylpyrrolidin-2-ylidene derivatives **16-20** of cyclic β-dicarbonyl compounds (Table 3). Synthesis of the latter can be achieved by chemoselective transformation of the nitro group into the amino function, which is prone to intramolecular reaction with the carbonyl group of the acyl chain in the intermediates **E**. Earlier, a similar approach was employed for the formation of pyrrolidinone moiety in synthetic schemes to obtain antidepressant (*S*)-rolipram [37] and alkaloid (+)-9a-*epi*-stemoamide [38].

For the selective reduction of nitro group in the derivatives **11-15**, the use of Raney nickel in the mixture of methanol and 90% formic acid [39] proved to be the most effective. This system is found to be compatible with many functionalities including ketones [39]. Reduction of compounds **11**, **13-15** by this system at room temperature leads to 4-arylpyrrolidin-2-ylidene derivatives **16**, **18-20** in 47-93% yield (Table 3). The low yield of enamino dicarbonyl compound **17** under these conditions can be attributed to fast decomposition of unstable nitromethyl derivative **12** in acidic medium.

The ^{1}H NMR spectra of carbocyclic enamino dicarbonyl compounds **16** and **18** display a broad singlet at 10.46 and 11.88 ppm, respectively, due to the hydrogen-bonded proton of NH group. Examination of the NMR spectra of the heterocyclic analogs **17**, **19**, **20** indicates that they are similar to those of the structurally related naturally occurring allelochemical agent fischerellin A (**21**) [40] and the alkaloid of marine origin plakoridine C (**22**) [41].

TABLE 3. Synthesis of 2(3)-(4-Arylpyrrolidin-2-ylidene)-1,3(2,4)-diones **16-20**

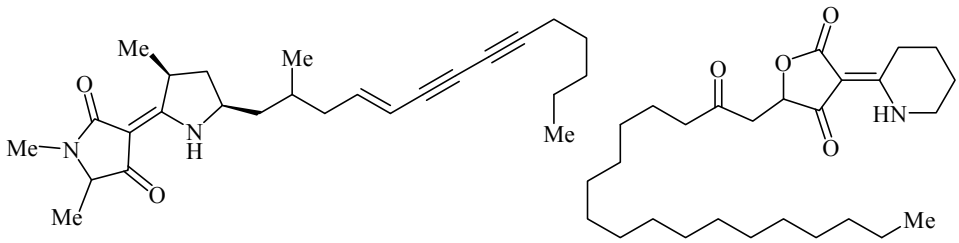


2(3)-(4-Arylpyrrolidin-2-ylidene)-1,3(2,4)-dione	(*E*/*Z*)-ratio	Yield, %
 **16**	—	47
 (*E*)-**17** (*Z*)-**17**	1.2:1*[2]	15
 **18**	—	93
 (*E*)-**19** (*Z*)-**19**	4:1*	52
 (*E*)-**20** (*Z*)-**20**	4.3:1*	65

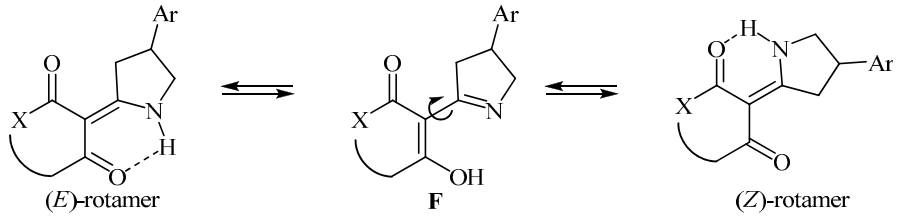
*In solution of $CDCl_3$.

*[2]In solution of DMSO-d_6.

Thus, as in the case of the aforementioned compounds, the ^1H and ^{13}C NMR spectra of the enaminodiones **17**, **19**, **20** are characterized by doubling of most of the signals. The proton of NH group resonates as two broad signals at 9.89-13.20 ppm. This is due to the fact that this proton can easily form hydrogen bonds with either the ketone or the ester/amide carbonyl oxygen atom. Hence, like natural compounds **21** and **22**, the enamino dicarbonyl compounds **17**, **19**, **20** in solution exist as inseparable equilibrium mixtures of enamino dicarbonyl (*E*,*Z*)-rotamers. Interconversion of the latter is believed to proceed *via* intermediate **F** [40].



21 **22**



(*E*)-rotamer **F** (*Z*)-rotamer

It is generally accepted that in the ^{1}H NMR spectra of exocyclic enaminodicarbonyl compounds, the signal of the enamine proton shows the most pronounced downfield shift when this proton is chelated with the more electron-withdrawing carbonyl group of the ketone rather than that of ester or amide [42, 43]. Taking into account that in the ^{1}H NMR spectra of compounds **17**, **19**, **20** the downfield signals of their NH protons are always more intensive, we can conclude that the (*E*)-rotamer of these enaminodiones predominates in solutions of deuterochloroform and dimethyl sulfoxide-d_6.

Enaminodiones **16**-**20** and related compounds are of great synthetic potential because they combine the ambident nucleophilicity of enamines with the ambident electrophilicity of enones. For this reason, these compounds can serve as valuable multipurpose precursors for the synthesis of new bioactive heterocycles, medicines, and other useful compounds [44, 45]. On the other hand, the enaminocarbonyl moiety has long been known to be a therapeutically valuable pharmacophore [44, 46]. Pyrrolidin- and piperidin-2-ylidene moieties represent biologically important entities that are present in numerous natural and synthetic biologically active compounds possessing a broad spectrum of pharmacological (histaminergic, anticonvulsant, anti-inflammatory, etc.) activity [47]. In light of these facts enaminodiones **16**-**20** and their congeners are of interest as new therapeutically useful molecules.

In conclusion, it has been shown that the reaction of nitromethane with cinnamoyl derivatives of carbo- and heterocyclic β-dicarbonyl compounds in the presence of more than 1 equiv. of 1,1,3,3-tetramethylguanidine proceeds according to the scheme of 1,4-conjugate addition to the enone fragment of cinnamoyl moiety to give the corresponding 2(3)-(3-aryl-4-nitrobutanoyl)-substituted carbo- and heterocyclic β-diones in good to excellent yields. Chemoselective reduction of the nitro group in the latter gives rise to 2(3)-(4-arylpyrrolidin-2-ylidene) derivatives of cyclic β-dicarbonyl compounds. Further synthetic application of the synthesized nitromethane Michael adducts and their congeners, in particular, as a source of nitrile oxides in the preparation of isoxazole and isoxazoline derivatives is currently under investigation.

EXPERIMENTAL

IR spectra were recorded on a FT IR Bomem Michelson 100 spectrometer with Fourier transform. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance 500 spectrometer (500 and 125 MHz, respectively), with the solvent residual signal used as internal standard ($CDCl_3$: 7.26 ppm for ^{1}H nuclei, 77.0 ppm for ^{13}C nuclei; DMSO-d_6: 2.50 ppm for ^{1}H nuclei, 39.5 ppm for ^{13}C nuclei). DEPT technique was used for

distinguishing carbon signals on the basis of the number of attached protons in ^{13}C NMR spectra. The mass spectra were recorded using an HPLC-MS/MS system consisting of an Accella chromatograph and LCQ Fleet mass-selective detector with positive ion detection (APCI, reactant gas – N_2). Elemental analyses were performed on CHN elemental analyzer EuroVector EA3000. Melting points were determined on a Boetius melting point apparatus. Progress of the reactions was monitored, and the purity of the isolated compounds was checked by TLC on Silufol UV-254 or Alufol UV-254 plates (Merck), visualization by fluorescence quenching under UV light. Kieselgel 60 HF_{254} (Merck) and Kieselgel 60 (Fluka) were used for chromatographic separation.

β-Diketone Cinnamoyl Derivatives 6, 10 were prepared according to the reported method A [22, 34].

(*E*)-2-[3-(*p*-Tolyl)acryloyl]cyclopentane-1,3-dione (6). Dark-yellow crystals. IR spectrum (KBr), ν, cm^{-1}: 1190, 1300, 1390 (shoulder), 1415, 1470, 1545 (shoulder), 1565 (shoulder), 1580, 1610 (max.), 1635, 1700. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.41 (3H, s, CH_3); 2.59-2.62 (2H, m, CH_2); 2.73-2.76 (2H, m, CH_2); 7.24 (2H, d, ^3J = 8.0, H Ar); 7.60 (2H, d, ^3J = 8.0, H Ar); 7.89 (1H, d, ^3J = 16.0, C(O)CH=); 8.01 (1H, d, ^3J = 16.0, =CH); the signal of enolic OH is not visible. ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.7 (CH_3); 31.2 (CH_2); 34.5 (CH_2); 111.4 (C); 117.8 (=CH); 129.5 (2CH Ar); 129.9 (2CH Ar); 131.7 (C); 142.6 (C); 147.7 (=CH); 181.6 (C); 200.6 (C); 209.2 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 243 $[M+H]^+$ (100). Found, %: C 74.43; H 5.85. $C_{15}H_{14}O_3$. Calculated, %: C 74.36; H 5.82.

(*E*)-1-(4-Methoxyphenyl)-6-methyl-3-[3-(*p*-tolyl)acryloyl]pyridine-2,4(1*H*,3*H*)-dione (10). Yellow solid. IR spectrum (KBr), ν, cm^{-1}: 1248, 1398, 1468, 1512 (max.), 1531, 1612 (shoulder), 1626 (max.), 1659 (max.). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.98 (3H, s, CH_3); 2.34 (3H, s, CH_3); 3.86 (3H, s, OCH_3); 5.96 (1H, s, CH=); 7.04 (2H, d, ^3J = 9.0, H Ar); 7.10 (2H, d, ^3J = 9.0, H Ar); 7.12 (2H, d, ^3J = 9.0, H Ar); 7.54 (2H, d, ^3J = 9.0, H Ar); 7.88 (1H, d, ^3J = 16.0, C(O)CH=); 8.53 (1H, d, ^3J = 16.0, =CH); 16.92 (1H, s, OH enolic). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.5 (CH_3); 22.4 (CH_3); 55.5 (OCH_3); 101.6 (CH); 105.5 (C); 115.2 (2CH Ar); 124.4 (CH); 129.1 (2CH Ar); 129.2 (2CH Ar); 129.4 (2CH Ar); 130.7 (C); 132.6 (C); 141.0 (C); 144.8 (CH); 154.2 (C); 159.8 (C); 163.9 (C); 177.9 (C); 194.1 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 376 $[M+H]^+$ (100). Found, %: C 73.56; H 5.61; N 3.75. $C_{23}H_{21}NO_4$. Calculated, %: C 73.58; H 5.64; N 3.73.

1,4-Conjugate Addition of Nitromethane to β-Diketone Cinnamoyl Derivatives 6-10 (General Method). 1,1,3,3-Tetramethylguanidine (0.19 ml, 1.5 mmol) was added dropwise to a solution or suspension of cinnamoyl derivative **6-10** (1.0 mmol) in dry $MeNO_2$ (10 ml) upon stirring. The homogeneous reaction mixture was stirred at room temperature for 24-72 h. After completion of the reaction, $MeNO_2$ was evaporated *in vacuo*. The residue was acidified with 1 N HCl (15 ml) at 5°C. Oily products **11**, **12** were extracted from the aqueous phase with $CHCl_3$ (3×15 ml). Organic phases were combined and dried over anhydrous Na_2SO_4. After evaporation of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel ($CHCl_3$–petroleum ether, 9:1). Solid compounds **13-15** were washed successively with cold 1 N HCl (15 ml) and distilled water (20 ml), then dried in air and recrystallized from EtOAc.

2-[4-Nitro-3-(*p*-tolyl)butanoyl]cyclopentane-1,3-dione (11). Light-yellow oil. IR spectrum (thin layer), ν, cm^{-1}: 1379, 1435 (shoulder), 1441, 1553 (max.), 1582 (br.), 1620, 1632, 1639, 1693, 1703. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.30 (3H, s, CH_3); 2.45-2.53 (2H, m) and 2.69-2.77 (2H, m, $(CH_2)_2$); 3.23 (1H, dd, ^2J = 17.5, ^3J = 6.5) and 3.55 (1H, dd, ^2J = 17.5, ^3J = 8.0, C(O)CH_2); 4.11 (1H, quint, ^3J = 7.5, CH); 4.60 (1H, dd, ^2J = 12.5, ^3J = 8.5) and 4.67 (1H, dd, ^2J = 12.5, ^3J = 7.5, CH_2NO_2); 7.09-7.17 (4H, m, H Ar); the signal of enolic OH is not visible. ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.1 (CH_3); 27.8 (CH_2); 33.4 (CH_2); 38.5 (CH); 42.0 (CH_2); 79.8 (CH_2); 114.7 (C); 127.4 (2CH Ar); 129.7 (2CH Ar); 135.4 (C); 137.6 (C); 198.7 (C); 199.7 (C); 203.1 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 304 $[M+H]^+$ (100). Found, %: C 63.30; H 5.59; N 4.65. $C_{16}H_{17}NO_5$. Calculated, %: C 63.36; H 5.65; N 4.62.

Methyl 4-[4-(2,4-Dioxotetrahydrofuran-3-yl)-1-nitro-4-oxobutan-2-yl]benzoate (12). The crude material is a yellow oil. IR spectrum (thin layer), ν, cm^{-1}: 1379, 1435-1485 (br.), 1556, 1568, 1607-1682 (br.), 1715. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.13 (1H, dd, ^2J = 15.5, ^3J = 9.0) and 3.29 (1H, dd, ^2J = 15.5, ^3J = 5.5, C(O)CH_2); 3.87 (3H, s, CO_2CH_3); 4.06-4.12 (1H, m, CH); 4.20 (2H, br. s, C(O)CH_2O); 4.62 (1H, dd,

^2J = 13.0, ^3J = 10.0) and 4.79 (1H, dd, ^2J = 13.0, ^3J = 5.5, CH_2NO_2); 7.34 (2H, d, ^3J = 8.5, H Ar); 7.90 (2H, d, ^3J = 8.5, H Ar); the signal of enolic OH is not visible. ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 39.9 (CH); 42.6 (CH_2); 52.1 ($CO_2\underline{C}H_3$); 70.5 (CH_2); 79.4 (CH_2); 97.0 (C); 127.8 (2CH Ar); 129.1 (C); 129.9 (2CH Ar); 145.8 (C); 166.9 (C); 177.1 (C); 192.1 (C); 195.4 (C). Mass spectrum, *m/z* (I_{rel}, %): 350 $[M+H]^+$ (100).

5,5-Dimethyl-2-(4-nitro-3-phenylbutanoyl)cyclohexane-1,3-dione (13). White solid, mp 80-81°C. IR spectrum (KBr), ν, cm^{-1}: 1381, 1431, 1555 (max.), 1562 (shoulder), 1601, 1664. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.04 (3H, s, CH_3); 1.07 (3H, s, CH_3); 2.34 (2H, s, CH_2); 2.52 (2H, s, CH_2); 3.41 (1H, dd, ^2J = 17.0, ^3J = 6.5) and 3.65 (1H, dd, ^2J = 17.0, ^3J = 7.5, C(O)CH_2); 4.14 (1H, quint, ^3J = 7.5, CH); 4.63 (1H, dd, ^2J = 12.5, ^3J = 8.5) and 4.70 (1H, dd, ^2J = 12.5, ^3J = 6.5, CH_2NO_2); 7.26-7.33 (5H, m, H Ph); 17.59 (1H, s, OH enolic). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 28.1 (CH_3); 28.2 (CH_3); 30.7 (C); 39.5 (CH); 43.8 (CH_2); 46.2 (CH_2); 52.4 (CH_2); 79.8 (CH_2); 112.3 (C); 127.6 (2CH Ar); 127.8 (CH Ar); 128.9 (2CH Ar); 139.0 (C); 195.3 (C); 196.8 (C); 202.0 (C). Mass spectrum, *m/z* (I_{rel}, %): 332 $[M+H]^+$ (100). Found, %: C 65.23; H 6.40; N 4.27. $C_{18}H_{21}NO_5$. Calculated, %: C 65.24; H 6.39; N 4.23.

3-[3-(4-Fluorophenyl)-4-nitrobutanoyl]-6-methyl-2*H*-pyran-2,4(3*H*)-dione (14). White solid, mp 125-126°C. IR spectrum (KBr), ν, cm^{-1}: 1225, 1387, 1441, 1512, 1556 (shoulder), 1562 (max.), 1603, 1639, 1724. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.28 (3H, s, CH_3); 3.42 (1H, dd, ^2J = 18.0, ^3J = 6.5) and 3.65 (1H, dd, ^2J = 18.0, ^3J = 7.5, C(O)CH_2); 4.18 (1H, quint, ^3J = 7.5, CH); 4.61 (1H, dd, ^2J = 12.5, ^3J = 8.5) and 4.72 (1H, dd, ^2J = 12.5, ^3J = 6.0, CH_2NO_2); 5.95 (1H, s, CH=); 7.02 (2H, dd, ^3J = $^3J_{HF}$ = 8.5, H Ar); 7.27 (2H, dd, ^3J = 8.5, $^4J_{HF}$ = 5.5, H Ar); 15.98 (1H, s, OH enolic). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 20.8 (CH_3); 38.3 (CH); 44.7 (CH_2); 79.7 (CH_2); 99.7 (C); 101.4 (CH heterocycl.); 115.9 (d, $^2J_{CF}$ = 21.3, C-3',5' Ar); 129.3 (d, $^3J_{CF}$ = 7.5, C-2',6' Ar); 134.7 (C); 161.1 (C); 162.2 (d, $^1J_{CF}$ = 245, C–F); 169.7 (C); 180.9 (C); 203.4 (C). Mass spectrum, *m/z* (I_{rel}, %): 336 $[M+H]^+$ (100). Found, %: C 57.28; H 4.20; N 4.15. $C_{16}H_{14}FNO_6$. Calculated, %: C 57.32; H 4.21; N 4.18.

1-(4-Methoxyphenyl)-6-methyl-3-[4-nitro-3-(*p*-tolyl)butanoyl]pyridine-2,4(1*H*,3*H*)-dione (15). White solid, mp 63-66°C. IR spectrum (KBr), ν, cm^{-1}: 1250, 1379, 1410, 1458, 1512, 1551, 1614 (max.), 1659. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.99 (3H, s, CH_3); 2.28 (3H, s, CH_3); 3.54 (1H, dd, ^2J = 18.5, ^3J = 7.0) and 3.68 (1H, dd, ^2J = 18.5, ^3J = 6.5, C(O)CH_2); 3.85 (3H, s, OCH_3); 4.13-4.19 (1H, m, CH); 4.54 (1H, dd, ^2J = 12.5, ^3J = 9.0) and 4.69 (1H, dd, ^2J = 12.5, ^3J = 6.5, CH_2NO_2); 5.92 (1H, s, CH=); 7.01-7.09 (6H, m, H Ar); 7.14 (2H, d, ^3J = 8.0, H Ar); the signal of enolic OH is not visible. ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.0 (CH_3); 22.4 (CH_3); 38.6 (CH); 45.7 (CH_2); 55.6 (OCH_3); 80.1 (CH_2); 101.0 (CH=); 105.5 (C); 115.2 (2CH Ar); 127.5 (2CH Ar); 128.9 (CH Ar); 129.0 (CH Ar); 129.4 (2CH Ar); 130.3 (C); 136.5 (C); 137.1 (C); 154.7 (C); 159.9 (C); 163.6 (C); 176.1 (C); 203.9 (C). Mass spectrum, *m/z* (I_{rel}, %): 437 $[M+H]^+$ (100). Found, %: C 66.04; H 5.51; N 6.46. $C_{24}H_{24}N_2O_6$. Calculated, %: C 66.04; H 5.54; N 6.42.

Synthesis of enaminodicarbonyl compounds 16-20 from nitromethyl derivatives **11-15** was carried out according to the literature procedure [39].

2-[4-(*p*-Tolyl)pyrrolidin-2-ylidene]cyclopentane-1,3-dione (16). White solid, mp 211-212°C. IR spectrum (KBr), ν, cm^{-1}: 1234, 1290, 1481, 1574 (shoulder), 1582, 1620 (max.), 1682. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.33 (3H, s, CH_3); 2.50-2.52 (2H, m) and 2.55-2.57 (2H, m, $(CH_2)_2$); 3.32 (1H, dd, ^2J = 19.0, ^3J = 7.0), 3.66-3.73 (2H, m), 3.79 (1H, dd, ^2J = 19.0, ^3J = 9.5) and 4.06-4.13 (1H, m, CH_2CHCH_2); 7.09 (2H, d, ^3J = 8.0, H Ar); 7.14 (2H, d, ^3J = 8.0, H Ar); 10.46 (1H, br. s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.9 (CH_3); 33.4 (CH_2); 34.3 (CH_2); 39.6 (CH_2); 39.8 (CH); 55.1 (CH_2); 105.0 (C); 126.6 (2CH Ar); 129.6 (2CH Ar); 137.1 (C); 138.0 (C); 171.7 (C); 202.2 (C); 205.6 (C). Mass spectrum, *m/z* (I_{rel}, %): 256 $[M+H]^+$ (100). Found, %: C 75.24; H 6.73; N 5.49. $C_{16}H_{17}NO_2$. Calculated, %: C 75.27; H 6.71; N 5.49.

Methyl (*E,Z*)-4-[5-(2,4-Dioxodihydrofuran-3(2*H*)-ylidene)pyrrolidin-3-yl]benzoate (17). White solid, mp 251-252°C. IR spectrum (KBr), ν, cm^{-1}: 1244, 1259, 1285, 1493, 1585, 1670 (max.), 1722, 1736 (shoulder). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.15 (0.55H, dd, ^2J = 19.0, ^3J = 8.0, (*E*)-isomer), 3.18 (0.45H, dd, ^2J = 19.0, ^3J = 7.5, (*Z*)-isomer), 3.61-3.75 (2H, m), 3.79-3.83 (1H, m) and 4.06-4.12 (1H, m, CH_2CHCH_2); 3.84 (3H, s, CO_2CH_3); 4.39 (0.9H, s, C(O)CH_2O, (*Z*)-isomer); 4.43 (1.1H, s, C(O)CH_2O,

(*E*)-isomer); 7.45 (2H, br. d, ^3J = 8.5, H Ar); 7.93 (2H, d, ^3J = 8.5, H Ar); 9.89 (0.45H, br. s, NH, (*Z*)-isomer); 10.37 (0.55H, br. s, NH, (*E*)-isomer). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 38.9 (CH); 39.3 (CH_2); 39.6 (CH_2); 52.0 ($CO_2\underline{C}H_3$); 54.6 (CH_2); 55.3 (CH_2); 70.5 (CH_2); 71.6 (CH_2); 87.1 (C); 88.1 (C); 127.4 (2CH Ar); 128.2 (C); 129.5 (2CH Ar); 147.1 (C); 166.0 (C); 169.6 (C); 169.7 (C); 172.0 (C); 173.3 (C); 193.0 (C); 194.7 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 302 $[M+H]^+$ (100). Found, %: C 63.63; H 5.06; N 4.57. $C_{16}H_{15}NO_5$. Calculated, %: C 63.78; H 5.02; N 4.65.

5,5-Dimethyl-2-(4-phenylpyrrolidin-2-ylidene)cyclohexane-1,3-dione (18). White solid, mp 132-135°C. IR spectrum (KBr), ν, cm^{-1}: 1439, 1556, 1583 (max.), 1643. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.06 (6H, s, $2CH_3$); 2.34 (2H, s, CH_2); 2.42 (2H, s, CH_2); 3.45 (1H, dd, ^2J = 19.5, ^3J = 6.5), 3.63-3.73 (2H, m), 3.93 (1H, dd, ^2J = 19.5, ^3J = 9.0) and 4.09 (1H, dd, ^2J = 11.5, ^3J = 8.5, CH_2CHCH_2); 7.21 (2H, br. d, ^3J = 7.0, H-2,6 Ph); 7.26 (1H, t, ^3J = 7.5, H-4 Ph); 7.33 (2H, t, ^3J = 7.5, H-3,5 Ph); 11.88 (1H, br. s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 28.3 (CH_3); 28.5 (CH_3); 30.5 (C); 40.3 (CH); 43.3 (CH_2); 51.8 (CH_2); 52.5 (CH_2); 54.9 (CH_2); 105.6 (C); 126.9 (2CH Ar); 127.2 (CH Ar); 128.9 (2CH Ar); 141.9 (C); 175.2 (C); 196.4 (C); 199.1 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 284 $[M+H]^+$ (100). Found, %: C 76.26; H 7.49; N 4.93. $C_{18}H_{21}NO_2$. Calculated, %: C 76.29; H 7.47; N 4.94.

(*E*,*Z*)-3-[4-(4-Fluorophenyl)pyrrolidin-2-ylidene]-6-methyl-2*H*-pyran-2,4(3*H*)-dione (19). White solid, mp 129-133°C. IR spectrum (KBr), ν, cm^{-1}: 1225, 1232, 1275, 1462, 1475, 1514, 1564 (shoulder), 1591 (max.), 1659, 1709. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.15 and 2.17 (3H total, 2s, CH_3, (*E*)- and (*Z*)-isomers); 3.45 (0.8H, dd, ^2J = 19.5, ^3J = 6.5, (*E*)-isomer), 3.56 (0.2H, dd, ^2J = 19.0, ^3J = 6.5, (*Z*)-isomer), 3.70-3.80 (2H, m), 3.93 (1H, dd, ^2J = 19.5, ^3J = 9.0), 4.08 (0.2H, dd, ^2J = 20.0, ^3J = 8.5, (*Z*)-isomer) and 4.19 (0.8H, dd, ^2J = 11.5, ^3J = 8.5, (*E*)-isomer, CH_2CHCH_2); 5.72 and 5.74 (1H total, 2s, CH=, (*E*)- and (*Z*)-isomers); 7.03 (2H, dd, ^3J = 8.5, $^3J_{HF}$ = 8.5, H Ar); 7.19 (2H, dd, ^3J = 8.5, $^4J_{HF}$ = 5.5, H Ar); 10.63 (0.2H, br. s, NH, (*Z*)-isomer); 12.39 (0.8H, br. s, NH, (*E*)-isomer). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 19.8 (CH_3, (*Z*)-isomer); 20.1 (CH_3, (*E*)-isomer); 39.3 (CH pyrrolidine, (*E*)-isomer); 40.0 (CH pyrrolidine, (*Z*)-isomer); 43.2 (CH_2, (*Z*)-isomer); 43.5 (CH_2, (*E*)-isomer); 55.0 (CH_2, (*Z*)-isomer); 56.0 (CH_2, (*E*)-isomer); 94.6 (C, (*E*)- and (*Z*)-isomers); 107.4 (CH=, (*E*)-isomer); 109.4 (CH=, (*Z*)-isomer); 115.9 (d, $^2J_{CF}$ = 21.3, CH-3',5' Ar, (*E*)- and (*Z*)-isomers); 128.4 (d, $^3J_{CF}$ = 7.5, CH-2',6' Ar, (*E*)- and (*Z*)-isomers); 137.2 (C, (*E*)- and (*Z*)-isomers); 162.0 (d, $^1J_{CF}$ = 245, C–F, (*E*)- and (*Z*)-isomers); 163.8 (2C, (*E*)- and (*Z*)-isomers); 176.9 (C, (*Z*)-isomer); 177.5 (C, (*E*)-isomer); 181.3 (C, (*Z*)-isomer); 184.2 (C, (*E*)-isomer). Mass spectrum, *m*/*z* (I_{rel}, %): 288 $[M+H]^+$ (100). Found, %: C 66.86; H 4.87; N 4.85. $C_{16}H_{14}FNO_3$. Calculated, %: C 66.89; H 4.91; N 4.88.

(*E*,*Z*)-1-(4-Methoxyphenyl)-6-methyl-3-[4-(*p*-tolyl)pyrrolidin-2-ylidene]pyridine-2,4(1*H*,3*H*)-dione (20). White solid, mp 189-190°C. IR spectrum (KBr), ν, cm^{-1}: 1248, 1294, 1466, 1512, 1574, 1622 (max.), 1649. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.85 and 1.87 (3H total, 2s, CH_3, (*E*)- and (*Z*)-isomers); 2.31, 2.33 (3H total, 2s, CH_3, (*E*)- and (*Z*)-isomers); 3.49 (0.81H, dd, ^2J = 19.5, ^3J = 7.0, C$\underline{\text{H}}\alpha$Hβ (*E*)-isomer); 3.61-3.71 (1.38H, m, CH (*E*)- and (*Z*)-isomers, C$\underline{\text{H}}\alpha\underline{\text{H}}\beta$ (*Z*)-isomer); 3.75 (0.81H, dd, ^2J = 12.0, ^3J = 7.0, NHC$\underline{\text{H}}\alpha$Hβ (*E*)-isomer); 3.83 and 3.85 (3H total, 2s, OCH_3, (*E*)- and (*Z*)-isomers); 3.96 (0.81H, dd, ^2J = 19.5, ^3J = 9.5, CHα$\underline{\text{H}}\beta$ (*E*)-isomer); 4.04 (0.19H, dd, ^2J = 10.5, ^3J = 8.5, NHC$\underline{\text{H}}\alpha$Hβ (*Z*)-isomer); 4.11-5.15 (0.19H, m, NHCHα$\underline{\text{H}}\beta$ (*Z*)-isomer); 4.15 (0.81H, dd, ^2J = 12.0, ^3J = 9.0, $NHCH_{\alpha}\underline{H}_{\beta}$ (*E*)-isomer); 5.77 and 5.79 (1H total, 2s, CH= (*E*)- and (*Z*)-isomers); 6.96-7.02 (2H, m, H Ar); 7.07-7.14 (6H, m, H Ar); 11.59 (0.19H, s, NH, (*Z*)-isomer); 13.20 (0.81H, s, NH, (*E*)-isomer). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: (*E*)-isomer: 21.0 (CH_3); 22.0 (CH_3); 39.8 (CH); 43.2 (CH_2); 55.48 (CH_2); 55.51 (OCH_3); 100.6 (C); 107.9 (CH=); 114.8 (2CH Ar); 126.6 (2CH Ar); 129.5 (2CH Ar); 129.8 (2CH Ar); 131.5 (C); 136.7 (C); 138.8 (C); 149.9 (C); 159.3 (C); 165.6 (C); 178.0 (C); 183.1 (C); (*Z*)-isomer: 21.0 (CH_3); 21.6 (CH_3); 40.3 (CH); 43.3 (CH_2); 54.8 (CH_2); 55.5 (OCH_3); 100.6 (C); 110.7 (CH=); 114.8 (2CH Ar); 126.7 (2CH Ar); 129.5 (2CH Ar); 129.7 (2CH Ar); 131.5 (C); 136.8 (C); 138.8 (C); 148.3 (C); 159.5 (C); 168.1 (C); 177.2 (C); 181.2 (C). Mass spectrum, *m*/*z* (I_{rel}, %): 389 $[M+H]^+$ (100). Found, %: C 74.18; H 6.21; N 7.24. $C_{24}H_{24}N_2O_3$. Calculated, %: C 74.21; H 6.23; N 7.21.

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