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Chichibabin-type condensation of cyclic ketones with 3-R-1,2,4-triazin-5(4H)-ones

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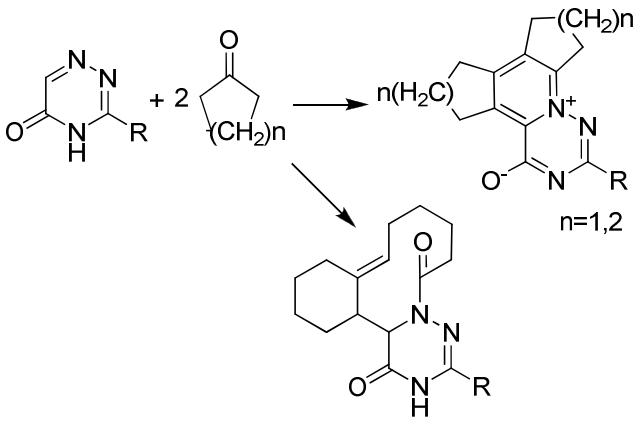
Abstract Graphic



Abstract

Reactions between substituted 1,2,4-triazines and ketones were investigated. General procedures for one-pot synthesis of hydrogenated derivatives of such polycyclic systems as benzo[c][1,2,4]triazino[1,6-a][2]azecine, [1,2,4]triazino[1,6-f]phenantridine and dicyclopenta[b,d]pyrido[1,2-f][1,2,4]triazine are described.

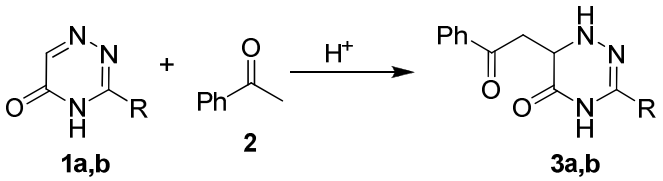
Keywords: 1,2,4-triazines, azecines, cyclic ketones, cycloaddition, fused pyridines, cyclic lactames

Introduction

Fused pyridines are widespread among natural organic compounds,[1] they are of great importance for medicine.[2] Pyridines, fused with two aliphatic rings draw considerable attention of researchers, as 1,2,3,4,7,8,9,10-octahydrophenantrene shows pesticide activity.[3] Triazine-fused pyridines are known to exhibit antidepressant activity.[4] The most popular synthetic route to bis-fused angular pyridines is Chichibabin's synthesis from cyclic ketones, ammonia and aldehydes. The reaction requires high pressure,[3,5] or hydrothermal conditions in aqueous ammonium chloride.[6] Procedures that utilize activated forms of cyclic ketones, such as the product of dimerization of cyclohexanone – 1,1'-bi(cyclohexilidene)-2-one,[7] enamines of cyclic ketones[2b,8] are noteworthy. Syntheses from pyrilium salts[9] and cyclobutadienes[10] are also known. The source of nitrogen in the molecule of fused pyridine in most cases is ammonia,[5,6,9] while amides,[7a] urea,[7b,8d] 2-azadienes,[8a] enamines,[8b] carbodiimides,[8c] ethylcyanoacetate,[10] dienamides[11] are also used.

Results and Discussion

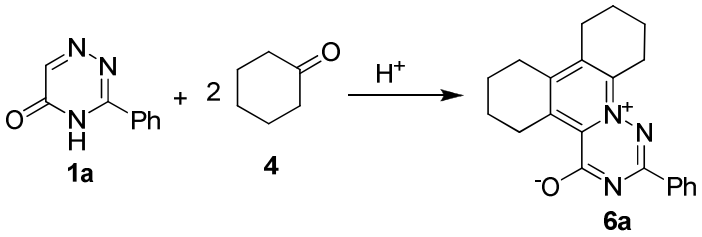
In this paper we describe a detailed study of synthetic methods for synthesis of 1,2,4-triazine derivatives of angular bis-fused pyridines in the reactions of cyclic ketones with 1,2,4-triazines. Compounds containing fragments of 1,2,4-triazine (6-azauridine) arouse interest because some of them show anticancer,[12] antivirus[13] and antibacterial activity[14]. It is known, that 3-R-1,2,4-triazin-5(4H)-ones react with C-nucleophiles such as indoles,[15] pyrroles,[15] phenols,[16] anilines[16]. We investigated the reaction between 3-R-1,2,4-triazin-5(4H)-ones and ketones. It was shown that the reaction of 3-R-1,2,4-triazin-5(4H)-ones (**1a,b**) with acetophenone (**2**) in the presence of acids leads to the formation of the expected products of nucleophilic addition to the double C=N bond of **3a,b** (Scheme 1). When acetone was used, resinification of the reaction mixture was observed, while butanone-2 and hexanone-2 did not react.



Scheme 1.

Earlier we had demonstrated that cycloaddition of 3-R-1,2,4-triazin-5(4H)-ones and cyclohexanone (**4**) or cyclopentanone (**5**) in the presence of trifluoroacetic acid leads to the formation of fused pyridines of Chichibabin's type.[17] In the course of our research we investigated the process of formation of fused pyridines. The search for proper conditions of the reaction of 3-R-1,2,4-triazin-5(4H)-one (**1a**) with cyclohexanone (**4**) under the action of bases showed only methanolic solution of $NaOCH_3$ to be a suitable reaction medium. This reaction gives product **6a** with low yield (7%). So our studies were then switched to acidic conditions. The following conditions were modified to find an optimal combination: temperature, acid strength, addition of some oxidative and dehydrating agents (Tables 1,2).

Table 1. Reaction of 3-Ph-1,2,4-triazin-5(4H)-one (**1a**) with cyclohexanone **4** under different conditions.

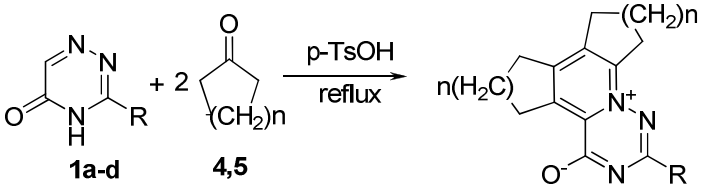


Acid	Solvent	T, ^{0}C	Time	Yield of **6a**, %
p-TsOH	DMF	153	0.5 h	29
p-TsOH	DMF	153	12 h	49
p-TsOH	CH_3CN	82	1 h	34
CF_3COOH	DMF	100	6 h	30
CF_3SO_3H	DMF	100	6 h	22 *
$AlCl_3$	DMF	20	1 day	36
p-TsOH, DDQ	CH_3CN	82	3 h	28
p-TsOH, DDQ, P_2O_5	CH_3CN	82	3 h	21
CF_3COOH, CAN	DMF	20	3 days	19
CF_3COOH	DMF	20	7 days	44 [17]
H_3PO_4	H_3PO_4	50	3 h	12
CH_3COOH	CH_3COOH	20	3 days	0
CH_3COOH	CH_3COOH	118	3 h	31
CF_3SO_3H	CH_3CN	82	6 h	31 *
CF_3SO_3H	CH_3OH	65	6 h	19 *
CF_3SO_3H	DMF	153	0.5 h	10 *
HCl	EtOH	20	1 day	40 **

*yield of **6a** triflate (**6aa**); **yield of the **6a** chloride (**6ab**).

Irrespective of the mechanism, Chichibabin synthesis of pyridines includes an oxidative stage, it is known that such oxidative agents as copper (II) acetate, nitrobenzene or air oxygen have no effect on the reaction.[18] We demonstrated the same to be true for DDQ and CAN ($(NH_4)_2Ce(NO_3)_6$). It turned out that if protic acids in the reaction are replaced by Lewis acids, such as $AlCl_3$, the same product **6a** is formed. Our results indicate that the most efficient route to cycloaddition products **6,7** in zwitter-ionic form is performing the reaction of 3-R-1,2,4-triazin-5(4H)-ones (**1a-d**) with ketones **4,5** in the presence of p-TsOH either in refluxing DMF or in refluxing acetonitrile (Tables 1,2). The addition of P_2O_5 in the reaction mixture as a dehydrating agent leads to increase in the yield of **6a,c-d**.

Table 2. Reaction of 3-R-1,2,4-triazin-5(4H)-ones (**1a-d**) with ketones **4**,**5** in the presence of p-TsOH (1 equiv).



4,6: n=2
5,7: n=1
(a) R = Ph; (b) R = SCH3;
(c) R = 4-MePh; (d) R = 4-ClPh

Starting material	R	n	Conditions	Time, h	Product	Yield, %
1a	Ph	2	DMF	1	**6a**	44
1a	Ph	2	CH_3CN, P_2O_5	3	**6a**	66
1a	Ph	2	CH_3CN, mol. sieves (3Å)	3	**6a**	21
1b	SMe	2	DMF	1	**6b**	11
1b	SMe	2	CH_3CN, P_2O_5	1	**6b**	0
1b	SMe	2	CH_3CN, P_2O_5	3	**6b**	0
1c	4-MePh	2	DMF	1	**6c**	24
1c	4-MePh	2	CH_3CN, P_2O_5	3	**6c**	42
1d	4-ClPh	2	DMF	1	**6d**	15
1d	4-ClPh	2	CH_3CN, P_2O_5	3	**6d**	18
1a	Ph	1	DMF	1	**7a**	30
1b	SMe	1	DMF	1	**7b**	21

Starting material	R	n	Conditions	Time, h	Product	Yield, %
1c	4-MePh	1	DMF	1	**7c**	24
1d	4-ClPh	1	DMF	1	**7d**	22

If strong acids were used in the reaction, salts of **6a-d** were formed. There was no noticed influence of acid strength on the reaction yield. The reaction of 3-R-1,2,4-triazin-5(4H)-ones (**1a-d**) with ketones **4,5** in the presence of trifluoromethanesulfonic acid leads to the salts **6aa-da** (Table 3). Reducing the amount of cyclohexanone in the reaction mixture from 2 equiv. to 1 equiv. leads to significant decrease of **6aa** yield. Increasing cyclohexanone or CF_3SO_3H concentrations does not have visible effects. Compounds **6ab-db** are soluble in acidic solutions and neutralization of reaction mixture leads to increased yield of products **6**. Triazines with aliphatic substituents in position 3 (**1e**, R = CH_2Ph) do not react with cyclic ketones either in the presence of CF_3SO_3H, or in ethanolic HCl solution. 1,2,4-Triazines without an oxo group in position 5 of the triazine ring (3-Ph-1,2,4-triazine, 3-SMe-1,2,4-triazine) also have no reactivity under such conditions.

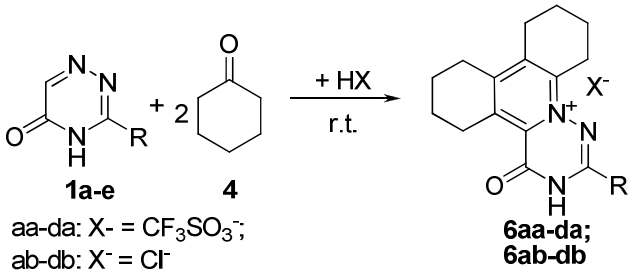


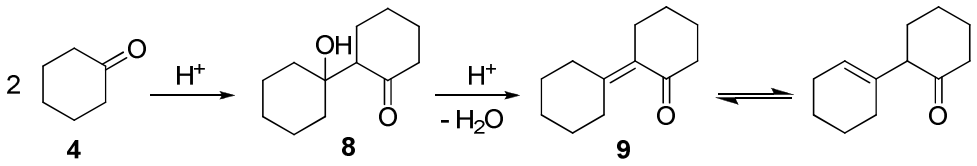
Table 3. Reaction of 3-R-1,2,4-triazin-5(4H)-ones (**1a-e**) with cyclohexanone (**4)** in the presence of 1 equiv. of CF_3SO_3H ($X^- = CF_3SO_3^-$).

Starting material	R	n	Time, days	Product	Yield, %
1a	Ph	2	7	**6aa**	8
1a	Ph	2	17	**6aa**	18
1a	Ph	2	35	**6aa**	26
1a	Ph	2	35 *	**6aa**	21
1a	Ph	2	35 **	**6aa**	3
1a	Ph	2	35 ***	**6aa**	25
1b	SMe	2	35	**6ba**	24
1c	4-MePh	2	35	**6ca**	26
1d	4-ClPh	2	35	**6da**	26

Starting material	R	n	Time, days	Product	Yield, %
1e	CH_2Ph	2	35	**-**	0

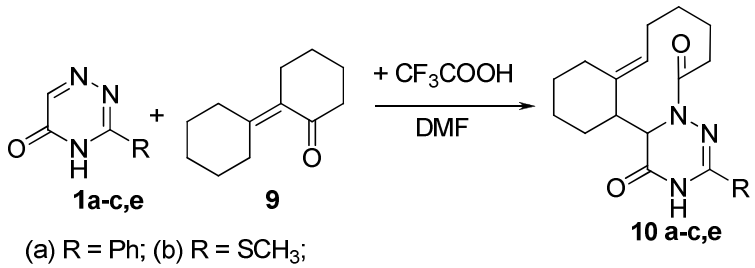
*3 equiv. triflic acid; **1 equiv. cyclohexanone; ***4 equiv. cyclohexanone.

It is known cyclohexanone **4** gives condensation product **9** in the presence of acids, for example in the presence of trifluoromethanesulfonic acid (Scheme 2).[19] It was logical to expect the formation of products **6a-d** in the reaction of 3-R-1,2,4-triazin-5(4H)-one (**1**) with 1,1'-bi(cyclohexilidene)-2-one (**9**) and we obtained them in refluxing DMF with addition of CF_3SO_3H (15% yield), but at ambient temperature in the presence of CF_3COOH the reaction leads to lactams **10a-c,e** (Table 4).



Scheme 2

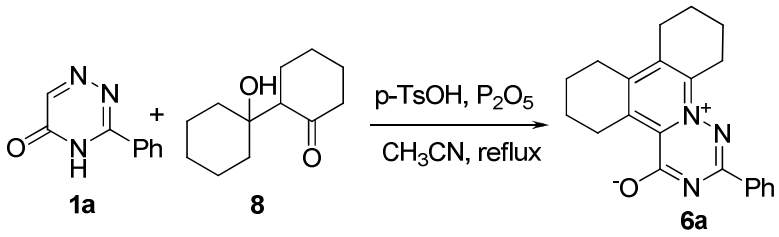
Table 4. Reaction of 3-R-1,2,4-triazin-5(4H)-ones (**1a-c,e**) with **9a** in the presence of CF_3COOH.



(a) R = Ph; (b) R = SCH_3;
(c) R = 4-MePh; (e) R = CH_2Ph

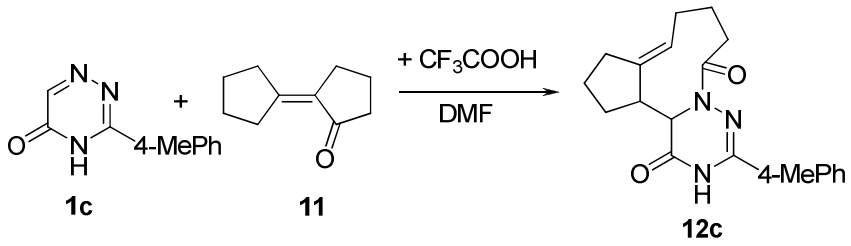
Starting material	R	Product	Yield, %
1a	Ph	**10a**	58
1b	SMe	**10b**	71
1c	4-MePh	**10c**	68
1e	CH_2Ph	**10e**	53

Our next step was to study the reaction of 1'-hydroxybi(cyclohexan)-2-one (**8**) with 3-Ph-1,2,4-triazin-5(4H)-one (**1a**). When the reaction was carried out at ambient temperature in the presence of CF_3COOH/CF_3SO_3H the formation of **6a** was not observed. Reaction in refluxing CH_3CN in the presence of P_2O_5 resulted in the formation of **6a** (54% yield) (Scheme 3).



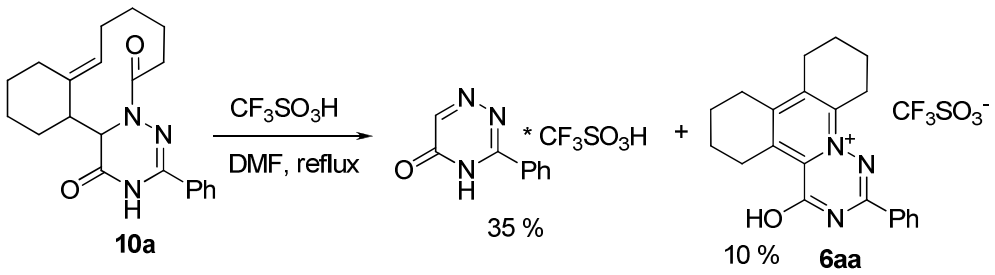
Scheme 3.

When we tried to use 1,1'-bi(cyclopentilidene)-2-one (**11**) instead of 1,1'- bi(cyclohexilidene)-2-one (**9**) in the reaction with 3-R-1,2,4-triazin-5(4H)-ones, only product **12c** (R = 4-MePh) could be isolated and identified. In all other cases we could not obtain pure products (Scheme 4). The structure of compound **12c** was assigned by analogy with compounds **10a-c**, and confirmed by mass-spectrometry data, ^1H and ^{13}C NMR spectra. When we attempted to carry out the reaction under other conditions, we observed no reaction in refluxing acetonitrile in the presence of CF_3COOH. The reaction was carried out in refluxing DMF in the presence of CF_3SO_3H and resulted in the formation of **7aa** (19% yield) after 1 hour.



Scheme 4.

To prove the assumption that compounds **10** are intermediate compounds in the reactions leading to **6** we investigated their behavior in different conditions. It appears that **10a** does not undergo transformations in refluxing DMF or in DMF at ambient temperature in the presence of CF_3COOH or p-TsOH. Refluxing of **10a** in DMF in the presence of CF_3SO_3H results in the formation of triflate of triazinone **1a** and the condensation product **6aa** in low yields (Scheme 5). The salt of **1a** is a decomposition product of **10a** and could be used as starting material for reaction with cyclohexanone residue from the reaction mixture resulting in the formation of **6aa**.

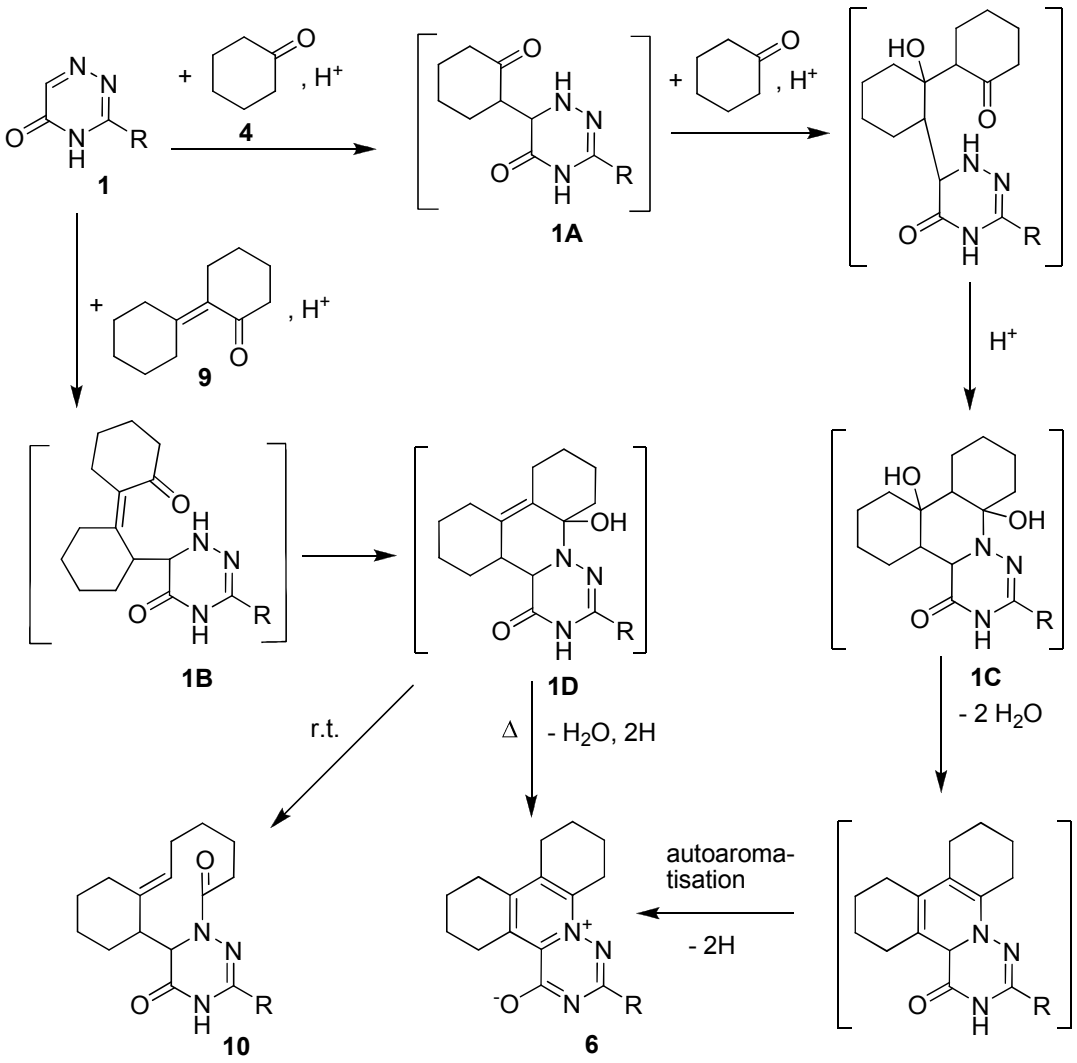


Scheme 5.

Liquid chromatography-mass spectrometry analysis of the reaction mixtures of 3-Ph-1,2,4-triazin-5(4H)-one (**1a**) with cyclohexanone in DMSO solutions in the presence of CF_3SO_3H after 24 hours shows intensive peaks of some molecular ions. There were observed peaks of **6ab** (ESI-MS, m/z = 332.1798 (calcld. 332.1757 for $[C_{21}H_{22}N_3O]^+$, $[M+H]^+$)), **10a** (ESI-MS, m/z = 352.2032 (calcld. 352.2020 for $[C_{21}H_{26}N_3O_2]^+$, $[M+H]^+$)), and peak of unidentified compound (ESI-MS, m/z = 258.1610 (calcld. 258.1601 for $[C_{15}H_{20}N_3O]^+$, $[M+H]^+$)). In the reaction of 3-Ph-1,2,4-triazin-5(4H)-one (**1a**) with cyclopentanone intensive peaks of **7ab** were observed (ESI-MS, m/z = 304.1488 (calcld. 304.1444 for $[C_{19}H_{18}N_3O]^+$, $[M+H]^+$)), **12a** (ESI-MS, m/z = 324.1729 (calcld. 324.1706 for $[C_{19}H_{22}N_3O_2]^+$, $[M+H]^+$)), benzonitrile (ESI-MS, m/z = 104.0520 (calcld. 104.0494 for $[C_7H_6N]^+$, $[M+H]^+$)), peak of unidentified compound (ESI-MS, m/z = 244.1470 (calcld. 244.1444 for $[C_{14}H_{18}N_3O]^+$, $[M+H]^+$)), its dimer (ESI-MS, m/z = 477.2034 (calcld. 477.2033 for $[C_{28}H_{25}N_6O_2]^+$, $[M+H]^+$)), and peak of unidentified compound (ESI-MS, m/z = 545.2625 (calcld. 545.2619 for $[C_{28}H_{33}N_8O_4]^+$, $[M+H]^+$)).

Absence of the formation of lactam products **10,12** in quantities sufficient for identification in the reactions of triazines **1** with cyclic ketones probably means that there are two different ways of formation of tetracyclic compounds **6,7** and lactam compounds **10,12**. We suggested two different routes for the reactions of triazines **1** with free cyclic ketones and their dimerization products.

The high activity of 3-R-1,2,4-triazin-5(4H)-ones in the reactions with C-nucleophiles suppose initial nucleophilic addition of cyclic ketones to 1,2,4-triazine ring with formation of high reactive compounds **1A** or **1B**. The attack of the cyclic ketone on **1A** leads to the series of transformations with the final product **6**. We suppose that the product **1B** after intermolecular addition gives **1D**. Compound **1D** at ambient temperature gives 10-membered lactame **10**, the high temperature of refluxing DMF and the presence of triflic acid lead to the loss of a water molecule and formation of **6** (Scheme 6).



Scheme 6.

Conclusions

In the course of the present study new heterocyclic systems of benzo[c][1,2,4]triazino[1,6-a][2]azecine and cyclopenta[c][1,2,4] triazino[1,6-a]azonine were obtained, optimal reaction conditions were found for the condensation between 1,2,4-triazine-5(4H)-ones and cyclic ketones. It was shown that benzo[c][1,2,4]triazino[1,6-a][2]azecines **10** are not intermediates in the reaction of formation of [1,2,4]triazino[1,6-f]phenantridine derivatives **6**.

It should be noted that C-C coupling reactions between azines and cyclic ketones had been described earlier,[20] but intramolecular condensation was observed and investigated for the first time.

Experimental Section

3-Ph-1,2,4-triazin-5(4H)-one (**1a**),[21] 3-SMe-1,2,4-triazin-5(4H)-one (**1b**),[22] 1'-hydroxybi(cyclohexan)-2-one (**8**),[23] 1,1'-bi(cyclohexilidene)-2-one (**9**)[24] and 1,1'-bi(cyclopentilidene)-2-one (**11**)[25] were synthesized by known methods, others starting materials are commercially available. ^{1}H, ^{13}C NMR spectra were recorded using 400MHz spectrometer; tetramethylsilane (TMS) was used as an internal standard. TOF mass analyzer was used for the HRMS.

3-(4-Tolyl)-1,2,4-triazin-5(4H)-one (1c). Methanol (10.1 ml, 0.170 mole) was added to the solution of 4-methylbenzonitrile (10.0 g, 0.085 mole) in ether (50 ml), resulting solution was chilled to T = 0÷-5 °C and then dry HCl was bubbled through the solution for 2-3h. The reaction mixture was stirred for 16h at room temperature. The sediment of methyl ether of 4-methylbenzimidate hydrochloride was filtered out, washed with ether and dried. The hydrochloride was dissolved in water and 50 ml of aqueous NaOH (5N) was added to the solution. Then the product was extracted with ether, the ether solution was dried over Na_2SO_4 and ether was evaporated.

On the next stage hydrazine hydrate (2.35 g, 0.047 mole) was added to solution of 4-methylbenzimidate (7.0 g, 0.047 mole) in 10 ml of methanol. The reaction mixture was stirred for 16 h, after that it was cooled to T = 5°C and glyoxylic acid monohydrate (4.32 g, 0.047 mmol) was added by portions to the solution. The temperature has to be lower 10°C. The reaction mixture was stirred 1 h at 5°C, then it was stayed in refrigerator for 16 h at 5°C. The formed yellow sediment was filtered, washed with cold methanol and dried. The yellow solid was dissolved in DMF (50ml) and refluxed for 30 min. After cooling of the solution to room temperature crystals formed. They were filtered and crystallized from ethanol. Yield 41 % (6.5 g), light brown crystals, mp 255 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.43 (s, 3H), 7.35 (d, J = 8.1 Hz, 2H), 7.63 (s, 1H), 7.98 (d, J = 8.2 Hz, 2H), 14.0 (br.s, 1H, NH); ^{13}C NMR (100MHz, DMSO-d_6) δ: 21.0, 127.5, 127.6, 129.5, 143.0, 143.4, 158.1, 162.2; ESI-MS, m/z = 188.0819 (calcld. 188.0818 for $[C_{10}H_{10}N_3O]^+$, $[M+H]^+$).

3-(4-Chlorophenyl)-1,2,4-triazin-5(4H)-one (1d). The procedure is the same as for **1c**. Yield 31 % (5.4 g), yellow crystals, mp 282-283 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.68 (d, 2H), 7.86 (s, 1H), 8.07 (d, 2H), 14.12 (br.s, 1H); ^{13}C NMR (100MHz, DMSO-d_6) δ: 129.6, 129.8, 130.1, 138.1, 144.3, 157.8, 162.5; ESI-MS, m/z = 208.0283 (calcld. 208.0272 for $[C_9H_7ClN_3O]^+$, $[M+H]^+$).

3-Benzyl-1,2,4-triazin-5(4H)-one (1e). The procedure is the same as for **1c**. Yield 39 % (6.2 g), yellow crystals, mp 165-166 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.11 (s, 2H), 6.43-6.54 (m,

5H), 6.92 (s, 1H), 13.68 (br.s, 1H); ^{13}C NMR (100MHz, CD_3OD) δ: 41.0, 128.7, 130.0, 130.1, 135.9, 144.7, 165.3, 165.4; ESI-MS, m/z = 188.0812 (calcld. 188.0818 for $[C_{10}H_{10}N_3O]^+$, $[M+H]^+$).

6-(2-Oxo-2-phenylethyl)-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4H)-one (3a). Acetophenone (270 µl, 2.310 mmol) and CF_3SO_3H (100 µl) were added to the suspension of 3-Ph-1,2,4-triazin-5(4H)-one (200 mg, 1.155 mmol) in 10 ml CH_3CN. The solution was refluxed for 3 h, then it was cooled, neutralized with NEt_3 and after 16 h formed sediment was filtered and crystallized from CH_3CN. Yield 35% (119 mg); yellow crystals; mp 194-195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.30 (dd, *J* = 18.5, 10.1Hz, 1H), 3.92 (dd, *J* = 18.5, 2.4 Hz, 1H), 4.29 (dd, *J* = 10.1, 2.3 Hz, 1H), 6.39 (br.s, 1H), 7.41-7.45 (m, 3H), 7.48-7.52 (m, 2H), 7.60-7.64 (m, 1H), 7.67-7.70 (m, 2H), 8.00-8.02 (m, 2H), 8.37 (br.s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 37.1, 52.3, 124.9, 128.2, 128.8, 129.0, 130.1, 131.2, 133.9, 136.0, 139.4, 167.7, 197.6; ESI-MS, m/z = 294.1291 (calcld. 294.1237 for $[C_{17}H_{16}N_3O_2]^+$, $[M+H]^+$).

3-(Methylthio)-6-(2-oxo-2-phenylethyl)-1,6-dihydro-1,2,4-triazin-5(4H)-one (3b). Acetophenone (326 µl, 2.794 mmol) and CF_3SO_3H (100 µl) were added to the suspension of 3-SMe-1,2,4-triazin-5(4H)-one (200 mg, 1.397 mmol) in 10 ml CH_3CN. The solution was refluxed for 3 h (emission of CH_3SH !), then it was cooled, neutralized with NEt_3 and evaporated. The residue was chromatographed by column using EtOAc as an eluent. Yield 13% (40 mg); yellow crystals; mp 132-133 °C; R_f = 0.3 (EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.33 (s, 3H), 3.10 (dd, *J* = 17.8, 6.0 Hz, 1H), 3.57 (dd, J = 17.8, 5.8 Hz, 1H), 3.86-3.89 (m, 1H), 6.56 (d, *J* = 3.0 Hz, 1H), 7.48-7.52 (m, 2H), 7.58-7.62 (m, 1H), 7.98-7.99 (m, 2H), 10.64 (s, 1H); ^{13}C NMR (100MHz, DMSO-d_6) δ: 12.8, 36.4, 52.2, 128.0, 128.7, 133.3, 136.3, 139.3, 167.3, 196.6; ESI-MS, m/z = 264.0791 (calcld. 264.0801 for $[C_{12}H_{14}N_3O_2S]^+$, $[M+H]^+$).

Procedures for synthesis of 6a.

Method A. Cyclohexanone **4** (239 µL, 2.310 mmol) and 1 equiv. of acid (CF_3COOH or $AlCl_3$, see Table 1) were added to the solution of 3-Ph-1,2,4-triazin-5(4H)-one (200 mg, 1.155 mmol) in the corresponding solvent (see Table 1). The solution was stirred or refluxed for the time mentioned in the Table 1. Formed sediment was filtered and crystallized from DMF. Otherwise the reaction mixture was poured to the water (50 ml) and extracted with CH_2Cl_2. The organic layer was separated, washed with water, brine and dried over Na_2SO_4. The solution in CH_2Cl_2 was evaporated and the residue was crystallized from DMF.

Method B. Cyclohexanone **4** (239 µL, 2.310 mmol) was added to the solution of 3-Ph-1,2,4-triazin-5(4H)-one (200 mg, 1.155 mmol) in the phosphoric acid (5 ml). The solution was stirred for 3 h at 50 °C then it was cooled and poured in water (50 ml). Formed sediment was filtered and chromatographed by column using EtOAc as an eluent.

Method C. Cyclohexanone **4** (239 μL, 2.310 mmol) was added to the solution of 3-Ph-1,2,4-triazin-5(4H)-one (200 mg, 1.155 mmol) in the acetic acid (5 ml). The reaction mixture was refluxed for 1 h and then it was evaporated. The residue was refluxed in $CHCl_3$ for 5 min and filtered. The chloroform solution was evaporated and the residue was crystallized from DMF.

Method D. 1,1'-Bi(cyclohexilidene)-2-one (**9**) (206 μL, 1.155 mmol) and CF_3SO_3H (1.155 mmol, 102 μL) were added to the solution of 3-Ph-1,2,4-triazin-5(4H)-one (200 mg, 1.155 mmol) in DMF (3 ml). The reaction mixture was refluxed for 1 h, neutralized with NEt_3 and then it was evaporated. The residue was crystallized from DMF.

Method E. 1'-Hydroxybi(cyclohexan)-2-one (**8**) (227 μL, 1.155 mmol), p-TsOH (203 mg, 1.155 mmol) and P_2O_5 (492 mg, 1.155 mmol) were added to the mixture of 3-R-1,2,4-triazin-5(4H)-one (200 mg, 1.155 mmol) and CH_3CN (10 ml). Then it was divided on two parts. The solution in CH_3CN was decanted and evaporated to the half volume. NEt_3 (100 μl) was added to the solution and after 2 h the sediment was filtered. Solid part of the reaction mixture was dissolved in water and neutralized with concentrated solution of $NaHCO_3$, the resulting sediment was filtered. Combined sediments were dried and crystallized from DMF.

Method F. Cyclohexanone **4** (239 μL, 2.310 mmol) was added to the solution of 3-Ph-1,2,4-triazin-5(4H)-one (200 mg, 1.155 mmol) in methanolic MeONa (1M) (4 ml). The reaction mixture was stirred for 24 h, then it was poured in water (50 ml) neutralized with HCl (2M), the product extracted with CH_2Cl_2. Solution in CH_2Cl_2 was washed with water, brine and dried over Na_2SO_4. Then it was evaporated and the residue was crystallized from DMF.

Procedures for synthesis of 6a-d, 7a-d.

Method A. Ketone **4** or **5** (2 equiv.), p-TsOH (1 equiv) and P_2O_5 (3 equiv.) (or 1 g of molecular sieves 3Å) were added to the mixture of 3-R-1,2,4-triazin-5(4H)-one (150 mg) and CH_3CN (10 ml). The reaction mixture was refluxed for 3 h. Then it was divided on two parts. The solution in CH_3CN was decanted and evaporated to the half volume. NEt_3 (100 μl) was added to the solution and after 2 h the sediment was filtered. Solid part of the reaction mixture was dissolved in water and neutralized with concentrated solution of $NaHCO_3$, the resulting sediment was filtered. Combined sediments were dried and crystallized from DMF.

Method B. Ketone **4** or **5** (2 equiv.) and p-TsOH (1 equiv) were added to the solution of 3-R-1,2,4-triazin-5(4H)-one (200 mg) in DMF (3 ml). The solution was refluxed for 1 h. After 16 h sediment was filtered. If there was no sediment the reaction mixture was poured in water, the product extracted with CH_2Cl_2. The organic layer was separated, washed with water, brine and dried over Na_2SO_4. The solution in CH_2Cl_2 was evaporated and the residue was crystallized from DMF.

2-Phenyl-5,6,7,8,9,10,11,12-octahydro[1,2,4]triazino[1,6-f]phenanthridin-13-ium-4-olate (6a). Yield 44% (169 mg), cream crystals, mp > 300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.77-1.81 (m, 4H), 1.90-1.99 (m, 4H), 2.67 (t, *J* = 6.1 Hz, 2H), 2.71 (t, *J* = 6.2 Hz, 2H), 3.35 (t, *J* = 6.2 Hz, 2H), 3.61 (t, *J* = 6.2 Hz, 2H), 7.38-7.46 (m, 3H), 8.36-8.38 (m, 2H). The spectral data of the compound are identical to literature values.[17]

2-(Methylthio)-5,6,7,8,9,10,11,12-octahydro-[1,2,4]triazino[1,6-f]phenanthridin-13-ium-4-olate (6b). Yield 21% (73 mg), cream crystals, mp 249 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.76-1.97 (m, 8H), 2.54 (s, 3H), 2.74 (dd, *J* = 13.3, 6.8Hz, 4H), 3.19 (t, *J* = 6.2Hz, 2H), 3.59 (t, *J* = 6.2Hz, 2H); ^{13}C NMR (100MHz, DMSO-d_6) δ: 13.5, 21.0, 21.2, 21.4, 21.9, 26.3, 27.1, 27.7, 28.8, 131.4, 136.1, 136.4, 142.4, 146.6, 163.8, 170.9; ESI-MS, m/z = 302.1355 (calcld. 302.1322 for $[C_{16}H_{20}N_3OS]^+$, $[M+H]^+$).

2-(p-Tolyl)-5,6,7,8,9,10,11,12-octahydro-[1,2,4]triazino[1,6-f]phenanthridin-13-ium-4-olate (6c). Yield 24% (96 mg), grey crystals, mp 304-305 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.77-1.79 (m, 4H), 1.90-1.99 (m, 4H), 2.38 (s, 3H), 2.72-2.78 (m, 4H), 3.39 (t, *J* = 6.3Hz, 2H), 3.66 (t, *J* = 6.1Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 8.22 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100MHz, DMSO-d_6) δ: 21.0, 21.3, 21.5, 21.9, 26.3, 27.1, 27.6, 28.8, 128.0, 128.7, 132.1, 132.9, 135.7, 136.3, 141.1, 143.3, 146.6, 161.5, 166.5; ESI-MS, m/z = 346.1903 (calcld. 346.1914 for $[C_{22}H_{24}N_3O]^+$, $[M+H]^+$). Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 859049). These data can be obtained via: www.ccdc.cam.ac.uk/data_request/cif

2-(4-Chlorophenyl)-5,6,7,8,9,10,11,12-octahydro-[1,2,4]triazino[1,6-f]phenanthridin-13-ium-4-olate (6d). Yield 15% (63 mg), yellow crystals, mp 257-258 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.76-1.96 (m, 8H), 2.76-2.77 (m, 4H), 3.30 (t, *J* = 5.7Hz, 2H), 3.45 (t, *J* = 5.9Hz, 2H), 7.44 (d, *J* = 8.5Hz, 2H), 8.23 (d, *J* = 8.5Hz, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 21.0, 21.3, 21.5, 21.9, 26.4, 27.1, 27.7, 28.9, 128.0, 129.2, 132.0, 134.1, 135.9, 136.7, 136.9, 143.6, 147.5, 160.2, 166.5; ESI-MS, m/z = 366.1354 (calcld. 366.1368 for $[C_{21}H_{21}ClN_3O]^+$, $[M+H]^+$).

2-Phenyl-5,6,7,8,9,10-hexahydrodicyclopenta[3,4:5,6]pyrido[2,1-f][1,2,4]triazin-11-ium-4-olate (7a). Yield 30% (105 mg), light green crystals, mp > 300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25-2.33 (m, 2H), 2.37-2.45 (m, 2H), 3.01 (t, *J* = 7.7Hz, 2H), 3.09-3.18 (m, 2H), 3.55 (t, *J* = 7.9Hz, 2H), 3.79 (t, *J* = 7.9Hz, 2H), 7.40-7.47 (m, 3H), 8.42-8.44 (m, 2H). The spectral data of the compound are identical to literature values.[17]

2-(Methylthio)-5,6,7,8,9,10-hexahydrodicyclopenta[3,4:5,6]pyrido[2,1-f][1,2,4]triazin-11-ium-4-olate (7b). Yield 21% (66 mg), grey crystals, mp 258-259 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.21-2.30 (m, 2H), 2.31-2.42 (m, 2H), 2.53 (s, 3H), 2.98 (t, *J* = 7.8 Hz, 2H), 3.10 (t, *J* = 7.6 Hz, 2H), 3.37 (t, *J* = 7.8 Hz, 2H), 3.70 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ:

13.5, 22.1, 24.7, 30.5, 31.2, 31.5, 34.0, 129.4, 139.2, 143.2, 149.4, 152.5, 162.8, 172.3. The spectral data of the compound are identical to literature values.[17]

2-(p-Tolyl)-5,6,7,8,9,10-hexahydrodicyclopenta[3,4:5,6]pyrido[2,1-f][1,2,4]triazin-11-ium-4-olate (7c). Yield 24% (88 mg), brown crystals, mp 236-237 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.20-2.27 (m, 2H), 2.34-2.42 (m, 5H), 2.88-2.96 (m, 2H), 3.08 (t, *J* = 7.6 Hz, 2H), 3.51 (t, *J* = 7.7 Hz, 2H), 3.74 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 8.28 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 21.4, 22.1, 24.5, 30.4, 31.3, 31.3, 34.1, 128.0, 128.7, 130.2, 133.0, 139.0, 141.1, 142.8, 150.4, 152.5, 162.8, 165.6; ESI-MS, m/z = 318.1620 (calcld. 318.1601 for $[C_{20}H_{20}N_3O]^+$, $[M+H]^+$).

2-(4-Chlorophenyl)-5,6,7,8,9,10-hexahydrodicyclopenta[3,4:5,6]pyrido[2,1-f][1,2,4]triazin-11-ium-4-olate (7d). Yield 22% (86 mg), yellow green crystals, mp > 300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.21-2.28 (m, 2H), 2.34-2.41 (m, 2H), 2.94 (t, *J* = 7.7 Hz, 2H), 3.07 (t, *J* = 7.6 Hz, 2H), 3.47 (t, *J* = 7.7 Hz, 2H), 3.70 (t, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 8.6Hz, 2H), 8.26 (d, *J* = 8.6Hz, 2H). The spectral data of the compound are identical to literature values.[17]

Procedures for synthesis of 6aa-da.

Method A. Cyclohexanone (2 equiv.) and CF_3SO_3H (1 equiv.) were added to the solution of 3-R-1,2,4-triazin-5(4H)-one (200 mg) in DMF (3 ml). The reaction mixture was stirred at room temperature for the period of time specified in Table 3. The sediment was filtered and crystallized from DMF.

Method B. Cyclohexanone (2 equiv.) and CF_3SO_3H (1 equiv.) were added to the solution of 3-R-1,2,4-triazin-5(4H)-one (200 mg) in DMF (3 ml). The reaction mixture was refluxed for the time in Table 1 and cooled, after 12 h formed sediment was filtered and crystallized from DMF.

4-Oxo-2-phenyl-3,4,5,6,7,8,9,10,11,12-decahydro-[1,2,4]triazino[1,6-f]phenanthridin-13-ium trifluoromethanesulfonate (6aa). Yield 25% (138 mg), green crystals, mp 252-253 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.78-2.04 (m, 8H), 2.85-2.66 (m, 4H), 3.40 (t, *J* = 6.4Hz, 2H), 3.67 (t, *J* = 6.1Hz, 2H), 7.42-7.50 (m, 3H), 8.41-8.44 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 21.1, 21.3, 21.6, 22.0, 26.3, 27.2, 27.6, 28.8, 128.0, 128.1, 130.8, 135.9, 136.0, 136.3, 143.4, 146.9, 161.7, 166.4; ^{19}F NMR (100MHz, $CDCl_3$) δ: -78.2; ESI-MS, m/z = 332.1762 (calcld. 332.1757 for $[C_{21}H_{22}N_3O]^+$, $[M+H]^+$). Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 820437). These data can be obtained via: www.ccdc.cam.ac.uk/data_request/cif

2-(Methylthio)-4-oxo-3,4,5,6,7,8,9,10,11,12-decahydro-[1,2,4]triazino[1,6-f]phenanthridin-13-ium trifluoromethanesulfonate (6ba). Yield 24% (150 mg), light yellow crystals, mp 215-216 °C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.74-1.80 (m, 2H), 1.84-1.95 (m, 6H), 2.52 (s, 3H), 2.72-2.77 (m, 4H), 3.16-3.19 (m, 2H), 3.54-3.57 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 13.6, 21.1,

21.3, 21.4, 22.0, 26.3, 27.2, 27.7, 28.9, 131.4, 136.2, 136.6, 146.2, 146.8, 163.8, 170.9; ^{19}F NMR (100MHz, $CDCl_3$) δ: -78.3; ESI-MS, m/z = 302.1318 (calcld. 302.1322 for $[C_{16}H_{20}N_3OS]^+$, $[M+H]^+$).

2-(4-Methylphenyl)-4-oxo-3,4,5,6,7,8,9,10,11,12-decahydro-[1,2,4]triazino[1,6-f]phenanthridin-13-ium trifluoromethanesulfonate (6ca). Yield 26% (140 mg), light yellow crystals, mp 277-278 °C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.72-1.83 (m, 4H), 1.87-2.01 (m, 4H), 2.38 (s, 3H), 2.62-2.65 (m, 2H), 2.68-2.71 (m, 2H), 3.31-3.34 (m, 2H), 3.57-3.60 (m, 2H), 7.19 (d, *J* = 7.6 Hz, 2H), 8.22 (d, *J* = 8.0 Hz, 2H); NMR ^{13}C (100MHz, $CDCl_3$) δ: 21.0, 21.3, 21.5, 22.0, 26.3, 27.2, 27.7, 28.9, 128.0, 128.8, 132.1, 132.9, 135.8, 136.4, 141.2, 143.5, 146.8, 161.4, 166.5; ^{19}F NMR (100MHz, $CDCl_3$) δ: -78.3; ESI-MS, m/z = 346.1914 (calcld. 346.1914 for $[C_{22}H_{24}N_3O]^+$, $[M+H]^+$).

2-(4-Chlorophenyl)-4-oxo-3,4,5,6,7,8,9,10,11,12-decahydro-[1,2,4]triazino[1,6-f]phenanthridin-13-ium trifluoromethanesulfonate (6da). Yield 26% (131 mg), wine red crystals, mp 252-253 °C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.75-1.98 (m, 8H), 2.65-2.71 (m, 4H), 3.25 (t, *J* = 6.0 Hz, 2H), 3.54-3.57 (m, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 8.22 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 21.0, 21.3, 21.5, 21.9, 26.4, 27.1, 27.7, 28.9, 128.0, 129.2, 132.0, 134.1, 135.9, 136.7, 136.9, 143.6, 147.5, 160.2, 166.5; ^{19}F NMR (100MHz, $CDCl_3$) δ: -77.3; ESI-MS, m/z = 366.1372 (calcld. 366.1368 for $[C_{21}H_{21}ClN_3O]^+$, $[M+H]^+$).

Procedure for synthesis of 4-Oxo-2-phenyl-3,4,5,6,7,8,9,10,11,12-decahydro-[1,2,4]triazino[1,6-f]phenanthridin-13-ium chloride 6ab. Cyclohexanone (239μL, 2.310mmol) was added to the solution of 3-Ph-1,2,4-triazin-5(4H)-one (200 mg, 1.155mmol) in conc. ethanol solution of HCl (5 ml). The reaction mixture was stirred at room temperature for 1 day. The sediment was filtered washed with ethanol, crystallized from DMF and dried. Yield 40% (172 mg), dark yellow crystals, mp 270-271 °C; ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.86-2.01 (m, 8H), 2.92-2.98 (m, 4H), 3.42-3.45 (m, 2H), 3.49-3.51 (m, 2H), 7.59-7.63 (m, 2H), 7.69-7.73 (m, 1H), 8.17 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100MHz, DMSO-d_6) δ: 20.6, 20.8, 21.1, 21.5, 26.4, 27.8, 28.0, 28.5, 128.7, 129.1, 129.1, 129.6, 132.7, 133.8, 137.2, 140.7, 147.7, 152.7, 154.1, 157.4, 157.5; ESI-MS, m/z = 332.1769 (calcld. 332.1757 for $[C_{21}H_{22}N_3O]^+$, $[M+H]^+$).

Procedure for synthesis of 10a-c,e. 1,1'-Bi(cyclohexilidene)-2-one (**9**) (1 equiv) and CF_3COOH (1 equiv) were added to the solution of 3-R-1,2,4-triazin-5(4H)-one (200 mg, 1.155 mmol) in DMF (3 ml). The reaction mixture was stirred at room temperature for 5 days, poured in Petri dish; residue from flask was washed off with ethanol (5 ml) to the same Petri dish. After 2 h formed sediment was filtered and crystallized from CH_3CN.

3-Phenyl-7,8,9,10,12,13,14,15,15a,15b-decahydro-1H-benzo[c][1,2,4]triazino[1,6-a]azecine-1,6(2H)-dione (10a). Yield 57% (232 mg), colorless crystals, mp 210-211 °C; ^{1}H NMR (400

MHz, $CDCl_3$) δ: 1.15-1.27 (m, 1H), 1.41-2.14 (m, 14H), 2.28-2.32 (m, 1H), 3.56 (dd, *J* = 14.3, 10.1, 1.5 Hz, 1H), 4.90 (d, *J* = 10.1 Hz, 1H), 5.12 (d, *J* = 11.4 Hz, 1H), 7.41-7.47 (m, 3H), 7.88-7.90 (m, 2H), 11.30 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ: 21.6, 24.7, 25.5, 25.8, 26.3, 27.6, 29.0, 32.4, 43.1, 57.0, 125.9, 129.0, 130.3, 130.4, 131.0, 135.1, 139.2, 167.8, 176.0; ESI-MS, m/z = 352.1996 (calcld. 352.2020 for $[C_{21}H_{26}N_3O_2]^+$, $[M+H]^+$). Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 859113). These data can be obtained via: www.ccdc.cam.ac.uk/data_request/cif

3-(Methylthio)-7,8,9,10,12,13,14,15,15a,15b-decahydro-1H-benzo[c][1,2,4]triazino[1,6-a]azecine-1,6(2H)-dione (10b). Yield 70% (315 mg), colorless crystals, mp 244-245 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.11-1.21 (m, 1H), 1.33-1.41 (m, 1H), 1.46-2.12 (m, 13H), 2.28 (d, *J* = 15.0 Hz, 1H), 2.46 (s, 3H), 3.33 (dd, *J* = 14.0, 9.6 Hz, 1H), 4.90 (d, *J* = 10.4 Hz, 1H), 5.01 (d, *J* = 11.4 Hz, 1H), 11.30 (br.s, 1H); ^{13}C NMR (100MHz, DMSO-d_6) δ: 13.6, 21.6, 24.5, 25.5, 25.7, 26.0, 27.4, 28.9, 32.2, 42.8, 57.5, 129.9, 135.2, 141.3, 166.1, 175.0; ESI-MS, m/z = 322.1580 (calcld. 322.1584 for $[C_{16}H_{24}N_3O_2S]^+$, $[M+H]^+$). Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 820598). These data can be obtained via: www.ccdc.cam.ac.uk/data_request/cif

3-p-Tolyl-7,8,9,10,12,13,14,15,15a,15b-decahydro-1H-benzo[c][1,2,4]triazino[1,6-a]azecine-1,6(2H)-dione (10c). Yield 67% (262 mg), colorless crystals, mp 205-206 °C; $[\alpha]_D$ = 0 (c = 0.6, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.11-1.28 (m, 1H), 1.39-2.15 (m, 14H), 2.30 (d, *J* = 14.5 Hz, 1H), 2.40 (s, 3H), 3.55 (dd, *J* = 14.1, 10.0 Hz, 1H), 4.89 (d, *J* = 10.3 Hz, 1H), 5.11 (d, *J* = 11.4 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 8.1 Hz, 2H), 11.24 (s, 1H); ^{13}C NMR (100MHz, DMSO-d_6) δ: 20.6, 21.1, 23.9, 24.9, 25.1, 25.4, 26.9, 28.3, 31.5, 41.8, 56.3, 126.2, 127.5, 129.1, 129.2, 134.4, 140.4, 140.5, 165.9, 174.7; ESI-MS, m/z = 366.2143 (calcld. 366.2176 for $[C_{22}H_{28}N_3O_2]^+$, $[M+H]^+$).

3-Benzyl-7,8,9,10,12,13,14,15,15a,15b-decahydro-1H-benzo[c][1,2,4]triazino[1,6-a]azecine-1,6(2H)-dione (10e). Yield 52% (203 mg), light brown crystals, mp 211-212 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.03-1.15 (m, 1H), 1.27-2.09 (m, 14H), 2.23-2.27 (m, 1H), 3.61 (s, 2H), 4.85 (d, *J* = 10.1 Hz, 1H), 4.96 (d, *J* = 11.4 Hz, 1H), 7.24-7.29 (m, 1H), 7.34-7.35 (m, 4H), 11.1 (s, 1H); ^{13}C NMR (100MHz, DMSO-d_6) δ: 21.0, 23.9, 24.8, 25.0, 25.2, 26.9, 28.2, 31.3, 37.5, 41.7, 55.8, 126.8, 128.3, 128.7, 129.1, 134.3, 135.8, 142.9, 165.6, 174.4; ESI-MS, m/z = 366.2142 (calcld. 366.2176 for $[C_{22}H_{28}N_3O_2]^+$, $[M+H]^+$).

3-(p-Tolyl)-7,8,9,11,12,13,13a,13b-octahydro-1H-cyclopenta[c][1,2,4]triazino[1,6-a]azonine-1,6(2H)-dione (12c). 1,1'-bi(cyclopentilidene)-2-one (**11**) (162 µL, 1.068 mmol) and CF_3COOH (100 µL) were added to the solution of 3-(4-Tol)-1,2,4-triazin-5(4H)-one (**1c**) (200 mg, 1.068 mmol) in DMF (3 ml). The reaction mixture was stirred at room temperature for 5 days and

evaporated. The residue was chromatographed by column using EtOAc as an eluent. Yield 9% (32 mg), yellow crystals, mp 229-230 °C, R_f = 0.6 (EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.64-1.75 (m, 4H), 1.77-1.85 (m, 1H), 2.08-2.15 (m, 1H), 2.23-2.44 (m, 7H), 2.58-2.64 (m, 1H), 2.71 (br.s, 2H), 3.71 (dd, *J* = 5.5, 2.1 Hz, 1H), 6.99 (d, *J* = 2.1 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 10.56 (s, 1H); ^{13}C NMR (100MHz, DMSO-d_6) δ: 20.5, 22.1, 24.4, 26.1, 26.7, 31.7, 33.3, 47.4, 51.7, 56.5, 99.2, 124.9, 127.3, 128.5, 129.2, 138.3, 138.9, 157.3, 165.7, 203.7; ESI-MS, m/z = 338.1849 (calcld. 338.1863 for $[C_{20}H_{24}N_3O_2]^+$, $[M+H]^+$).

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Supporting Information Available: ^{1}H, ^{13}C NMR spectra of products and other data. This material is available free of charge via the Internet at http://pubs.acs.org.

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