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Efficient synthesis of quinazolinones as intermediates of CNS agents via inverse-electron demand Diels–Alder reaction†

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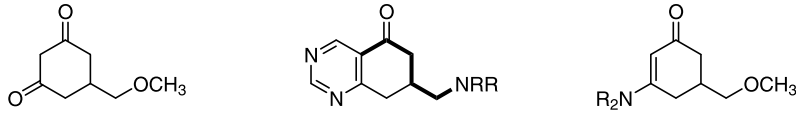
Abstract—Enaminones undergo inverse electron demand Diels–Alder reaction with 1,3,5-triazine, allowing access to functionalised quinazolinones as intermediates in the synthesis of CNS agents. This reaction is highly dependent of the solvent: 1,3,5-triazine undergoes single or double [4+2] cycloadditions with enaminones, and quinazolinones or acridinediones can be selectively obtained.

For some time we have been interested in the utilization of cyclohexanedione **1** being a versatile synthon in the preparation of condensed heterocyclic systems as intermediates in the synthesis of CNS agents.[1] In connection with this, we want to study its utilization in the synthesis of quinazolinones **2**, as part of our program concerning the elaboration of aza-analogues of the antipsychotic butyrophenones.[2] The synthetic strategy would consist of the conversion of **1** in the enaminone **3** and subsequent treatment with 1,3,5-triazine (**4**) in an inverse-electron demand Diels–Alder reaction. This process could serve as a useful and regiospecific pyrimidine annulation applicable to our current synthetic studies.

The inverse-electron demand Diels–Alder (IDA) reaction is controlled mainly by the interaction of $HOMO_{dienophile}$ and $LUMO_{diene}$ and it requires an electron-rich dienophile and an electron-poor diene. The chemistry of IDA has been the subject of recent intensive investigation and is widely used in the synthesis of heterocyclic compounds.[3] The IDA reaction of 1,3,5-triazines (electron-poor dienes) with enamines (electron-rich dienophiles) has been extensively investigated, and the latter have proven to be good substrates for the synthesis of substituted or condensed pyrimidines.[4] However, the use of electron-poor enamines (such as enaminones) as dienophiles in these IDA reactions has been poorly explored, and these compounds only undergo IDA reactions with triazines having electrodonating groups.[5] Here we report our investigations on the behavior of 1,3,5-triazine towards simple enaminones derived from dimedone (Scheme 1), and the utility of such cycloaddition reaction for the synthesis of our CNS agents precursor.

The synthesis of enaminones from 1,3-diketones is well known, and enamino ketones **5a** (R = 1-morpholinyl)[6] and **5b** (R = 1-pyrrolidinyl)[6] could be obtained in high yields by refluxing dimedone and the amine in THF in the presence of molecular sieves. The enaminone **5c** ($R = NH_2$)[7] was quantitatively obtained by refluxing dimedone with ammonium acetate in benzene/acetic acid.[8]



1 2 3

Keywords: Diels–Alder reactions; enamino ketones; quinazolinones; triazines.

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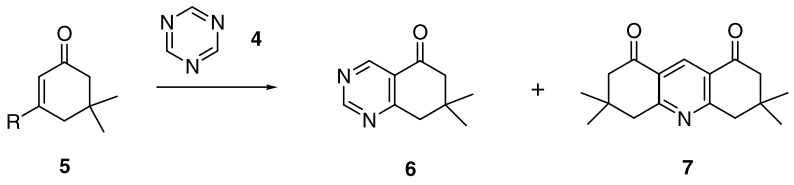


5 6 7

Scheme 1.

The results of the assays are summarized in Table 1. First attempts of reaction between enaminones **5a**–**5c** with 1,3,5-triazine afforded only traces of quinazolinone **6**; attempts of increasing cycloaddition yields failed, even when long times, different solvents, high temperatures, or pressure were used (Table 1, entries 1–3). Neither the addition of HCl to the reaction mixture (entry 4) did enhance the amount of compound **6** obtained.[9] No cycloaddition intermediates were detected, proven that dienophiles **5** are not sufficiently reactive to participate in productive [4+2] cycloaddition reactions with the triazine.[10]

However, when the hydrochloride salt of the enaminone was used, the quinazolinone was obtained regiospecifically in acceptable yields (35–40%, entries 5 and 8).[11] The presence of the protonated nitrogen atom in the enaminone should reduce the electronic density in the double bond and hence its HOMO level, increasing the $HOMO_{dienophile}$–$LUMO_{diene}$ gap and making the cycloaddition more difficult: according to calculations using the AM1 semi-empirical method[12] (Table 2), the protonation of the enaminone increase the gap in about 5.4 eV (from 8.01–8.43 to 13.62–13.87 eV). The relative basicity of both diene (triazine) and dienophile (enaminone) could explain this unexpected behavior. Triazine, which is probably more basic than enaminones **5a**–**c**, can be protonated by **5a**–**c** hydrochloride. The consequence is a better LUMO–HOMO interaction: the calculated energy differences (ΔE) between LUMO of protonated triazine and HOMO of enaminone comprise from 1.80 to 2.22 eV, in comparison with $\Delta E = 8.01$–8.43 eV for triazine-enaminone LUMO–HOMO interaction (Table 2).

Table 2. Energy values of the HOMO of dienophiles calculated by the AM1 semiempirical method, and $LUMO_{diene} - HOMO_{dienophile}$ energy differences (ΔE)

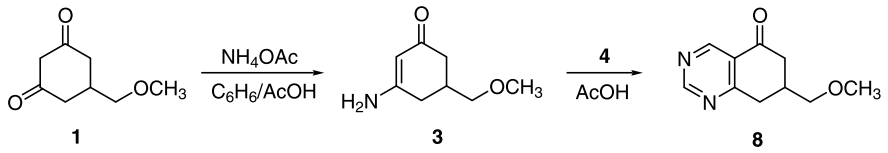
Dienophile	E_{HOMO} (eV)	ΔE (eV)	
		($E_{LUMO\ 4a} - E_{HOMO\ dienophile}$)[a]	($E_{LUMO\ 4a\cdot H^+} - E_{HOMO\ dienophile}$)[b]
5a	−8.891	8.339	2.127
5a·H^+	−14.177	13.625	–
5b	−8.561	8.009	1.797
5b·H^+	−14.110	13.558	–
5c	−8.986	8.434	2.222
5c H^+	−14.427	13.875	–

[a] $E_{LUMO\ 4a} = -0.552$ eV.
[b] $E_{LUMO\ 4a\cdot H^+} = -6.764$ eV.

Table 1. Inverse-demand Diels–Alder reaction of triazine (**4**) with dimedone derivatives (**5**)[a]

Entry	Diene	Dienophile	R	Solvent	Product	Yield (%)
1	**4**	**5a**	Morpholino	[b]	6	<5
2	**4**	**5b**	Pyrrolidino	[b]	6	<5
3	**4**	**5c**	NH_2	[b]	6	<5
4	**4**	**5b**	Pyrrolidino	Dioxane/HCl	6	<5
5	**4**	**5b** HCl	Pyrrolidino	Dioxane	6	34
6	**4**	**5b** HCl	Pyrrolidino	DMF	6	5
7	**4**	**5a** HCl	Morpholino	DMF	6	22
8	**4**	**5a** HCl	Morpholino	Dioxane	6	38
9	**4**·HCl	**5b**	Pyrrolidino	–	6+7	8/12
10	**4**·HCl	**5a**	Morpholino	Dioxane	7	30
11	**4**·HCl	**5b**	Pyrrolidino	DME	6	16
12	**4**·HCl	**5c**	NH_2	DME	6+7	30/36
13	**4**·HCl	**5c**	NH_2	H_2O	7	40
14	**4**·HCl	**5c**	NH_2	AcOH	6	58
15	**4**	**5a** HCl	Morpholino	CH_3CN	6	10
16	**4**	**5a** HCl	Morpholino	DME	6	34
17	**4**	**5c** HCl	NH_2	DME	6+7	75/9
18	**4**	**5c** HCl	NH_2	H_2O	7	65
19	**4**	**5c** HCl	NH_2	AcOH	6	87

[a] Reactions were conducted with 1 equiv. of the dienophile and 1.5 equiv. of the diene (**4** or **4** HCl).
[b] Dioxane, acetonitrile, dimethoxyethane (DME), dimethylformamide (DMF), or toluene were used as solvent.



Scheme 2.

In order to optimize the yields of the cyclization, different solvents, enaminones as hydrochlorides, and reaction conditions were assayed. Also, triazine as hydrochloride was reacted with different enaminones in dioxane, dimethoxyethane or in absence of solvent (entries 9–12).

Heating triazine hydrochloride with enaminone **5b** in the absence of solvent at 130°C (entry 9) led to the formation of two products. One of them (8% yield) proved to be the quinazolinone **6**, and the other (12% yield) was identified as the product of double cycloaddition, the 3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione (**7**).[13]

Also, mixtures of quinazolinone **6** and acridinodione **7** were obtained when the reaction was carried out with **5c** in dimethoxyethane (entry 12), or when the enaminone **5c** as hydrochloride salt was treated with triazine **4** in dimethoxyethane (entry 17).

The acridinodione **7** was obtained in 65% yield as the only product when H_2O was used as the solvent (entries 13 and 18). Few examples of IDA reactions performed in H_2O have been reported so far,[14] and, to our knowledge, this is the first example of a double [4+2] cycloaddition reported in this solvent. Both, the enaminone hydrochloride and the triazine were soluble in H_2O (entry 18); on the contrary, the acridinodione **7** precipitated in this solvent, and was isolated in pure form by simple filtration.

However, when glacial acetic acid is used as the solvent (entries 14 and 19), the reaction occurs under homogeneous conditions, and the quinazolinone **6** is obtained as a single product in excellent yield (87%, entry 19), showing the high influence of the solvent in this [4+2] cycloaddition. This different behavior of triazines in [4+2] cycloadditions has been previously found by Rykowski and colleagues: 5,5′-bi-1,2,4-triazines undergo IDA reactions with cyclic enamines by different pathways if the reactions are carried out in the presence or absence of solvent.[15]

From the comparison between reactions with a protonated diene or dienophile carried out in the same solvent (entries 8 and 10; 12 and 17; 13 and 18; 14 and 19), we can conclude that reactions using dienophile hydrochloride give better yields than those using triazine hydrochloride. With regard to the dienophiles, the best results were obtained with the primary enaminone (**5c**), probably due to the smaller steric hindrance of the NH_2 group in comparison with the morpholino or pyrrolidino groups.

As application of this IDA reaction methodology to the synthesis of our CNS agents precursor, we submitted the enaminone **3** ($NRR = NH_2$)[2] as hydrochloride, obtained in 80% yield from **1**, to [4+2] cycloaddition reaction with 1,3,5-triazine in acetic acid (Scheme 2), affording 7-methoxymethyl-5,6,7,8-tetrahydro-5-quinazolinone (**8**) in 66% yield.[16]

In summary, we have demonstrated that enaminones undergo inverse electron demand Diels–Alder reaction with 1,3,5-triazine, allowing access to functionalised quinazolinones as intermediates in the synthesis of CNS agents. This reaction is highly dependent of the solvent: 1,3,5-triazine undergoes single or double [4+2] cycloadditions with enaminones, and quinazolinones or acridinediones can be selectively obtained.

Acknowledgements

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9. In some cases, acids (such as HCl or acetic acid) have been reported to facilitate the cycloaddition of triazines. See: Boger, D. L.; Dang, Q. *Tetrahedron* **1988**, *44*, 3379–3390.
10. As alternative dienophile to the enaminones in the IDA reaction, the methyl enolether of dimedone **5d** ($R = OCH_3$) [Shapiro, B. L.; Johnston, M. D., Jr.; Praulx, T. W. *J. Am. Chem. Soc.* **1973**, *95*, 520–526] was prepared by reaction with methanol and conc. HCl. Again, attempts of cycloaddition with triazine **4** were unsuccessful.
11. Typical procedure: A mixture of triazine **4** (180 mg, 2.25 mmol) and enaminone **5** (1.5 mmol) in the appropriate solvent was stirred under reflux (or heated in a sealed tube at 110°C) for 16–48 h. On cooling, the solvent was evaporated and the residue was purified by column chromatography (AcOEt/hexane 1:1) to give acridinedione **7**[13] and/or quinazolinone **6**. Compound **6**: mp 71–73°C; IR (KBr) 2954, 1699, 1576, 1553; MS (EI) 176 (M+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.25 (s, 1H, H-2), 9.19 (s, 1H, H-4), 3.01 (s, 2H, H-8), 2.59 (s, 2H, H-6), 1.14 (s, 6H, 2 x CH_3).
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16. Experimental procedure: A mixture of diketone **1** (150 mg, 0.97 mmol), ammonium acetate (149 g, 1.94 mmol), and acetic acid (0.5 mL) in benzene (10 mL) was refluxed for 1 h. After cooling the mixture was concentrated in vacuo, the residue dissolved in CH_2Cl_2, and solid Na_2CO_3 was added. The solution was filtered, dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Purification of the residue by column chromatography (silica gel, AcOEt/MeOH 4:1) afforded 120 g (80% yield) of **3**[2] as yellow solid. Hydrochloride: mp 240°C (decomp.). A solution of **3** HCl (90 mg, 0.47 mmol) and 1,3,5-triazine (**4**, 57 mg, 0.70 mmol) in glacial acetic acid (7 mL) was heated in a sealed tube at 110°C for 18 h. On cooling, the solution was concentrated at reduced pressure and the residue purified by silica gel chromatography (AcOEt/hexane 3:1) to give 60 mg (66% yield) of **8** as yellowish oil. IR (film) 2878, 1698, 1576, 1553; MS (EI) 192 (M+), 147 (100%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.17 (s, 1H, H-2), 9.12 (s, 1H, H-4), 3.41 (d, 2H, $J = 4.3$ Hz, CH_2O), 3.31 (s, 3H, CH_3), 3.15 (dd, 1H, $J = 17.7$, 4.0 Hz, H-8), 2.99 (dd, 1H, $J = 18.0$, 10.0 Hz, H-8), 2.80–2.73 (m, 1H, H-7), 2.60–2.46 (m, 2H, H-6).