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Cascade synthesis of the first imidazo[4,5-*e*]thiazolo[2,3-*c*][1,2,4]triazine derivative

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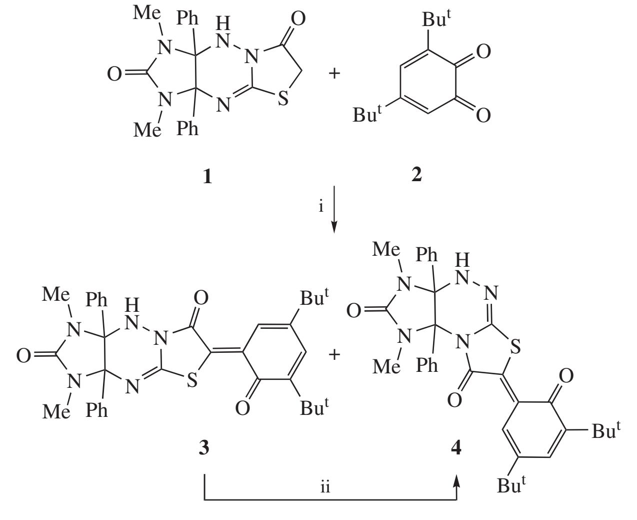
(*Z*)-7-(3,5-Di-*tert*-butyl-6-oxocyclohexa-2,4-dien-1-ylidene)-1,3-dimethyl-3a,9a-diphenyl-1,3a,4,9a-tetrahydroimidazo[4,5-*e*]thiazolo[2,3-*c*][1,2,4]triazine-2,8(3*H*,7*H*)-dione was obtained by aldol condensation of 3,5-di-*tert*-butyl-1,2-benzoquinone with 1,3-dimethyl-3a,9a-diphenyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*]thiazolo[3,2-*b*][1,2,4]triazine-2,7(1*H*,6*H*)-dione followed by intramolecular thiazole ring-opening/closing in the condensation primary adduct.

Thiazolo[3,2-*b*]- or thiazolo[2,3-*c*][1,2,4]triazines show various biological activities including antidepressant,[1] anti-HIV and anticancer activity.[2,3] Among biologically active thiazolidinones, there is a considerable family of their derivatives substituted on methylene group.[4–7] Recently we started to study aldol condensation of 1,3-dimethyl-3a,9a-diphenyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*]thiazolo[3,2-*b*][1,2,4]triazine-2,7(1*H*,6*H*)-dione **1** with isatins,[8] aromatic and heterocyclic aldehydes.[9]

Sterically hindered 1,2-benzoquinones and relative quinonoid compounds that contain branched alkyl groups, *e.g.*, *tert*-butyl groups, represent an interesting family of compounds.[10–14] For instance, reactions of sterically hindered 1,2-benzoquinones with heterocycles containing an active methylene group do not stop at the expected aldol condensation products which are unstable and readily undergo further transformations.[11–14]

In the present communication aiming to prepare new imidazothiazolotriazine derivatives, we have studied the condensation of 3,5-di-*tert*-butyl-1,2-benzoquinone **2** with imidazothiazolotriazine **1** (Scheme 1).[†]

Earlier we found that aldol condensation of compound **1** with isatins occurs on refluxing in AcOH for 2.5 h.[8] However, these conditions proved inappropriate for the reaction **1** + **2** and resulted in resinification. Meanwhile, this reaction was found to be accomplished at lower temperature (60 °C) and with longer heating (5 h) (method A, Scheme 1).[‡]



Scheme 1 *Reagents and conditions*: i, AcOH, 60 °C, 5 h; ii, AcOH, reflux, 20 min.

According to TLC, the reaction gives two major compounds which were separated by column chromatography. Product **3** (yield 35%) was red, product **4** (yield 60%) was violet. Molecular ions of both products were 596.2 $[M+H]^+$;[§] their elemental analysis

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[†] Starting 3,5-di-*tert*-butyl-1,2-benzoquinone **2** was synthesized by oxidation of 3,5-di-*tert*-butylpyrocatechol with $NaNO_2$.[17] 1,3-Dimethyl-3a,9a-diphenyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*]thiazolo[3,2-*b*][1,2,4]triazine-2,7(1*H*,6*H*)-dione **1**, 2-[(5,7-dimethyl-6-oxo-4a,7a-diphenyl-4,4a,5,6,7,7a-hexahydro-1*H*-imidazo[4,5-*e*][1,2,4]triazin-3-yl)thio]acetic acid **5** and 5,7-dimethyl-4a,7a-diphenyl-3-thioxoperhydroimidazo[4,5-*e*][1,2,4]triazin-6-one **6** were prepared according to known procedures.[18,19]

[‡] *Method A.* A mixture of compounds **2** (1.10 g, 5 mmol) and **1** (1.96 g, 5 mmol) in AcOH (10 ml) was heated at 60 °C for 5 h. Then the solution was cooled and diluted with cold water, and the precipitate that formed was filtered off. The precipitate was washed with warm water (200 ml) and dried to give 3 g of a product, which was then dissolved in a minimum chloroform. The chloroform solution was dried with anhydrous Na_2SO_4 for 3–4 h. The dried solution was passed through a chromatography column packed with silica gel (eluent: ethyl acetate–light petroleum, 1:4) to collect the bright-red compound **3** ($R_f = 0.3$), 1.03 g (35%), and the violet compound **4** ($R_f = 0.15$), 1.78 g (60%).

Method B. A mixture of compounds **2** (1.10 g, 5 mmol) and **5** (2.06 g, 5 mmol) in AcOH (10 ml) was heated at 60 °C for 5 h. The solution was cooled and diluted with cold water, and the precipitate that formed was filtered off. The further processing was similar to that in method A. The yield of red crystals **3** was 0.42 g (14%), the yield of violet crystals **4** was 1.19 g (40%).

Method C. A mixture of compound **2** (0.44 g, 2 mmol), imidazotriazine **6** (0.71 g, 2 mmol), $BrCH_2COOH$ (0.28 g, 2 mmol) and AcONa (0.16 g, 2 mmol) in AcOH (10 ml) was refluxed for 1.5 h. The solution was cooled and diluted with cold water, and the precipitate that formed was filtered off. The further processing was analogous to those in methods A and B. The yield of violet crystals **4** was 0.27 g (23%).

[§] A 1100 LC/MSD (Agilent Technologies, USA) LC-mass spectrometer equipped with an ELSD PL-ELS-1000 mass detector and Onyx monolithic C18 column (50×4.6 mm) was used. The flow rate of eluent was 3.75 ml min^{-1} [eluent A: acetonitrile–water (2.5 : 97.5) containing 0.1% of trifluoroacetic acid, eluent B: acetonitrile containing 0.1% of trifluoroacetic acid; elution mode: 100% A (0 min) → 100% B (2.2–2.6 min) → → 100% A (2.8 min)].

data were consistent with formula $C_{34}H_{37}N_5O_3S$. Their NMR spectra were close enough, however, the most pronounced difference was indicated for the signals of NMe and NH groups.[¶]

Isomer **4** is the first representative of a new heterocyclic system, imidazo[4,5-*e*][1,3]thiazolo[2,3-*c*][1,2,4]triazine. Its structure was ultimately proven by X-ray diffraction analysis (Figure 1).[††] The most interesting feature of its molecular geometry, being rather typical of this type of compounds, is the presence of a shortened O···S intramolecular contact [S···O 2.488(3) Å] that was observed previously.[8,15] Described as a charge transfer from an electron lone pair of the oxygen atom to the σ*-orbital of the C–S bond [∠OSC 167.6(1)°], it additionally stabilizes a planar disposition of the thiazolo and benzoquinone moieties in the molecule of compound **4**, together with a rather weak intramolecular C–H···O bond [C···O 2.875(3) Å, ∠CHO 123(1)°]. In crystal, these molecules are assembled into infinite chains through the N–H···O hydrogen bond [N···O 2.871(3) Å, ∠NHO 170(1)°].

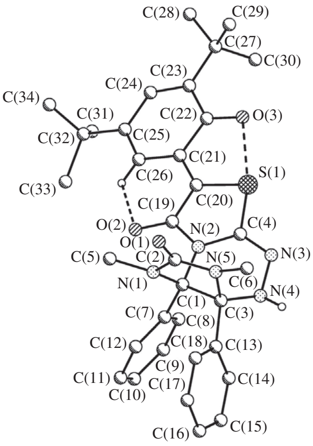
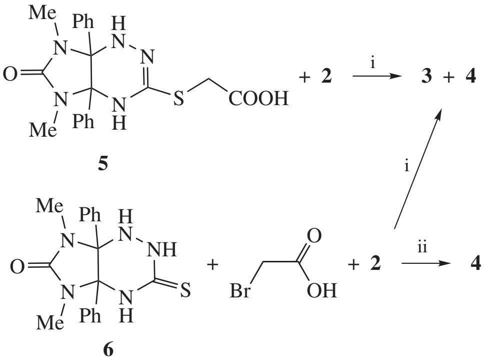


Figure 1 General view of compound **4**. The hydrogen atoms except for those of the NH group and at the atom C(26) are omitted for clarity.



Scheme 2 *Reagents and conditions*: i, AcOH, 60 °C, 5 h; ii, AcOH, reflux, 1.5 h.

To better rationalize the mechanism of the process studied, carboxymethylthioimidazotriazine **5** was introduced into a similar reaction with *o*-quinone **2** under the same conditions (method B, Scheme 2). The yields of isomers **3** and **4** were 14% and 40%, respectively. In addition, *o*-quinone **2** was subjected to three-component reaction with imidazotriazine **6** and bromoacetic acid (method C, Scheme 2). After 5 h at 60 °C, isomers **3** and **4** were isolated in 12% and 20% yields, respectively. Refluxing of the reaction mixture for 1.5 h afforded the individual isomer **4** in a 21–23% yield. Note that heating imidazo[4,5-*e*]thiazolo[3,2-*b*]triazine **1** in AcOH for 5 h without *o*-quinone **2** does not lead to rearrangement to imidazo[4,5-*e*]thiazolo[2,3-*c*]triazine derivative. This derivative, most probably, does not form on cyclization of compound **5** serving as a precursor of only **1**. Evidently, product **4** could be formed upon isomerization of compound **3**.

In order to stop the process at the isomer **3**, the reaction duration was shortened to 3 h (method A) or 1 h (method C). However, both isomers **3** and **4** were formed in lower yields, 12–15% and 5–8%, respectively. Apparently, transformation **3** → **4** is irreversible, whereas it proceeds at comparable rate with that of the formation of compound **3**. In a control experiment, isomer **3** was fully converted into **4** upon 20 min reflux in AcOH (see Scheme 1).

A plausible mechanism for the formation of imidazo[4,5-*e*]-[1,3]thiazolo[2,3-*c*][1,2,4]triazine derivative **4** is outlined in Scheme 3. Initially alkylation of imidazotriazine **6** with bromoacetic acid leads to carboxymethylthioimidazotriazine **5** which undergoes concomitant cyclization *via* intramolecular acylation to form imidazothiazolotriazine **1**. The latter reacts with *o*-quinone **2** affording aldol condensation product **3**, which, in its protonated form **7**, enters intramolecular consecutive thiazole ring-opening/closing reactions. Obviously, the cationic intermediate **7** is crucial in the **3** → **4** recyclization, in which the N–(C=O) bond is readily cleaved.

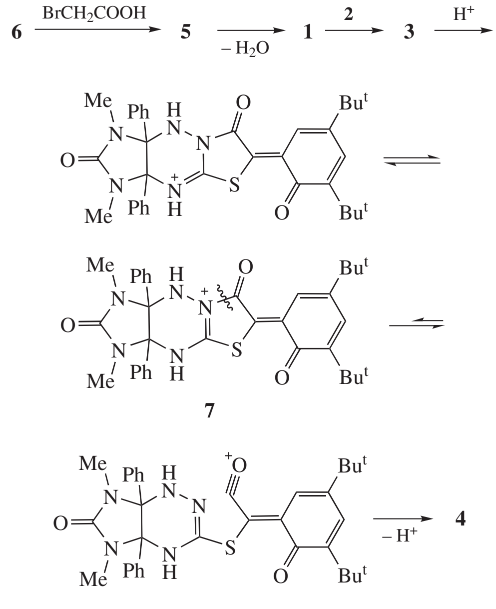
o-Quinones and their derivatives tend to exhibit electro- and photochemical properties.[16] Therefore, these properties were studied for isomers **3** and **4**. The UV-VIS spectra of compound **3**

[¶] *(Z)-6-(3,5-Di-*tert*-butyl-6-oxocyclohexa-2,4-dien-1-ylidene)-1,3-dimethyl-3a,9a-diphenyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*][1,3]thiazolo[3,2-*b*]-[1,2,4]triazine-2,7(1*H*,6*H*)-dione* **3**: red crystals, mp 134–136 °C (Pr^iOH) ^1H NMR ($CDCl_3$) δ: 1.30 (s, 9H, 3-Bu^t), 1.37 (s, 9H, 5-Bu^t), 2.74 (s, 3H, MeN), 2.85 (s, 3H, MeN), 6.31 (s, 1H, HN), 6.80–6.89 (m, 4H, Ph), 7.04–7.20 (m, 6H, Ph), 7.31 (d, 1H, C^4H, *J* 2.2 Hz), 8.38 (d, 1H, C^6H, *J* 2.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 25.09, 26.55 (MeN), 29.27, 29.33 (*Me_3*C), 35.24, 35.34 (Me_3*C*), 80.72, 85.26 (*C*Ph), 118.33, 127.05, 127.59, 128.19, 128.37, 129.03, 131.28, 133.32, 134.17, 134.38, 136.13, 143.78, 147.62, 148.96, 159.31, 159.88, 186.01 (C=O). ^{13}C NMR ([$^2H_6$]DMSO) δ: 25.38, 26.12 (MeN), 29.07, 29.13 (*Me_3*C), 34.95, 35.04 (Me_3*C*), 79.94, 82.48 (*C*Ph), 118.09, 126.42, 127.44, 127.65, 128.02, 128.34, 129.62, 134.02, 134.31, 134.64, 138.33, 143.01, 146.32, 149.75, 159.24, 159.77, 185.37 (C=O). LC/MS, *m*/*z*: 596.2 $[M+H]^+$, $t_R = 4.29$ min. Found (%): C, 68.55; H, 6.25; N, 11.75; S, 5.31. Calc. for $C_{34}H_{37}N_5O_3S$ (%): C, 68.55; H, 6.26; N, 11.76; S, 5.38.

*(Z)-7-(3,5-Di-*tert*-butyl-6-oxocyclohexa-2,4-dien-1-ylidene)-1,3-dimethyl-3a,9a-diphenyl-1,3a,4,9a-tetrahydroimidazo[4,5-*e*][1,3]thiazolo[2,3-*c*]-[1,2,4]triazine-2,8(3*H*,7*H*)-dione* **4**: violet crystals, mp 151–153 °C (Pr^iOH). ^1H NMR ($CDCl_3$) δ: 1.22 (s, 9H, 3-Bu^t), 1.39 (s, 9H, 5-Bu^t), 2.77 (s, 3H, MeN), 3.12 (s, 3H, MeN), 5.89 (s, 1H, HN), 6.79–7.24 (m, 10H, 2Ph), 7.31 (d, 1H, C^4H, *J* 2.2 Hz), 8.25 (d, 1H, C^6H, *J* 2.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 25.39 (MeN), 29.33, 29.63 (*Me_3*C), 31.58 (MeN), 35.16, 35.25 (Me_3*C*), 81.98, 86.92 (*C*Ph), 118.19, 127.35, 127.95, 128.45, 128.85, 129.48, 129.69, 131.50, 132.49, 133.62, 139.33, 142.47, 142.95, 145.84, 158.86, 163.77, 184.84 (C=O). LC/MS, *m*/*z*: 596.2 $[M+H]^+$, $t_R = 4.34$ min. Found (%): C, 68.57; H, 6.29; N, 11.71; S, 5.33. Calc. for $C_{34}H_{37}N_5O_3S$ (%): C, 68.55; H, 6.26; N, 11.76; S, 5.38.

[††] *X-ray diffraction data*. Crystals of **4** ($C_{34}H_{37}N_5O_3S$, $M = 595.75$) are monoclinic, space group $P2_1$, at 120 K: $a = 9.0385(6)$, $b = 10.8893(7)$ and $c = 17.0539(11)$ Å, $\beta = 104.1060(10)°$, $V = 1627.88(18)$ Å^3, $Z = 2$ ($Z' = 1$), $d_{calc} = 1.215$ g cm^{-3}, μ(MoKα) = 1.40 cm^{-1}, $F(000) = 632$. Intensities of 14296 reflections were measured with a Bruker SMART 1000 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 56°$], and 7549 independent reflections ($R_{int} = 0.0341$) were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The hydrogen atom of NH group was located from the Fourier density synthesis and refined in isotropic approximation. The H(C) atom positions were calculated. All hydrogen atoms were refined in the isotropic approximation in riding model. The refinement converged to $wR_2 = 0.0952$ and GOF = 0.999 for all independent reflections [$R_1 = 0.0491$ was calculated against F for 5215 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.[20]

CCDC 947683 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2014.



Scheme 3

contain peaks at 493, 383, 369 and 258 nm and the spectra of compound **4** – at 547 and 259 nm.

By cyclic and differential pulse voltammetry on glassy-carbon and platinum electrodes, isomers **3** and **4** were reduced similarly to the starting 3,5-di-*tert*-butyl-1,2-benzoquinone **2** giving stable radical anions at the first stage and unstable dianions at the second stage of reduction (Table 1). All compounds are oxidized irreversibly, isomer **3** being less stable than isomer **4**.

In conclusion, 3,5-di-*tert*-butyl-1,2-benzoquinone **2** reacts with imidazotriazine derivatives containing active methylene groups according to the aldol condensation pathway. Rearrangement of isomer **3** to isomer **4** induced by acetic acid was found. The latter is a representative of a new heterocyclic system. One-pot three-component synthesis from 5,7-dimethyl-4a,7a-diphenyl-3-thioxoperhydroimidazo[4,5-*e*][1,2,4]triazin-6-one, bromoacetic acid and 3,5-di-*tert*-butyl-1,2-benzoquinone *via* alkylation–intramolecular acylation reaction–aldol condensation–ring-opening/closing cascade sequence has also been developed.

Table 1 The potentials of oxidation and reduction of compounds **1**–**4** in acetonitrile.

Compound	$-E_{pk}$/V	$-E_{pa}$/V	E_{pa}/V	E_{pk}/V
1	1.00		1.00 1.80	0.8 —
2	0.60 1.25	0.52 1.40	>2.50	—
3	0.50 1.00	0.80	1.70	0.10
4	0.75	0.70	1.30	1.10
Ferrocene	—	—	0.46	0.40

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