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Tautomerism and Stereodynamics of Indophenols, Amidines, Their Derivatives, and Analogs: XIII.[1] Intramolecular Cyclization of 2,6-Di-*tert*-butyl-4-(*o*-alkoxyphenylimino)-2,5-cyclohexadienones as a Method of Synthesis of Spiro Benzoxazines

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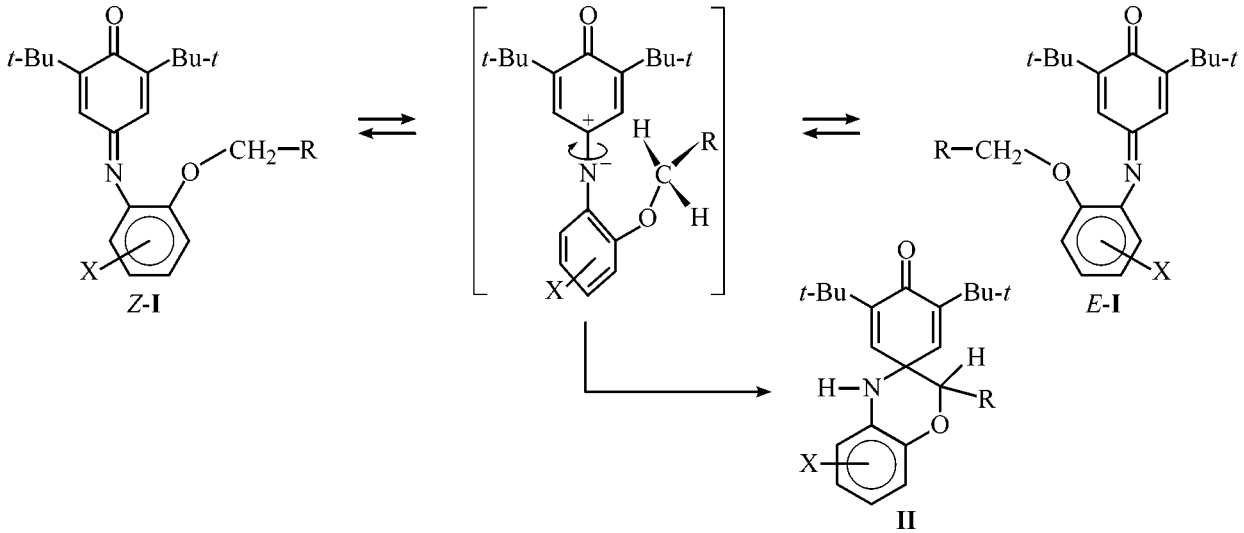
Abstract—A new method was developed for synthesizing benzoxazine derivatives by *O*-alkylation of 2,6-di-*tert*-butyl-4-(*o*-hydroxyphenylimino)-2,5-cyclohexadienones with allyl or benzyl halides and subsequent thermal heterocyclization of allyl or benzyl ethers thus formed. The cyclization of ethers derived from 2,6-di-*tert*-butyl-4-(*o*-hydroxyphenylimino)-2,5-cyclohexadienones and phenacyl bromides or diethyl bromomalonate is so fast that these compounds cannot be isolated.

We previously reported [2] on a new noncatalytic intramolecular rearrangement of allyl and benzyl ethers **I** derived from 2,6-di-*tert*-butyl-4-(*o*-hydroxyphenylimino)-2,5-cyclohexadienones, which afforded the corresponding spiro benzoxazines **II** (Scheme 1). The mechanism of this transformation includes concerted [1,5]-C→N sigmatropic proton shift and electrocyclic formation of C–C bond; these processes are promoted by electronic polarization of ethers **I** during *Z*/*E* topomerization via rotation about the C–N bond [3]. The kinetic and activation parameters of the rearrangements **I**→**II** are as follows: $k_{298} \approx 10^{-7}$–10^{-11} s^{-1}, $\Delta G^{\neq}_{298} \approx 108$–130 kJ mol^{-1} [2].

Scheme 1.



R = $C_6H_4NO_2$-4, –CH=CH_2; X = 3,5-(*t*-Bu)$_2$, 4-NO_2, 5-NO_2.

[1] For communication XII, see [1].

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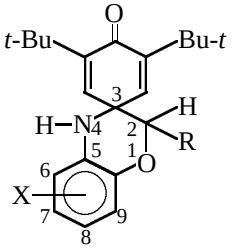
The goal of the present study was to determine the scope of application of the above method for building up benzoxazine ring and to develop preparative procedures for synthesizing previously inaccessible benzoxazine derivatives with a spiro-fused cyclohexadienone fragment.

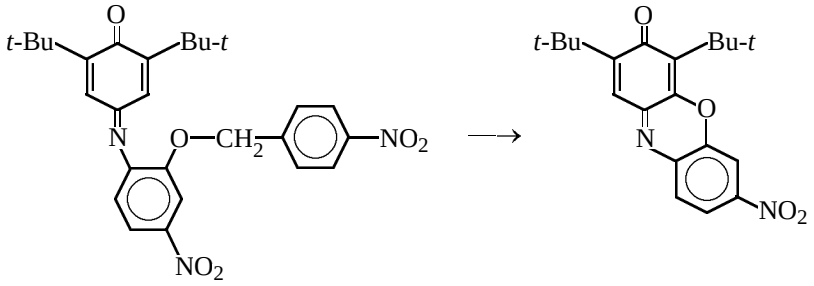


III–**IX**

III, X = H, R = –CH=CH_2; **IV**, X = H, R = Ph; **V**, X = H, R = 4-$NO_2C_6H_4$; **VI**, X = 7-Cl, R = CH=CH_2; **VII**, X = 7-Cl, R = Ph; **VIII**, X = 7-Br, R = CH=CH_2; **IX**, X = 7-Br, R = Ph.

Compounds **III**–**IX** were synthesized by heating solutions of the corresponding 2,6-di-*tert*-butyl-4-[*o*-allyloxy(or benzyloxy)phenylimino]-2,5-cyclohexadienones [2] in solvents with boiling boints in the range from 100 to 180°C (perfluorotoluene, *o*-xylene, chlorobenzene, *o*-dichlorobenzene, diphenyl ether). The cyclization in higher-boiling solvents, e.g., in diphenyl ether, was faster, but the yield of the product was reduced because of appreciable tarring. In lower-boiling solvents, the reaction takes much time or does not occur at all (as in toluene). The optimal conditions were heating in freshly distilled xylenes under reflux for 2–5 h. The progress of the reaction can be monitored visually, following the disappearance of the original bright red color, or by thin-layer chromatography on Al_2O_3 using petroleum ether as eluent. The transformation **I**→**II** can also be monitored by ^{1}H NMR spectroscopy: the CH_2 signal at δ 4.5 ppm disappears, and NH and CH signals appear at δ 5.1 and 6.5 ppm, respectively.

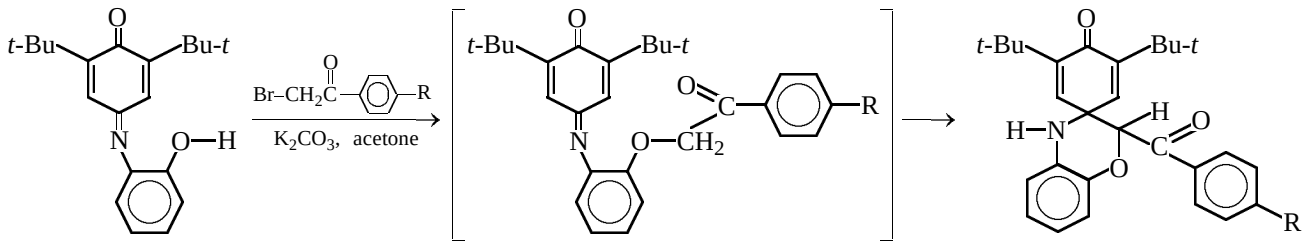
The cyclization of *p*-nitrobenzyl ether **X** in boiling *p*-xylene was accompanied by formation of a considerable amount (~30%) of phenoxazinone **XI**, presumably as a result of homolytic cleavage of the O–CH_2 bond under severe conditions. The structure of compound **XI** was established on the basis of its ^{1}H NMR and mass spectra.



X **XI**

Taking into account that the key stage in the transformation under study is proton transfer from the active methylene group to the imino nitrogen atom, it was interesting to examine the effects of different electron-acceptor groups on the C→N proton shift and cyclization kinetics. We have found that alkylation of compound **XII** with phenacyl bromides (Scheme 2) is accompanied by so fast cyclization into benzoxazines **XV** and **XVI** that intermediate phenacyl ethers **XIII** and **XIV** cannot be isolated or even detected.

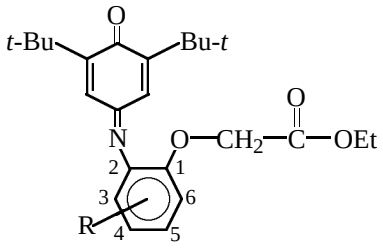
Scheme 2.



XII **XIII**, **XIV** **XV**, **XVI**

XIII, **XV**, R = H; **XIV**, **XVI**, R = Br.

The ^{1}H NMR spectra of benzoxazines **XV** and **XVI** are characterized by isochronous signals from both *tert*-butyl groups, as well as from protons in the cyclohexadiene ring. Despite mild consitions of the transformations **XII**→**XV** and **XII**→**XVI**, the yields of the final products were considerably lower than the yields of benzoxazines **II**–**IX** in the thermal cyclization of allyl and benzyl ethers. In this connection it seemed surprising that compounds **XVII** and **XVIII** which were obtained by alkylation with ethyl bromoacetate did not undergo cyclization into benzoxazines even on prolonged heating in boiling xylene or *o*-dichlorobenzene.



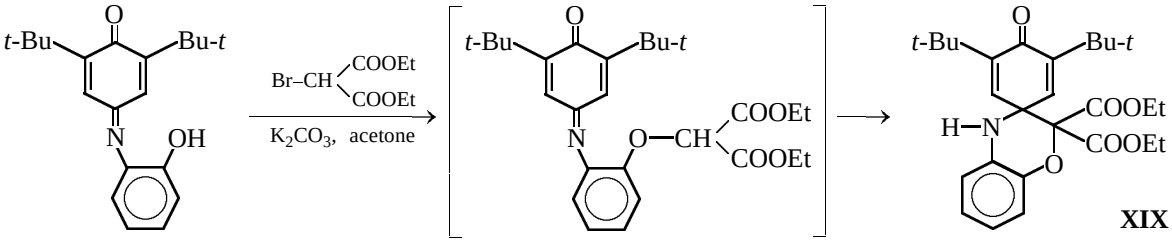
XVII, **XVIII**

XVII, R = 4-NO_2; **XVIII**, R = 5-NO_2.

By contrast, the reaction of 2,6-di-*tert*-butyl-4-(*o*-hydroxyphenylimino)-2,5-cyclohexadienone with diethyl bromomalonate, as with phenacyl bromides, directly yielded spiro diester **XIX** (Scheme 3). The structure of **XIX** is confirmed by the presence in the ^{1}H NMR spectrum of isochronous signals from the *tert*-butyl groups (δ 1.39 ppm) and cyclohexadiene ring protons (δ 7.29 ppm).

Thus, the rearrangement of 2,6-di-*tert*-butyl-4-(*o*-alkoxyphenylimino)-2,5-cyclohexadienones can be regarded as a convenient method for preparation of various spirobenzoxazine derivatives.

Scheme 3.



XIX

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Bruker DPX-250 instrument (250 MHz) at 25°C. The mass spectrum of compound **XI** was recorded on a Perkin–Elmer Q-Mass 910 GC–MS system. The elemental compositions of compounds **III**–**XIX** were consistent with the calculated values.

General procedure for synthesis of compounds III–IX. To a solution of 1 mmol of appropriate 2,6-di-*tert*-butyl-4-(*o*-hydroxyphenylimino)-2,5-cyclohexadienone in 20 ml of acetone we added 1.5 mmol of freshly calcined potassium carbonate and 1 mmol of allyl bromide or benzyl halide. The progress of the reaction was monitored by chromatography on Al_2O_3 (eluent petroleum ether). When the reaction was complete, the mixture was filtered, the filtrate was evaporated to dryness, and the residue was recrystallized from methanol. The product was refluxed in *o*-xylene for 2–5 h, the solvent was removed under reduced pressure, and the residue was recrystallized from methanol or 2-propanol.

3',5'-Di-*tert*-butyl-2-vinyl-2,3-dihydro-1,4-benzoxazine-3-spiro-1'-cyclohexa-2',5'-dien-4'-one (III). mp 126°C. Yield 75%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.18 s (9H), 1.20 s (9H), 3.88 s (1H), 5.30 m (2H), 4.41 d (1H), 5.62 m (1H), 6.38 d (1H), 6.8 d (1H), 6.69 d (1H), 6.76 d.d (1H), 6.86 d.d (1H), 6.91 d (1H).

3',5'-Di-*tert*-butyl-2-phenyl-2,3-dihydro-1,4-benzoxazine-3-spiro-1'-cyclohexa-2',5'-dien-4'-one (IV). mp 212°C. Yield 70%. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 1.08 s (9H), 1.12 s (9H), 5.19 s (1H), 5.77 s (1H), 6.70 m (3H), 6.85 m (3H), 7.27 m (5H).

3',5'-Di-*tert*-butyl-2-*p*-nitrophenyl-2,3-dihydro-1,4-benzoxazine-3-spiro-1'-cyclohexa-2',5'-dien-4'-one (V). mp 198°C. Yield 65%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.18 s (9H), 1.22 s (9H), 4.05 s (1H), 4.56 s (1H), 6.33 d (1H), 6.49 d (1H), 6.75–8.86 m (4H), 7.35 d (2H), 8.00 d (2H).

3',5'-Di-*tert*-butyl-7-chloro-2-vinyl-2,3-dihydro-1,4-benzoxazine-3-spiro-1'-cyclohexa-2',5'-dien-4'-one (VI). mp 168°C. Yield 80%. ^{1}H NMR spectrum

($CDCl_3$), δ, ppm: 1.17 s (9H), 1.21 s (9H), 3.88 s (1H), 4.39 d (1H), 5.28 m (2H), 5.57 m (1H), 6.31 d (1H), 6.47 d (1H), 6.58 d (1H), 6.67 s (1H), 6.70 d (1H).

3',5'-Di-*tert*-butyl-7-chloro-2-phenyl-2,3-dihydro-1,4-benzoxazine-3-spiro-1'-cyclohexa-2',5'-dien-4'-one (VII). mp 223°C. Yield 80%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.07 s (9H), 1.08 s (9H), 4.07 s (1H), 5.02 m (1H), 6.42 d (1H), 6.61 d (1H), 6.69 d (1H), 6.73 d (1H), 6.87 d (1H), 7.20 m (5H).

7-Bromo-3',5'-di-*tert*-butyl-2-vinyl-2,3-dihydro-1,4-benzoxazine-3-spiro-1'-cyclohexa-2',5'-dien-4'-one (VIII). mp 175°C. Yield 65%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.17 s (9H), 1.21 s (9H), 3.93 s (1H), 4.37 d (1H), 5.29 m (2H), 5.54 m (1H), 6.33 d (1H), 6.49 d (1H), 6.78 m (3H).

7-Bromo-3',5'-di-*tert*-butyl-2-phenyl-2,3-dihydro-1,4-benzoxazine-3-spiro-1'-cyclohexa-2',5'-dien-4'-one (IX). mp 228°C. Yield 75%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.07 s (9H), 1.09 s (9H), 4.01 s (1H), 5.00 s (1H), 6.38 d (1H), 6.59 d (1H), 6.82 m (3H), 7.19 m (5H).

2,4-Di-*tert*-butyl-7-nitrophenoxazin-3-one (XI). mp 95°C. Yield 25%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.33 s (9H), 1.49 s (9H), 7.11 s (1H), 7.76 d (1H), 8.07 d.d (1H), 8.11 d. Mass spectrum: *m*/*z* 354 (M^+).

2-Benzoyl-3',5'-di-*tert*-butyl-2,3-dihydro-1,4-benzoxazine-3-spiro-1'-cyclohexa-2',5'-dien-4'-one (XV). To a solution of 0.14 g of compound **XII** in 10 ml of acetone we added 0.3 g of potassium carbonate and 0.07 g of phenacyl bromide. The mixture was refluxed for 1–2 min and was kept for 7–8 h at room temperature. The solution was filtered, the filtrate was evaporated, and the residue was purified by column chromatography on Al_2O_3 (eluent chloroform), followed by recrystallization from 2-propanol. mp 179°C. Yield 45%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.35 s (18H), 5.02 s (1H), 6.56 s (1H), 6.7–6.9 m (4H), 6.98 s (2H), 7.44 m (2H), 7.56 m (1H), 8.02 d (2H).

2-*p*-Bromobenzoyl-3',5'-di-*tert*-butyl-2,3-dihydro-1,4-benzoxazine-3-spiro-1'-cyclohexa-2',5'-dien-4'-one (XVI) was synthesized as described above for compound **XV** by reaction of compound **XII** with *p*-bromophenacyl bromide. mp 180°C. Yield 35%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.36 s (18H), 5.07 s (1H), 6.46 s (1H), 6.81 m (3H), 6.95 s (2H), 7.58 m (3H), 7.88 d (2H).

Compounds **XVII** and **XVIII** were synthesized as described above for compound **III** using ethyl bromoacetate as alkylating agent.

Ethyl 2-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadienylidenamino)-4-nitrophenoxyacetate (XVII). mp 120°C. Yield 60%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.17 s (9H), 1.25 s (9H), 1.31 t (3H), 4.22 q (2H), 4.72 s (2H), 6.61 d (1H), 6.85 d (1H), 7.06 d (1H), 7.69 d (1H), 8.05, d. d (1H).

Ethyl 2-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadienylidenamino)-5-nitrophenoxyacetate (XVIII). mp 118°C. Yield 55%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.16 s (9H), 1.25 m (3H), 1.30 s (9H), 4.22 q (2H), 4.52 s (2H), 6.54 d (1H), 6.86 d (1H), 7.05 d (1H), 7.68 d (1H), 7.93 d.d (1H).

Diethyl 3',5'-di-*tert*-butyl-4'-oxo-2,3-dihydro-1,4-benzoxazine-3-spiro-1'-cyclohexa-2',5'-diene-2,2-dicarboxylate (XIX). To a solution of 0.31 g of compound **XII** in 10 ml of acetone we added 0.5 g of potassium carbonate and 0.34 g of diethyl bromomalonate [4], and the mixture was left overnight at room temperature. It was then filtered, the filtrate was evaporated, and the residue was purified by column chromatography on Al_2O_3 (eluent chloroform), followed by recrystallization from 2-propanol. mp 95°C. Yield 75%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.08 m (6H), 1.39 s (18H), 4.08–4.17 m (4H), 5.18 s (1H), 6.52 d.d (1H), 6.72–6.85 m (3H), 7.29 s (2H).

ACKNOWLEDGMENTS

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