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Superacidic Activation of 1- and 3-Isoquinolinols and Their Electrophilic Reactions[1]

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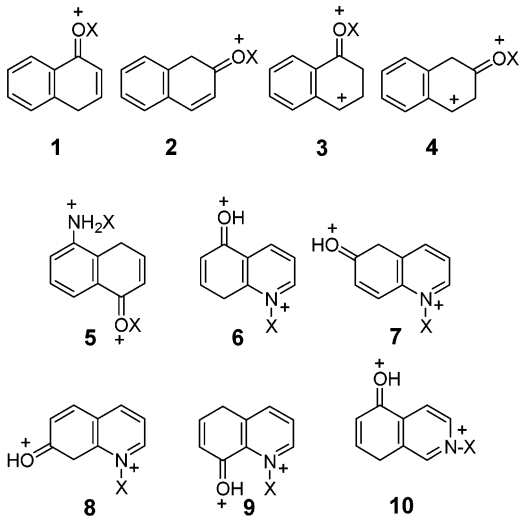
Isomeric 1- and 3-isoquinolinols (**11** and **12**) when activated in $CF_3SO_3H-SbF_5$ acid system undergo selective ionic hydrogenation with cyclohexane to give 5,6,7,8-tetrahydro-1(2*H*)- and 5,6,7,8-tetrahydro-3(2*H*)-isoquinolinones (**22** and **27**). Under the influence of aluminum chloride similar products were also obtained along with 3,4-dihydro-1(2*H*)- and 1,4-dihydro-3(2*H*)-isoquinolinones (**23** and **28**), respectively. Compounds **11** and **12** also condense with benzene in the presence of aluminum halides, under mild conditions, to give 3,4-dihydro-3-phenyl-1(2*H*)- and 1,4-dihydro-1-phenyl-3(2*H*)-isoquinolinones (**24** and **29**), respectively. Prolonged reaction time or catalysis under strongly acidic $HBr-AlBr_3$ provides an alternative reaction pathway to yield 5,6-dihydro-6,8-diphenyl-1(2*H*)- and 5,6,7,8-tetrahydro-6,8-diphenyl-3(2*H*)-isoquinolinones (**25** and **30**), respectively. Products **24** and **29** were also found to revert back to **11** and **12** in the presence of aluminum halides in *o*-dichlorobenzene. The mechanism of these intriguing reactions, which involves superelectrophilic dicationic intermediates, is discussed.

Introduction

Isomeric naphthols have been found to form C-monoprotonated cations (structures **1**, **2** (X = H)) in Bronsted superacids[2] or similar complexes (**1**, **2** ($X = Al_nCl_{3n}^-$ or $Al_nBr_{3n}^-$)) with aluminum halides.[3] They were also found to condense with benzene[3,4] and undergo selective ionic hydrogenation with cyclohexane[5] in the presence of excess aluminum halides. The key reactive intermediates of these reactions were, however, found to be superelectrophilic[6] C,C-diprotonated dications **3** and **4**.[7]



Recently, we have shown that 5-amino-1-naphthol, isomeric 5-, 6-, 7-, 8-quinolinols, and 5-isoquinolinol containing a nitrogen atom and a hydroxy group in different rings of the naphthalene (quinoline, isoquinoline) system produce superelectrophilic N,C-diprotonated dications **5**−**10**, which were recognized to be somewhat weaker electrophiles than dications **3** and **4**. However, they were electrophilic enough to react with benzene and cyclohexane.[1,8] The practical importance of compounds with the isoquinoline skeleton (including partly hydrogenated and arylated derivatives) as bioactive substances and pharmacophores[9] attracted our interest in investi-

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(7) Dications **4** (X = H, CH_3) and the derivatives of dications **3** (X = H, CH_3) bearing an electron-donating substituent at C^4 were generated as long-living species by protonation of respective naphthols and their methyl ethers in $HF-SbF_5$(1:1)$-SO_2ClF$ and HSO_3F-SbF_5(1:1)$-SO_2ClF$ acid systems at low temperature, see refs 2c,e.

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gating the analogous reactivity for isoquinolinols containing the hydroxy group in the pyridine ring of the isoquinoline system. We now report a study of the superacid-catalyzed reactions of 1- and 3-isoquinolinols (**11** and **12**) with cyclohexane and benzene to synthesize such useful intermediates.

Results and Discussion

NMR Study of Protonation of 1- and 3-Isoquinolinols and Theoretical Study of Possible Diprotonated Forms. In contrast to the ease of formation of dications **5**−**10** as long-living species,[1,8] protonation of 1-isoquinolinol **11** in a similar manner in CF_3SO_3H (triflic acid, Ho = −14.1) as well as the $CF_3SO_3H-SbF_5$ acid system produced only the N-protonated monocation **11a**. Protonation of 3-isoquinolinol **12** in triflic acid and in $CF_3SO_3H-SbF_5$ gave the N-protonated monocation **12a** along with an additional ion **12b** (5 and 30%, respectively), a dicationic species, which undergo rapid proton exchange with the acid. Similar dicationic species were observed with other isomeric quinolinols and 5-isoquinolinol.[8a] All the signals of ion **12b** in the ^1H and ^{13}C NMR spectra were found to be shifted downfield (deshielded) with respect to the signals of the monocation **12a**, indicating an additional positive charge. However, no clear signal corresponding to the appearance of a CH_2 group was observed. At the same time the signal of the hydrogen atom attached to C^5 was absent, clearly indicating a proton exchange process at this position with the acid.

In principle, additional protonation of monocations **11a** and **12a** could lead to a number of isomeric dications, among which structures **13**−**17** and **18**−**21**, respectively, seemed the most probable (Table 1). Dications **16** and **20**, for example, were preferred as analogues of ions **1** and **2** or respective dications **5**−**10**. Dication **15** can be considered as an analogue of the dication **3**. C-Protonation of the benzene ring of **11a** and **12a**, as well as the additional N-protonation producing dications **13**, **14**, **19**, **20** and **17**, **21**, also seemed probable due to participation of the lone electron pairs of both heteroatoms in charge delocalization. Depending on their relative electrophilicities and concentrations in the reaction media, dications **13**−**21** (or similar complexes with aluminum halides) could give respective products with the nucleophiles.

To understand the relative stabilities and electrophilicities of dications **13**−**21** we have computed their relative energies, the energies of the lowest unoccupied molecular orbital (ϵ_{LUMO}), the squares of the coefficients of carbon atoms at the LUMO of electrophilic centers ($c_\bullet^2$), and the atomic charges of electrophilic centers ($q_\bullet$) localized at carbon atoms and pendent hydrogen atoms. Calculations were performed with the Gaussian 98 program system.[10] The geometry optimization was carried out using the DFT[11] method at the B3LYP[12]/6-31G* level.[13] Vibrational frequency at the B3LYP/6-31G*// B3LYP/6-31G* level was used to characterize the stationary point as a minimum (number of imaginary frequencies (NIMAG) = 0). The values of $q_\bullet$ were obtained using the natural bond orbital analysis[14] (NBO) method. Results of calculations are summarized in Table 1.

All dications **13**−**21** according to the calculated values of ϵ_{LUMO} (−12.71 to −12.31 eV) must be stronger electrophiles than isomeric dications **6**−**10** (ϵ_{LUMO} = −12.263 to −11.988 eV).[8a] Moreover, the values of ϵ_{LUMO} of dications **15** and **16** are close to that of parent C,C-diprotonated dication **3** (ϵ_{LUMO} = −12.936, q_4 = 0.46 eV),[8a] indicating their similar electrophilicities. Surprisingly, dications **18**−**21** were found to be kinetically and thermodynamically (according to their $q_\bullet$ and ϵ_{LUMO} values, respectively) more electrophilic than the parent C,C-diprotonated dication **4** (ϵ_{LUMO} = −12.244 eV, q_4 = 0.38).[8a]

The computed relative energies show the N,C-diprotonated dications **13**−**16** and **18**−**20** to be energetically similar. Furthermore, due to their effective delocalization of positive charge, they are more stable than *N*,*N*-diprotonated dications **17** and **21** (almost by 37.5 kcal/mol compared to **13**). According to theory all dications **13**−**21** appear to be electrophilic enough to react with benzene and cyclohexane; however, the kinetic factors for their generation is the key.

On this basis, the dications **15**, **17**, and **21** seem to be unfavorable candidates for the real reactive intermediates.[15]

Previously, we have shown that a good correlation exists between the computed distribution of values of q_i as well as c_i^2 at the LUMO of dicationic superelectrophiles and their experimentally found positional selectivity in their reactivities with nucleophiles.[1,4b,c,8a,b] The reason for the significant contribution of the orbital control (c_i^2 at LUMO) along with the charge control (q_i) is explained by close energetic levels of the LUMO of strong electrophiles and the HOMO of such nucleophiles as benzene and cyclohexane. Moreover, in the case of the one-electron transfer pathway of these reactions the positional selectivity would mainly correlate with the values of c_i^2 at the LUMO. The significant values both of $c_\bullet^2$ and $q_\bullet$ predict electrophilic (reaction) centers C^6 and C^8, C^8, C^4, C^3, and C^1 for dications **13**−**17**, respectively. Similarly, one can

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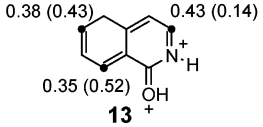
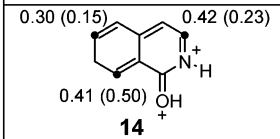
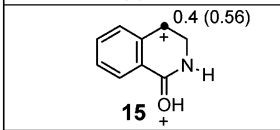
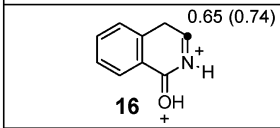
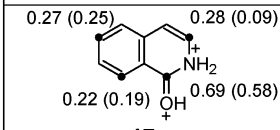
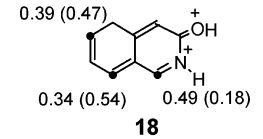
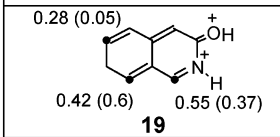
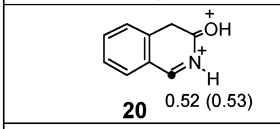
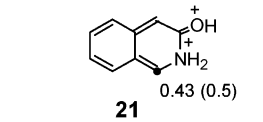
(12) Becke's three-parameter hybrid method using the LYP correlation functional: (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (c) Stephens, P. J.; Devlin, F. J.; Chabalovski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.

(13) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley-Interscience: New York, 1986.

(14) Reed, A. E.; Curtiss, L. A.; Wienhold, F. *Chem. Rev.* **1988**, *88*, 899.

(15) Obviously, the additional protonation of C^3 of ion **11a** as well as the nitrogen atom of ions **11a** and **12a**, producing dications **15**, **17**, and **21**, respectively, requires overcoming significant charge−charge repulsion.

TABLE 1. Energies of the LUMO (ϵ_{LUMO}), the Square of the Coefficients on Carbon Atoms at the LUMO (c_i^2),[a] NBO Charges on CH Groups (q_i),[a] and Total Energies (−au), ZPE, and Relative Energies of Dications 13−21 Calculated by the DFT Method

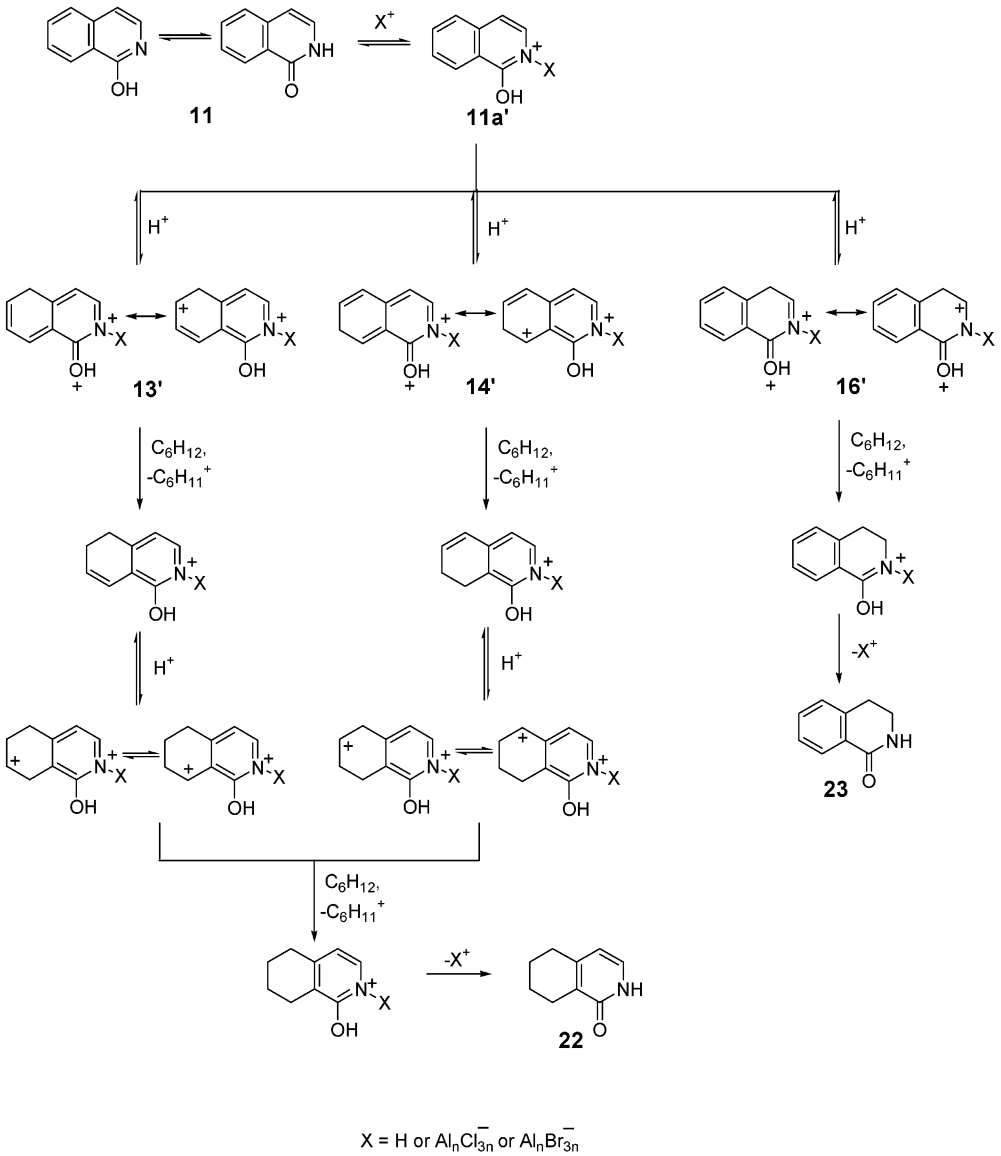
dication, q• and (c•^{2})	ϵ_{LUMO}, eV	B3LYP/6-31G*// B3LYP/6-31G*	ZPE	rel energy, kcal/mol
 0.38 (0.43) 0.43 (0.14) 0.35 (0.52) **13**	-12.31	477.70210	100.9	2.2
 0.30 (0.15) 0.42 (0.23) 0.41 (0.50) **14**	-12.332	477.69489	100.7	6.6
 0.4 (0.56) **15**	-12.71	477.69245	101.3	8.7
 0.65 (0.74) **16**	-12.653	477.67974	100.7	16.1
 0.27 (0.25) 0.28 (0.09) 0.22 (0.19) 0.69 (0.58) **17**	-12.354	477.64651	101.3	37.5
 0.39 (0.47) 0.34 (0.54) 0.49 (0.18) **18**	-12.312	477.70597	101.1	0.0
 0.28 (0.05) 0.42 (0.6) 0.55 (0.37) **19**	-12.377	477.69571	100.7	6.0
 0.52 (0.53) **20**	-12.581	477.69601	101.4	6.6
 0.43 (0.5) **21**	-12.629	477.64668	101.4	37.5

[a] These parameters are given for positions with the most significant values of c_i^2 at the LUMO or q_i.

easily predict a single electrophilic center C^1 for dications **20** and **21**. The dications **18** and **19**, according to their considerable values of q_1, q_6, and q_8, could have electrophilic centers at C^1, C^6, and C^8. On the other hand, position C^1 of the dication **18** and position C^6 of the dication **19** are unlikely to be real reaction centers according to their negligible values of $c_•^2$. Moreover, reaction with the electrophilic center C^1 in dications **18** and **19** will lead to the destruction of aromaticity of both rings, clearly unfavorable on the basis of energy considerations.

Summarizing the results of calculations, the superelectrophiles derived from isoquinolinols **11** and **12** seem to be N,C-diprotonated dications **13**, **14**, **16**, and **18**−**20** with reaction centers C^6 or C,^{8} C,^{8} C^3 and C^6 or C,^{8} C,^{8} C^1, respectively. Relative reactivity of considered dications based on theory can be presented as follows: **16** > **14** > **13** and **20** > **19** > **18**.

SCHEME 1

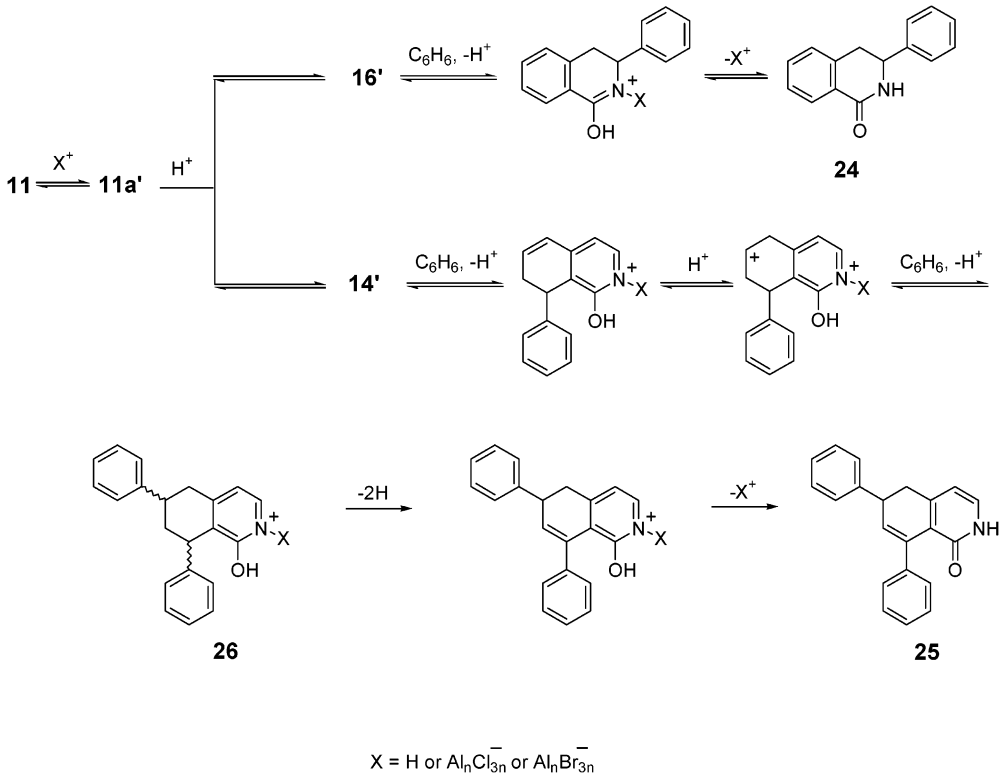


Reactions of 11 with Cyclohexane and Benzene. Isoquinolinol **11** does not react with cyclohexane and benzene in triflic acid. However, **11** readily reacts with cyclohexane in the $CF_3SO_3H-SbF_5$ system at room temperature to give 5,6,7,8-tetrahydro-1(2*H*)-isoquinolinone (**22**) in 90% yield. The likely mechanism of this reaction, according to Scheme 1, includes generation of dication **13** or **14** followed by their selective ionic hydrogenation with cyclohexane. Reaction of **11** with cyclohexane in the presence of aluminum chloride at 90 °C gave a mixture of **22** and 3,4-dihydro-1(2*H*)-isoquinolinone (**23**) (molar ratio ~5:4) in 96% overall yield.[16] Formation of **23** can be explained by participation of dicationic species **16′** as a key intermediate (Scheme 1). It is gratifying to note that theoretical estimates of higher electrophilicity of dications **13**, **14**, and **16** in comparison with that of dications **5**−**10** are in agreement with the observed experimental results. For example, the time to complete the reaction of **11** with cyclohexane in the presence of aluminum chloride required only 2 h. However, to complete similar reactions of 8-quinolinol, 5-isoquinolinol, 5-quinolinol, and 5-amino-1-naphthol at the same temperature (90 °C) required much longer time (15, 50, 90, and >150 h, respectively). This roughly correlates with the values of ϵ_{LUMO} and $q_{\cdot}$ of their dications **9** (−12.263 eV and 0.36), **10** (−12.157 eV and 0.36), **6** (−11.988 eV and 0.34), and **5** (−10.979 eV and 0.3), respectively.[1,8a]

Reaction of **11** with benzene was also found to follow two pathways. In the presence of 4 molar excess of aluminum halides at room temperature, dicationic species **16′** is considered to be the key intermediate reacting with benzene to give 3,4-dihydro-3-phenyl-1(2*H*)-isoquinolinone (**24**) in ~75% yield (Scheme 2). Further experiments, however, have shown that the reaction is reversible and the yield corresponds to the equilibrium concentrations of the products obtained over 70 and 15 h reaction time in the case of $AlCl_3$ and $AlBr_3$, respectively. Increasing the reaction time did not change the ratio of **11** and **24**. Moreover, **24** gave precursor **11** in

(16) Under the reaction conditions cyclohexane exists in an equilibrium with methylcyclopentane, see: Nenitzescu, C. D.; Cantuniari, R. *Chem. Ber.* **1933**, *66*, 1097.

SCHEME 2



~20% equilibrium concentration in the presence of aluminum chloride over 220 h of reaction time under conditions similar to that of condensation. The analogous behavior was found previously in the case of 5-amino-1-naphthol, isomeric quinolinols, and 5-isoquinolinol, which gave respective condensation products in 15−40% yields.[1,8] The higher yield of **24** is also is in accord with the recognized higher electrophilicity of dication **16** in comparison with that of **5**−**10**. The reversibility of the reaction can be utilized for a reversed synthesis of isoquinolinol **11**. The latter was obtained in quantitative yield by reaction of **24** with aluminum halides in *o*-dichlorobenzene medium.

Prolonged reaction time or, more effectively, catalysis with highly acidic HBr−$AlBr_3$ results in an alternative pathway of the reaction of **11** with benzene to give 5,6-dihydro-6,8-diphenyl-1(2*H*)-isoquinolinone (**25**) as the end product in ~70% yield.[17] Obviously, this pathway is possible due to the reversibility of the former reaction path. Dication **13′** or **14′** is considered to be the key intermediate of this reaction. The preferred mechanism including generation of **14′** is shown in Scheme 2. Formation of the C^7−C^8 double bond in **25** might be explained by ionic dehydrogenation of the intermediate **26** with acid or, more likely, as a result of side reactions including ionic hydrogenation−dehydrogenation processes.[18] On the other hand, the double-bond formation is less likely when compared to disproportionation reactions of 1,2-dihydronaphthalenes under the action of strong acids.[19] The unique behavior can be better explained by the oxidative dehydrogenation of **26** as a result of its protonation or protosolvation according to Scheme 3.

Reactions of 12 with Cyclohexane and Benzene. Similar to **11**, isoquinolinol **12** also does not react with cyclohexane in triflic acid, but readily reacts in the CF_3SO_3H−SbF_5 system to give 5,6,7,8-tetrahydro-3(2*H*)-isoquinolinone (**27**) in 94% yield. The mechanism of this reaction, according to Scheme 4, includes generation of dication **18** or **19** followed by their selective ionic hydrogenation with cyclohexane. Reaction with cyclohexane under aluminum chloride catalysis at 90 °C gave a mixture of **27** and 1,4-dihydro-3(2*H*)-isoquinolinone (**28**) (1:4, respectively) in quantitative overall yield.[16] The main pathway of this reaction corresponds to the participation of dicationic species **20′** as a key intermediate (Scheme 4).

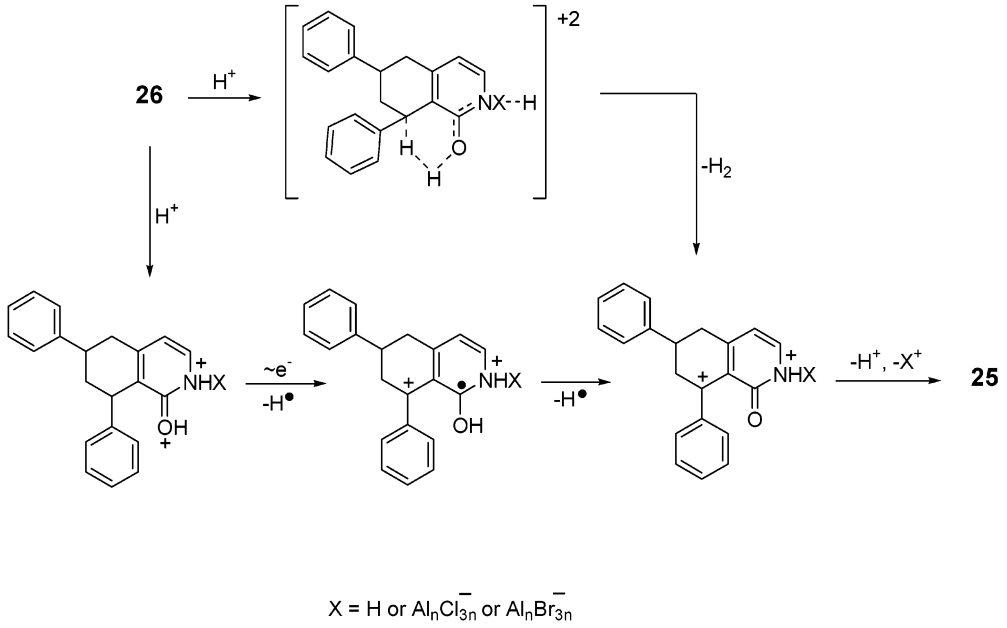
Isoquinolinol **12** also readily reacts with benzene in the presence of 4−6 molar excess of aluminum halides. Full conversion of **12** required only 1.5 h in the presence of aluminum chloride at room temperature to give 1,4-dihydro-1-phenyl-3(2*H*)-isoquinolinone (**29**) in ~80% yield along with 5,6,7,8-tetrahydro-6,8-diphenyl-3(2*H*)-isoquinolinone (**30**) (~15% yield). Dicationic species **20′** and **19′** (or **18′**) are considered to be the key intermediates of the reaction leading to products **29** and **30**, respectively (Scheme 5). Increasing the reaction time (>70 h) as well as the use of $AlBr_3$ instead of $AlCl_3$ makes the latter pathway predominant and gives product **30** in quantita-

(17) The detailed mechanism of this reaction was not explored, and intermediate products were characterized only by NMR and TLC monitoring. Hydrogenation of the product **25** in ethanol over Pd/C (5%) at room temperature and 1 atm of hydrogen for 8 h gave 5,6,7,8-tetrahydro-6,8-diphenyl-1(2*H*)-isoquinolinone (mixture of cis/trans isomers 10:1) in quantitative yield.

(18) (a) Olah, G. A.;Prakash, G. K. S.; Sommer, J. In *Superacids*; Wiley: New York, 1985. (b) Benner, L. S.; Lai, Y.-H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1981**, *103*, 3609, and references therein.

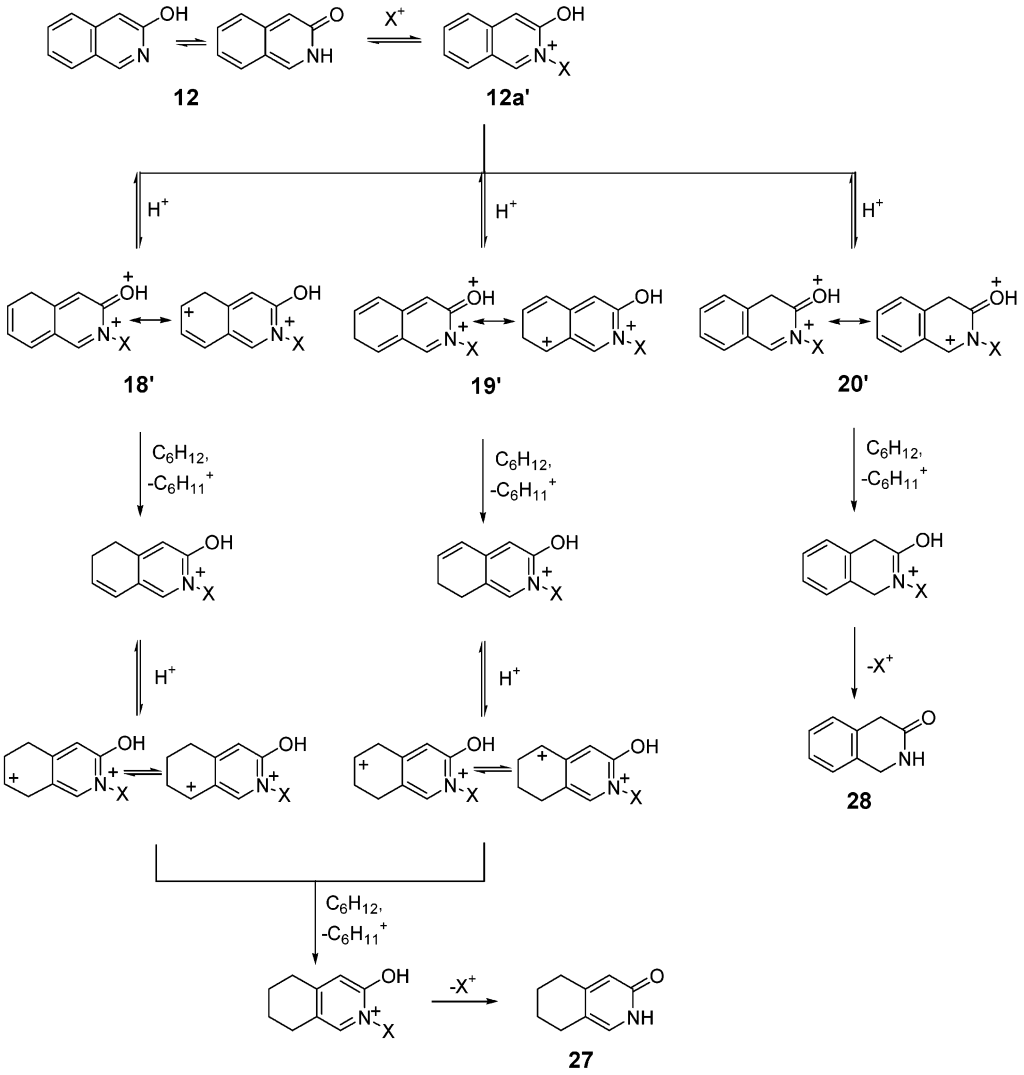
(19) Tournier, H.; Longeray, R.; Dreux, J. *Tetrahedron Lett.* **1969**, *21*, 1629.

SCHEME 3



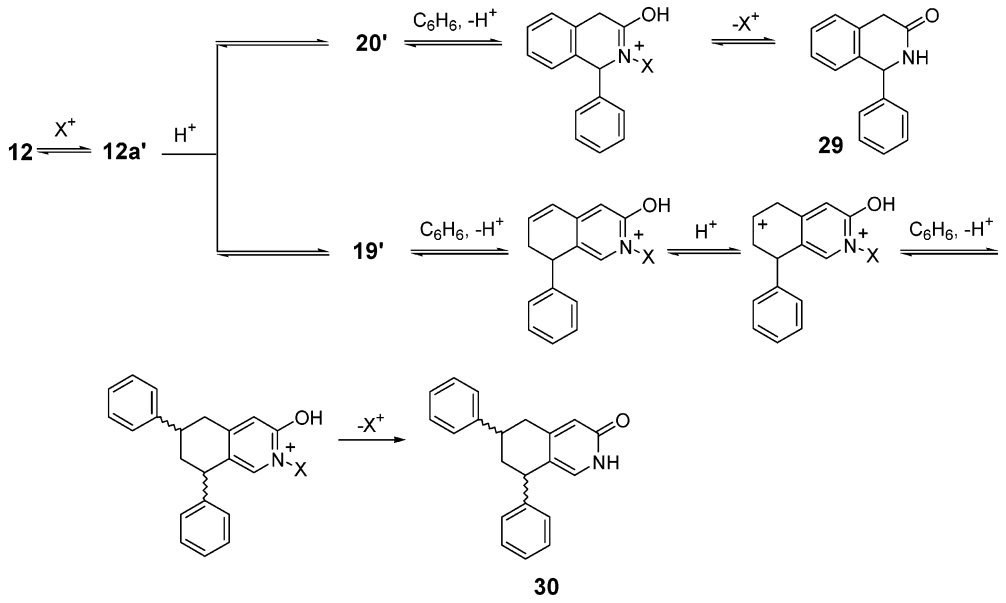
X = H or $Al_nCl^-_{3n}$ or $Al_nBr^-_{3n}$

SCHEME 4



X = H or $Al_nCl^-_{3n}$ or $Al_nBr^-_{3n}$

SCHEME 5



X = H or $Al_nCl_{3n}^-$ or $Al_nBr_{3n}^-$

tive yield. This can be explained by reversibility of the former reaction pathway. Analogous to the behavior of compound **24**, product **29** gave precursor **12** under the influence of aluminum halides in *o*-dichlorobenzene, but in comparatively lower yields (≤62%) due to the parallel formation of **30**. Nevertheless, this reaction seems to be interesting as a new synthetic route to **12** and its derivatives from corresponding arylisoquinolinones.

Compound **12** also slowly reacts with benzene in triflic acid. The disappearance of starting material was observed over a period of ∼750 h at room temperature to give a mixture **29**/**30** (∼1:1) along with byproducts. This is in accord with the earlier observations.[8] Reaction of **12** with benzene with $AlBr_3$−HBr at room temperature or $AlCl_3$ at 90 °C gave **30** and its reaction products. The reaction, however, was not further explored.

The experimentally found high reactivity of isoquinolinol **12** (appears to be even more reactive, than 2-naphthol[4c,5b]) also correlates with the significant electrophilicity of dications **18**−**20**, in accordance with the theoretical calculations.

Conclusions

In summary, we have found that isoquinolinols **11** and **12** undergo ionic hydrogenation with cyclohexane and condense with benzene in superacids to give respective products **22**−**25** and **27**−**30** depending on reaction conditions. All the experimental results can be successfully explained by involving the intermediacy of N,C-diprotonated dications **13**, **14**, **16**, and **18**−**20** or analogous complexes with aluminum halides. The experimental data are also supported by the results of the theoretical calculations on these dications. Ionic hydrogenation with cyclohexane can be conveniently used in selective reduction of **11**, **12**, and their derivatives. Reactions with benzene provide new, effective and simple ways for the synthesis of arylisoquinolinones. The reversibility of reactions can be useful for the synthesis of **11**, **12**, and their derivatives from the corresponding arylamides.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz superconducting NMR spectrometer. High-resolution mass spectra were measured at the Southern California Mass Spectrometry Facility at the University of California at Riverside. Triflic acid, aluminum halides, 1-isoquinolinol **11** (mp 211−214 °C), and 3-isoquinolinol **12** (mp 192−194 °C) were purchased and used as received. Antimony pentafluoride was distilled under argon. Elevated temperature reactions were carried out in 15 mL pressure tubes.

Procedure for the protonation of 11 and 12 was similar to that for quinolinols as previously reported.[8a]

Ion 11a: ^{1}H NMR (CF_3SO_3H) δ 6.8−6.9 (m, 2H), 7.03 (t, *J* 8.7 Hz, 1H), 7.15 (d, *J* 8.7 Hz, 1H), 7.22 (t, *J* 9.3 Hz, 1H), 7.56 (d, *J* 9.3 Hz, 1H), 10.2 (br s, 1H);[20] ^{13}C NMR (CF_3SO_3H) δ 116.8, 117.6, 124.1, 124.8, 127.1, 129.9, 136.7, 139.5, 158.9.[21]

Ion 12a: ^{1}H NMR (CF_3SO_3H) δ 6.67 (d, *J* 2.2 Hz, 1H), 6.84 (t, *J* 8.3 Hz, 1H), 7.03 (d, *J* 8.3 Hz, 1H), 7.12 (t, *J* 8.3 Hz, 1H), 7.27 (d, *J* 8.3 Hz, 1H), 8.08 (d, *J* 7.1 Hz, 1H), 10.8 (br s, 1H);[20] ^{13}C NMR (CF_3SO_3H) δ 106.5, 123.2, 125.7, 128.7, 129.2, 137.6, 142.5, 143.3, 151.3.[21]

Ion 12b: ^{1}H NMR (CF_3SO_3H) δ 7.02 (t, *J* 8.1 Hz, 1H), 7.38 (s, 1H), 7.67 (d, *J* 8.1 Hz, 1H), 7.92 (d, *J* 8.1 Hz, 1H), 8.36 (d, *J* 7.2 Hz, 1H), 11.4 (br s, 1H);[20] ^{13}C NMR (CF_3SO_3H) δ 104.7, 123.7, 127.3, 130.4, 137.4, 138.3, 140.5, 144.5, 153.4.[21]

5,6,7,8-Tetrahydro- and 3,4-Dihydro-1(2H)-isoquinolinones (22 and 23). Method a. To a solution of **11** (0.025 g, 0.17 mmol) in CF_3SO_3H (0.7 g, 4.7 mmol) was added SbF_5 (0.33 g, 1.5 mmol) at room temperature. Subsequently, cyclohexane (0.3 mL) was introduced, and the reaction mixture was stirred at 25 °C for 1 h followed by a quench with several grams of ice. The resulting mixture was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was dried over

(20) Protons bonded to oxygen are not observed due to rapid proton exchange with the acid.

(21) The chemical shifts were measured with reference to the signals of $(CD_3)_2CO$ as external standard (2.04 and 206 ppm in the ^{1}H and ^{13}C NMR spectra, respectively).

anhydrous $MgSO_4$. Concentration in vacuo provided a residue that was washed by hexanes to obtain **22** (0.023 g, 90%) as a crystalline product: mp 211−213 °C (acetone), lit.[22] mp 212−214 °C; ^{1}H NMR ($CDCl_3$) δ 1.65−1.85 (m, 4H), 2.5−2.65 (m, 4H), 6.12 (d, *J* 6.5 Hz, 1H), 7.28 (d, *J* 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.8, 22, 23, 29.4, 109.7, 126.6, 130.2, 150.2, 164.5.

Method b. To a suspension of $AlCl_3$ (0.68 g, 5 mmol) in cyclohexane (3 mL) was added **11** (0.1 g, 0.7 mmol). The resulting mixture was stirred at 90 °C for 2 h, followed by cooling, and the mixture was poured over several grams of ice and extracted with CH_2Cl_2. The treatment of the organic phase with 20% aqueous NaOH gave a precipitate, which was filtered off and combined with the alkaline aqueous phase. The combined mixture was neutralized with hydrochloric acid and extracted with CH_2Cl_2. The obtained organic phase was dried ($MgSO_4$) and concentrated to afford **22** (0.057 g, 55%). The residual organic phase was washed with water, dried ($MgSO_4$), and concentrated to provide **23** (0.042 g, 41%) as a crystalline product: mp 67−69 °C (cyclohexane), lit.[23] mp 64−66 °C; ^{1}H NMR ($CDCl_3$) δ 2.99 (t, *J* 6.6 Hz, 2H), 3.58 (td, *J* 6.6, 2.3 Hz, 2H), 6.94 (br s, 1H), 7.21 (d, *J* 7.6 Hz, 1H), 7.35 (t, *J* 7.6 Hz, 1H), 7.45 (t, *J* 7.6 Hz, 1H), 8.05 (d, *J* 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3, 40.1, 127, 127.3, 127.8, 128.9, 132.1, 138.9, 166.6.

3,4-Dihydro-3-phenyl-1(2*H*)-isoquinolinone (24). To a suspension of $AlCl_3$ (0.27 g, 2 mmol) in benzene (4 mL) was added **11** (0.073 g, 0.5 mmol). The resulting mixture was stirred at 25 °C for 72 h,[24] followed by pouring the mixture over several grams of ice and its subsequent extraction with $CHCl_3$. The organic phase was washed with aqueous $NaHCO_3$, then dried ($MgSO_4$) and concentrated to give the mixture, which was separated by silica gel column chromatography[25] with CCl_4−$CHCl_3$ (10:1), providing precursor **11** (0.016 g, 22%, mp 210−212 °C) and crystalline product **24** (0.083 g, 74%): mp 129−130 °C, lit.[26] mp 130−131 °C; ^{1}H NMR ($CDCl_3$) δ 3.1−3.3 (m, 2H), 4.86 (dd, *J* 12, 5.5 Hz, 1H), 6.15 (br s, 1H), 7.18 (d, *J* 8.3 Hz, 1H), 7.3−7.4 (m, 6H), 7.46 (td, *J* 8.3, 1.5 Hz, 1H), 8.12 (dd, *J* 8.3, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 37.4, 56.1, 126.4, 127.2, 127.3, 128, 128.3, 128.4, 128.9, 132.5, 137.5, 140.9, 166.3.

1-Isoquinolinol (11). Method a. A mixture of $AlCl_3$ (0.1 g, 0.75 mmol) and **24** (0.04 g, 0.18 mmol) in *o*-dichlorobenzene (1.5 mL) was stirred at 25 °C for 300 h, then poured over ice and extracted with $CHCl_3$. The organic phase was separated, washed with water and aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated. The crystalline residue was washed with ether to provide isoquinolinol **11** (0.025 g, 96%): mp 210−212 °C.

Method b. A mixture of $AlBr_3$ (0.5 g, 1.9 mmol) and **24** (0.04 g, 0.18 mmol) in *o*-dichlorobenzene (1.5 mL) was stirred at 25 °C for 24 h and after workup as described above gave **11** (0.026 g, 100%).

5,6-Dihydro-6,8-diphenyl-1(2*H*)-isoquinolinone (25). To a solution of $AlBr_3$ (1.33 g, 5 mmol) in benzene (2.5 mL) was added **11** (0.145 g, 1 mmol). The resulting mixture was saturated with gaseous HBr (0.16 g, 2 mmol) and stirred at 25 °C for 24 h, then poured over ice and extracted with benzene. The organic phase was separated, washed with water and aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated. The crude material was dissolved in acetone (1.5 mL). After 10 h at room temperature the precipitated crystalline product **25** (0.126 g) was filtered and washed with cold acetone. The combined acetone solution was concentrated, and the residue was purified by silica gel column chromatography (10:1 CCl_4−$CHCl_3$), providing an additional portion of **25** (0.09 g) in 72% overall yield: mp 188−189 °C (acetone); ^{1}H NMR ($CDCl_3$) δ 2.61 (dd, *J* 13.3, 8.8 Hz, 1H), 3.05 (dd, *J* 13.3, 6.4 Hz, 1H), 3.77 (ddd, *J* 8.8, 6.4, 2.2 Hz, 1H), 6.2 (dd, *J* 6.8, 1.7 Hz, 1H), 6.41 (d, *J* 2.2 Hz, 1H), 6.44 (br s, 1H), 7.18−7.42 (m, 8H), 7.48−7.56 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 37.8, 48.4, 108.7, 119, 120.6, 123.3, 125.2, 126.9, 127.6, 127.7, 128.5, 133.8, 134.1, 135.4, 143.2, 144.8, 147.3, 155.4, 165.2; HRMS $C_{21}H_{17}NO$ calcd 299.1310, found 299.1307.

5,6,7,8-Tetrahydro-3(2*H*)-isoquinolinone (27). To a solution of **12** (0.03 g, 0.2 mmol) in CF_3SO_3H (0.7 g, 4.7 mmol) was added SbF_5 (0.33 g, 1.5 mmol) at room temperature. After subsequent addition of cyclohexane (0.3 mL) the reaction mixture was stirred at 25 °C for 1 h, followed by pouring over several grams of ice. The resulting mixture was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was dried over anhydrous $MgSO_4$. Concentration in vacuo provided a residue that was washed by hexanes to obtain **27** (0.029 g, 94%) as a crystalline product: mp 199−201 °C (acetone), lit.[27] mp 201−203 °C. ^{1}H NMR ($CDCl_3$) δ 1.6−1.8 (m, 4H), 2.53 (m, 2H), 2.66 (m, 2H), 6.31 (s, 1H), 7.11 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.1, 22.7, 25.2, 29.4, 117.2, 117.5, 132.1, 154.4, 164.4.

1,4-Dihydro-3(2*H*)-isoquinolinone (28). To a suspension of $AlCl_3$ (0.68 g, 5 mmol) in cyclohexane (3 mL) was added **12** (0.1 g, 0.7 mmol). The resulting mixture was stirred at 90 °C for 3 h until two distinct layers were formed, followed by cooling. Then the mixture was poured over several grams of ice and extracted with $CHCl_3$. The organic phase was dried ($MgSO_4$) and concentrated to give a residue that was washed by hexanes to obtain a crystalline crude product[28] (0.1 g). The latter was recrystallized from benzene to provide **28** (0.068 g, 67%): mp 146−148 °C, lit.[29] mp 150−151 °C; ^{1}H NMR ($CDCl_3$) δ 3.6 (s, 2H), 4.52 (s, 2H), 6.95 (br s, 1H), 7.1−7.3 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 36.4, 45.3, 125.4, 126.7, 127.5, 127.8, 130.9, 131.6, 173.4.

1,4-Dihydro-1-phenyl-3(2*H*)-isoquinolinone (29). To a stirred suspension of $AlCl_3$ (0.75 g, 5.6 mmol) in benzene (4 mL) at 0 °C was added **12** (0.145 g, 1 mmol). The resulting mixture was stirred at 25 °C for 1.5 h, followed by pouring the mixture over several grams of ice and its subsequent extraction with CH_2Cl_2. The organic phase was washed with aqueous $NaHCO_3$, then dried ($MgSO_4$) and concentrated to give the residue,[30] which was recrystallized from benzene (1 mL) to provide **29** (0.172 g, 77%): mp 165−167 °C, lit.[9b] mp 165−167 °C; ^{1}H NMR ($CDCl_3$) δ 3.7 (AB, *J* 20.5 Hz, 2H), 5.65 (s, 1H), 6.6 (br s, 1H), 6.96 (d, *J* 7.5 Hz, 1H), 7.15−7.4 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 36.5, 60.2, 126.7, 126.8, 127.4, 127.8, 127.9, 128.3, 129.1, 131.7, 134.6, 141.3, 171.4.

3-Isoquinolinol (12). Method a. A mixture of $AlCl_3$ (0.15 g, 1.1 mmol) and **29** (0.04 g, 0.18 mmol) in *o*-dichlorobenzene (3 mL) was stirred at 25 °C for 240 h, then poured over ice and extracted with $CHCl_3$. The organic phase was extracted with 20% aqueous NaOH. The alkaline aqueous part was washed with $CHCl_3$ and neutralized with hydrochloric acid, followed by the extraction with $CHCl_3$. The obtained organic phase was dried ($MgSO_4$) and concentrated to provide **12** (0.016 g, 62%): mp 194−196 °C (benzene), lit.[31] mp 195−196 °C.

Method b. A mixture of $AlBr_3$ (0.2 g, 0.75 mmol) and **29** (0.04 g, 0.18 mmol) in *o*-dichlorobenzene (1 mL) was stirred at 25 °C for 1 h and after workup as described above gave **7** (0.09 g, 35%).

5,6,7,8-Tetrahydro-6,8-diphenyl-3(2*H*)-isoquinolinone (30). Method a. To a solution of $AlBr_3$ (1.2 g, 4.5 mmol) in

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(24) After 24 h of the reaction the molar ratio of **11**/**24** was 1:2.3.
(25) The treatment of an ether−chloroform solution of a similar reaction mixture with 20% aqueous NaOH (3 × 3 mL) easily removes precursor **11**, providing the pure product **24**.
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(27) Ershov, L. V.; Bogdanova, G. A.; Granik, V. G. *Chem. Heterocycl. Compd.* **1990**, *26*, 183.
(28) The mixture of **28** /**27** (83:17), according to ^{1}H NMR data.
(29) Gramain, J. C.; Simonet, N.; Vermeersch, G.; Febvay-Garot, N.; Caplain, S.; Lablashe-Combier, A. *Tetrahedron* **1982**, *38*, 539.
(30) The mixture of **29**/**30** (84:16), according to ^{1}H NMR data.
(31) Baumgarten, H. E.; Murdock, W. F.; Dirks, J. E. *J. Org. Chem.* **1961**, *26*, 803.

benzene (3 mL) was added **12** (0.145 g, 1 mmol). The resulting solution was stirred at 25 °C for 4 h, then poured over ice and extracted with CH_2Cl_2. The organic phase was washed with water and aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated to provide crystalline product **30** (0.292 g, 97%) as a mixture of cis−trans isomers (~3:1). HRMS: $C_{21}H_{19}NO$ calcd 301.1467, found 301.1470. Recrystallization of the mixture from acetone gave *cis*-**30** (0.15 g, 50%): mp 258−260 °C; ^{1}H NMR ($CDCl_3$) δ 2.03 (q, *J* 12.4 Hz, 1H), 2.25−2.35 (m, 1H), 2.85−3.2 (m, 3H), 3.95 (dd, *J* 12.4, 4.5 Hz, 1H), 6.31 (s, 1H), 6.81 (s, 1H), 7.2−7.4 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 38.5, 40.4, 40.5, 44.7, 116.8, 121.1, 126.6, 126.8, 127.1, 128.4, 128.7, 128.9, 134.6, 144.4, 144.9, 153.8, 164.1.

Method b. To a suspension of $AlCl_3$ (0.7 g, 5.2 mmol) in benzene (2 mL) was added **12** (0.145 g, 1 mmol). The resulting mixture was stirred at 25 °C for 72 h, then poured over ice and after workup as described above gave the product **30** (0.285 g, 95%).

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Supporting Information Available: Cartesian coordinates and total energies (hartrees) of the optimized geometries of **13**−**21** and the ^{1}H and ^{13}C NMR spectra of **25** and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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