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Facile One-Pot Synthesis of Benzo[*h*]isoquinolines *via* Strong Acid Triggered [1,2]-Sigmatropic Rearrangement: A Theoretical and Experimental Studies

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Benzo[*h*]isoquinoline scaffold is of interest as a rigid subunit that can be useful for constructing biologically active products. However, no good-yielded synthetic pathway to this ring system has been reported yet. Herein, a facile one-pot synthesis from *N*-aryl itaconimides and 1,3-diarylisobenzofuran *via* strong acid triggered skeletal rearrangement reaction is described. Theoretical study for this rearrangement is provided at M11/cc-pVDZ level of theory. Antitumor activity of obtained benzo[*h*]isoquinoline derivatives against human erythroleukemia K562 cell line was evaluated *in vitro* by MTS-assay.

Keywords: Benzo[*h*]isoquinoline, *N*-Aryl Itaconimides, 1,3-Diarylisobenzofuran, Acid induced rearrangement, Antitumor activity.

INTRODUCTION

Efficient creation of structural, functional and stereochemical complexity from simple precursors is one of the most desired aspects of new synthetic methodology development. Pericyclic reactions are the powerful tool in organic synthesis and often simplify design complicated heterocyclic natural [1-6] and pharmacologically active compounds [7-13].

Benzo[*h*]isoquinoline scaffold appears in compounds displaying a broad range of biological activity: D1 dopamine agonists [14-16], serotonin (5-HT2) receptor antagonists [17-19], histamine (H3) receptor antagonists [20,21], inhibitors of Chk1 kinase [22] and c-Src inhibitors [23].

Due to such activity these substances have widely pharmaceutical implementation and are used in the treatment of Alzheimer′s disease, Parkinson′s disease, schizophrenia, memory disorder (including drug-induced memory disorder), movement disorder and central nervous system, treatment or prevention of central nervous disorders such as depressions, bipolar disorders, anxiety states, *etc*. cardiovascular disorders such as hypertension, thrombosis, stroke, *etc*. gastrointestinal disorders such as dysfunction of gastrointestinal tract motility.

On these grounds there is significant interest in the synthesis of benzo[*h*]isoquinoline ring systems and several multistage approaches have been reported [14-19,22,24-27]. Main disadvantage of all known methods is their multistage, that lead to low overall yield (about 10%). Two more articles were published last decade but these are rather the last step towards benzo[*h*]isoquinoline skeleton from bulky precursors: Klumpp *et al*. [28] have reported a novel synthetic method by the super acid-promoted cyclization of alkenyl-substituted *N*-heterocycles and Harrowven *et al.* [29] reported the first example of an intramolecular radical cyclisation of (*Z*)-azastilbenes, both in good yields.

EXPERIMENTAL

Hexane and ethyl acetate for the chromatography were distilled before use. IR spectra were obtained in KBr or $CHCl_3$ and wavelengths are reported in cm^{-1}. Melting points were determined on a Boetius instrument and are uncorrected. ^1H

and ^{13}C NMR spectra were recorded in $CDCl_3$ using Bruker Avance 400 spectrometer. Chemical shifts are reported in ppm relative to residual $CHCl_3$ (^1H, δ = 7.26 ppm), $CDCl_3$ (^{13}C, δ = 77.17 ppm) as internal standard. The X-ray diffraction data were performed by means of an Agilent Technologies SuperNova diffractometer with Cu-Kα X-ray radiation. Reactions were monitored by TLC analysis using Silufol UV-254 plates. Thin layer chromatography was performed on silica gel 5-40 mesh eluted with ethyl acetate/hexane. HRMS spectra were obtained with a Bruker-micrOTOF and Bruker-maXis (QTOF). N-Aryl itaconimides were prepared following known procedures [30]. Analytical data for known compounds **3a-h** were identical with previously published data [31].

Typical procedure: A solution of 1,3-diphenylisobenzofuran (**2**) (1 mmol) and the corresponding imide **1** (1 mmol) in anhydrous dichloromethane (10 mL) was magnetically stirred for 48 h at room temperature. Methanesulfonic acid (6 mmol) was then added and the stirring was further maintained for 6 h at room temperature. After completion of the reaction (TLC-control), 10 mL of aq. Na_2CO_3 was added carefully to the reaction mixture. The aqueous layer was extracted with dichloromethane (3 × 5 mL), the organic layers were combined, dried over $MgSO_4$ and evaporated to dryness. The residue was then purified by preparative thin-layer chromatography using a mixture of hexane/ethyl acetate as eluent.

2-(4-Methylphenyl)-6,10b-diphenylbenzo[*h*]isoquinoline-1,3(2*H*,10bH)-dione (3a): Pale-yellow solid, yield: 37 %; m.p. 238-240 ºC; IR (KBr, ν_{max}, cm^{-1}): 700, 737, 769, 1212, 1372, 1510, 1687, 1726, 2851, 2921, 3029; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.34 (s, 3H, Me), 7.00-7.70 (m, 20H, 18ArH + 2HC=); HRMS (ESI) calcd. (found) for $C_{32}H_{24}NO_2$ ($[M+H]^+$): 454.1807 (454.1809).

2-(4-Methoxyphenyl)-6,10b-diphenylbenzo[*h*]isoquinoline-1,3(2*H*,10bH)-dione (3b): Pale-yellow solid, yield: 41%; m.p.: > 260 ºC; IR ($CHCl_3$, ν_{max}, cm^{-1}): 740, 769, 839, 1032, 1164, 1230, 1373, 1509, 1686, 1725, 2927, 2998; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.80 (s, 3H, MeO), 6.94 (d, 2H, *J* = 9.0 Hz, ArH), 7.05 (d, 2H, *J* = 9.0 Hz, ArH), 7.25-7.70 (m, 16H, 14ArH + 2HC=); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.7, 55.8, 115.1 (2C), 121.1, 126.5, 126.8, 127.0, 127.4, 128.5 (2C), 128.7 (2C), 129.0 (2C), 129.2 (2C), 129.8 (2C), 129.9 (2C), 130.0 (2C), 133.3, 134.9, 137.8, 138.5, 140.2, 145.3, 159.8, 165.2, 170.7; HRMS (ESI) calcd. (found) for $C_{32}H_{24}NO_3$ ([M+H]+): 470.1756 (470.1754).

2-(4-Fluorophenyl)-6,10b-diphenylbenzo[*h*]isoquinoline-1,3(2*H*,10bH)-dione (3c): Yellow solid, yield: 52 %; m.p.: 156-158 ºC; IR ($CHCl_3$, ν_{max}, cm^{-1}): 740, 767, 830, 1152, 1237, 1372, 1508, 1697, 1715, 2919, 3057; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.10 (br. s, 4H, ArH), 7.20-7.65 (m, 16H, 14ArH + 2HC=); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.4, 116.7 (d, *J* = 22.6 Hz, 2C), 118.5, 126.3, 126.8 (d, *J* = 12.8 Hz, 2C), 127.5, 128.4, 128.6 (2C), 128.9 (2C), 129.0 (2C), 129.2 (2C), 129.3, 129.8, 130.0, 133.4, 135.0, 137.7, 138.7, 140.2, 145.5, 146.7, 155.6, 165.1, 167.0 (d, *J* = 406.8 Hz), 172.2; HRMS (ESI) calcd. (found) for $C_{31}H_{21}NO_2F$ ($[M+H]^+$): 458.1556 (458.1550).

2-(4-Bromophenyl)-6,10b-diphenylbenzo[*h*]isoquinoline-1,3(2*H*,10bH)-dione (3d): Pale-yellow solid, yield: 47 %; m.p.: 223-225 ºC; IR ($CHCl_3$, ν_{max}, cm^{-1}): 737, 770, 874, 1012, 1070, 1228, 1369, 1442, 1487, 1685, 1714, 2922, 3055; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.03 (d, 2H, *J* = 9.0 Hz, ArH), 7.25-7.70 (m, 18H, 16ArH + 2HC=); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.4, 118.4, 120.7, 124.1, 126.5, 126.7, 126.9, 128.6 (2C), 128.8 (2C), 128.9 (2C), 129.0 (2C), 129.2 (2C), 129.8 (2C), 130.0, 132.9 (2C), 140.1, 142.1, 145.6, 146.7, 155.7, 164.3, 164.8, 170.2, 171.9; HRMS (ESI) calcd. (found) for $C_{31}H_{21}NO_2Br$ ($[M+H]^+$): 518.0756 (518.0751).

2-(3,5-Dichlorophenyl)-6,10b-diphenylbenzo[*h*]isoquinoline-1,3(2*H*,10bH)-dione (3e): Pale-yellow solid, yield: 49 %; m.p.: 231-233 6C; IR ($CHCl_3$, ν_{max}, cm^{-1}): 730.7, 763.6, 804.8, 1227.7, 1365.2, 1435.1, 1576.2, 1682.8, 1714.3, 3056. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.50 (br. s, 1H, ArH), 7.07 (s, 2H, ArH), 7.25-7.70 (m, 16H, 14ArH + 2HC=); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.5, 118.1, 124.0, 126.7 (2C), 127.1, 127.7 (2C), 128.1 (2C), 128.2, 128.6 (2C), 128.8 (2C), 129.0, 129.3, 129.9 (2C), 130.0 (2C), 135.1, 135.7, 137.1, 138.2, 141.8, 147.0, 156.1, 163.9, 169.9, 171.7; HRMS (ESI) calcd. (found) for $C_{31}H_{20}NO_2Cl_2$ ($[M+H]_+$): 508.0871 (508.0863).

2-(4-Chloro-3-fluorophenyl)-6,10b-diphenylbenzo[*h*]-isoquinoline-1,3(2H,10bH)-dione (3f): Pale-yellow solid, yield: 57 %; m.p.: 220-222 °C; IR ($CHCl_3$, ν_{max}, cm^{-1}): 893.4, 1077.9, 1230.9, 1260.9, 1369.4, 1445.6, 1496.8, 1624.6, 1681.6, 1712.1, 2920.9, 3051.6; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.50 (br. s, 2H, ArH), 6.90-7.65 (m, 16H, 14ArH + 2HC=), 8.55 (br. s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.5, 117.4 (d, J = 22.6 Hz), 118.2, 122.1 (d, *J* = 19.6 Hz), 124.0, 126.7 (2C), 128.5 (2C), 128.8 (4C), 129.0 (3C), 129.2 (3C), 129.3 (2C), 131.5, 133.7, 135.2, 138.3, 141.9, 146.9, 155.9, 158.0 (d, *J* = 250.6 Hz), 164.2, 171.9; HRMS (ESI) calcd. (found) for $C_{31}H_{20}NO_2ClF$ ($[M+H]^+$): 492.1167 (492.1165).

2-(3-Nitrophenyl)-6,10b-diphenylbenzo[*h*]isoquinoline-1,3(2*H*,10bH)-dione (3g): Pale-yellow solid, yield: 69 %; m.p.: > 260 ºC; IR ($CHCl_3$, ν_{max}, cm^{-1}): 719.5, 744.6, 882.9, 1239.2, 1348.3, 1372.7, 1531.4, 1683.2, 1714.0, 3053.7; ^1H NMR (400 MHz, DMSO-d_6) δ: 6.70 (br. d, 2H, ArH), 7.20-7.50 (m, 13H, 11ArH + 2HC=), 7.65-7.85 (m, 2H, ArH), 8.17 (br. s, 1H, ArH), 8.32 (br. d, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.3, 119.0, 124.3, 125.0, 125.2, 127.1 (2C), 128.5, 129.0 (3C), 129.1 (2C), 129.2 (2C), 129.5 (2C), 129.6, 129.7, 131.2, 134.0, 135.4, 136.9, 137.3, 138.3, 142.7, 145.3, 149.0, 155.6, 164.1, 172.1; HRMS (ESI) calcd. (found) for $C_{31}H_{21}N_2O_4$ ($[M+H]^+$): 485.1501 (485.1505).

2-(3,4-Dichlorophenyl)-6,10b-diphenylbenzo[*h*]isoquinoline-1,3(2*H*,10bH)-dione (3h): Pale-yellow solid, yield: 51 %; m.p.: 243-244 ºC; IR ($CHCl_3$, ν_{max}, cm^{-1}): 719, 741, 766, 824, 892, 1035, 1218, 1367, 1493, 1623, 1678, 1711, 2923, 3051; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.52 (s, 2H, ArH), 7.01 (d, 1H, *J* = 9.0 Hz, ArH), 7.20-7.50 (m, 14H, 12ArH + 2HC=); 7.53 (d, 1H, *J* = 9.0 Hz, ArH), 8.53 (d, 1H, *J* = 6.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.5, 118.2, 124.0, 126.7 (2C), 128.5 (2C), 128.6 (2C), 128.8 (2C), 128.9 (2C), 129.0 (2C), 129.1 (2C), 129.3 (2C), 131.25, 131.27, 133.6, 133.7, 134.5, 135.1, 138.2, 141.9, 146.9, 156.0, 164.1, 171.8; HRMS (ESI) calcd. (found) for $C_{31}H_{20}NO_2Cl_2$ ($[M+H]^+$): 508.0871 (508.0866).

2-(3-Bromophenyl)-6,10b-diphenylbenzo[*h*]isoquinoline-1,3(2*H*,10bH)-dione (3i): Pale-yellow solid, yield: 47 %, m.p.: 233-234 ºC; IR (KBr, ν_{max}, cm^{-1}): 703.1, 775.4, 1161.2,

1232.6, 1369.5, 1472.7, 1577.8, 1683.9, 1710.0, 1732.2, 3025.8, 3065.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.51 (s, 2H, ArH), 7.15-7.50 (m, 17H, 15ArH + 2HC=); 8.50-8.60 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.0, 118.0, 122.5, 123.6, 126.3 (2C), 127.5, 128.0, 128.2, 128.3, 128.5 (2C), 128.55 (2C), 128.58, 128.6, 128.8 (2C), 129.4, 129.6, 130.4, 131.9, 133.4, 134.8, 136.1, 137.9, 141.6, 146.4, 155.4, 163.9, 171.5; HRMS (ESI) calcd. (found) for $C_{31}H_{21}NO_2Br$ ($[M+H]^+$): 518.0750 (518.0752).

2-(3-Chlorophenyl)-6,10b-diphenylbenzo[*h*]isoquinoline-1,3(2H,10bH)-dione (3j): Pale-yellow solid, yield: 45 %, m.p.: 217-218 ºC; IR ($CHCl_3$, ν_{max}, cm^{-1}): 731.1, 777.4, 883.4, 1237.4, 1370.5, 1473.7, 1590.4, 1632.8, 1682.0, 1711.9, 3044.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.52 (s, 2H, ArH), 7.00-7.50 (m, 17H, 15ArH + 2HC=); 8.55 (d, 1H, *J* = 6.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.0, 118.0, 123.6, 126.3 (2C), 127.0, 128.0, 128.3, 128.4, 128.45 (2C), 128.53, 128.55 (2C), 128.6, 128.8, 128.9 (2C), 129.0, 129.1, 130.1, 133.4, 134.8, 134.9, 136.0, 137.9, 141.6, 146.4, 155.4, 163.8, 171.5; HRMS (ESI) calcd. (found) for $C_{31}H_{21}NO_2Cl$ ($[M+H]^+$): 474.1255, (474.1258).

2-(4-Chlorophenyl)-6,10b-diphenylbenzo[*h*]isoquinoline-1,3(2H,10bH)-dione (3k): Pale-yellow solid, yield: 38 %; m.p.: > 260 ºC; IR (KBr, ν_{max}, cm^{-1}): 700.5, 737.8, 766.7, 1089.8, 1227.7, 1370.5, 1490.1, 1561.4, 1683.9, 1727.3, 3031.1, 3062.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.52 (s, 2H, ArH), 7.20-7.45 (m, 17H, 15ArH + 2HC=); 8.50-8.60 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.0, 123.7, 126.1, 126.3, 126.5, 127.2, 128.2 (2C), 128.3, 128.45, 128.55, 128.57 (2C), 128.7, 128.8, 129.4, 129.5 (2C), 129.6, 130.0 (2C), 132.9, 133.9, 134.4, 134.6, 137.3, 139.7, 145.1, 155.3, 164.0, 169.9; HRMS (ESI) calcd. (found) for $C_{31}H_{21}NO_2Cl$ ($[M+H]^+$): 474.1255 (474.1264).

Computational methodology: A number of minima and saddle points were located on the potential energy surface to obtain equilibrium structures and transition states. The double-ended anharmonic downward distortion following (D-ADDF) methodology was used for search of the transition states [32-35]. The types of all the stationary points found were confirmed by harmonic frequency calculations. The accessibility of products and reactants from a given transition state was confirmed by IRC calculations. Gibb′s free energies were calculated at 273 K using energies and harmonic frequencies calculated in the previous step. Calculations were done at M11/cc-pVDZ (PCM = methanol) level of theory. The Gaussian 09 quantum chemistry software package [36] was used for all calculations except D-ADDF calculations for which we used our home-build code ReaNet.

Bioassay details: The human erythroleukemia K562 cell line was obtained from the Bank of Cell Cultures of the Institute of Cytology of Russian Academy of Sciences. Cells were cultured in RPMI-1640 medium (Thermo scientific, USA) with the addition of 10 % fetal calf serum (FCS) (Thermo-Scientific, USA) and 40 μg/mL gentamicin (Sigma, USA).

MTS assay: A colorimetric MTS assay was used for assessing cell metabolic activity. This method in based on the reduction of 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)--2-(4-sulfophenyl)-2*H*-tetrazolium compound (MTS) to coloured and soluble in cell culture media formazan product by NAD(P)H-dependent dehydrogenase enzymes. Since this conversion and such decrease of MTS can only occur in metabolically active cells, the level of activity is the measure of the viability of the cells. Shortly, cells were seeded in a 96-well microtiter plates at a density of 1×10^4 cells per well in 100 μL of complete medium and allowed to grow and adhere onto the wells during 24 h at 37 ºC. After that the cells were treated with various concentrations of the compounds for a period of 48 h. After the treatment, 20 μL of MTS reagent was added into each well and incubated at 37 ºC for 2 h. Finally the absorbance was recorded at 490 nm using 96 well plate reader "Multiskan GO" (Thermo Fisher Scientific, USA). For colored solutions the protocol was modified as followed: the absorbance was recorded directly before the addition of MTS reagent and measured values were further subtracted from final absorbance.

Statistical analysis: Significance of results was performed using Student T criterion. Statistical processing of results was performed using Origin Pro software. IC_{50} was calculated using Prism 6 for Windows. Differences between groups were considered significant at $p \leq 0.05$.

RESULTS AND DISCUSSION

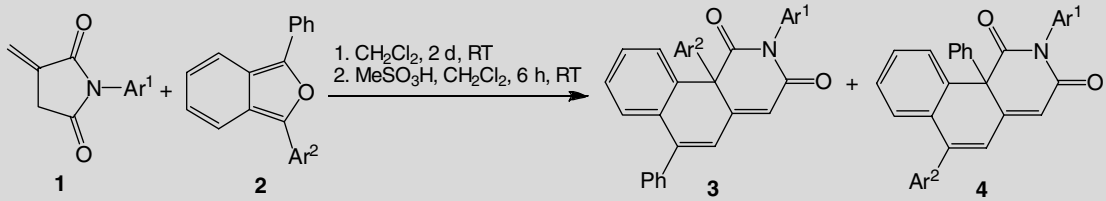
Recently, spirocyclic Diels-Alder adducts of 1,3-diphenylisobenzofuran and N-aryl itaconimides by treatment with strong acid undergo a cascade of cationic rearrangement reactions leading to compounds with benzo[*h*]isoquinoline skeleton [31]. In this paper, we present facile one-pot synthesis of desired benzo[*h*]isoquinolines in moderate to good yields and theoretical investigation of undergoing reactions including [1,2]-sigmatropic rearrangement. *In vitro* antitumor activity of synthesized derivatives against K562 cell line was also evaluated.

The reactions of N-aryl itaconimides (**1a-i**) with 1,3-diarylisobenzofurans **2** in dichloromethane at room temperature followed by addition of methansulfonic acid (6 equiv.) led to the formation of desired benzo[*h*]isoquinolines (**3a-m**) and (**4l-m**) in moderate to good yields. The results are summarized in Table-1. The main advantage of presented one-pot procedure is the yield enhancement up to two-fold (compared with two-step procedure) as well as source and time-saving.

It should be noticed that cycloaddition to unsymmetrically substituted isobenzofuran occurs unspecifically and lead to the chromatographically inseparable 1:1 mixture of benzo[*h*]-isoquinolines (Table-1, entries 12-13). Despite that it crystallizes from ethanol as 2:1 mixture as could be seen by X-ray diffraction analysis from 4-chlorphenyl substituent disorder: 70 % at position 10b benzo[*h*]isoquinoline structure (according to compound **3l**, marked as Cl2 at ORTEP representation) and 30 % at position 6 (compound **4l**, marked as Cl3 at ORTEP representation) (Fig. 1) [37]. Consecutive repeated recrystallization does not lead to further enrichment unfortunately.

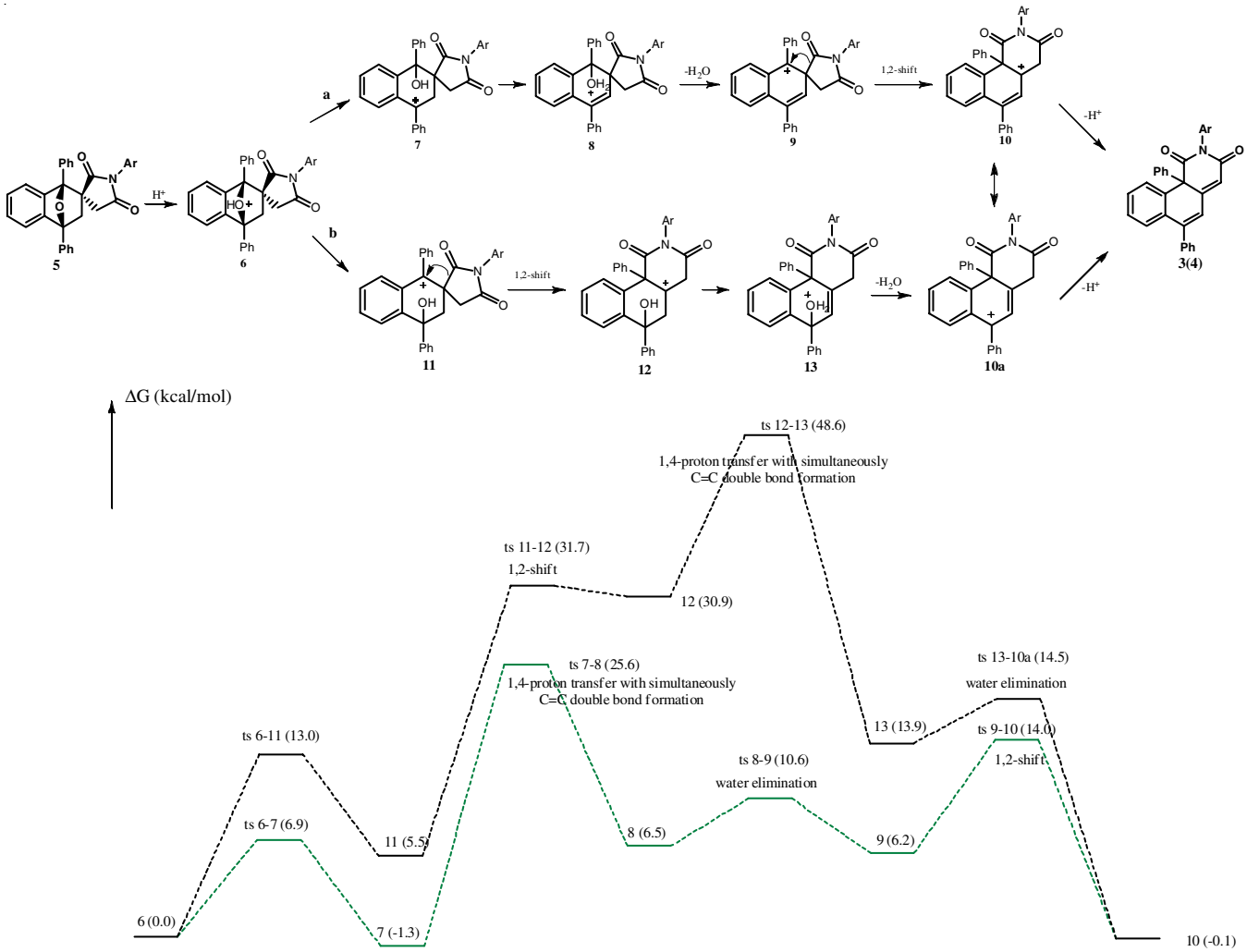
Computational investigation of the reaction mechanisms: Based on the above results, a plausible mechanism for the formation of compounds **3(4)** is proposed and proved by theoretical calculation at M11/cc-pVDZ level of theory (**Scheme-I**). The calculated Gibb′s free energy for the reagents, intermediates, transition states and possible products are given in **Scheme-I**. It was shown that [4+2]-cycloaddition of *N*-aryl itaconimides and 1,3-diphenylisobenzofurans proceeds stereoselectively with the formation of single diastereomer **5** as the

TABLE-1
ONE-POT SYNTHESIS OF SUBSTITUTED BENZO[*h*]ISOQUINOLINES (**3a-m**,**4l-m**)



Entry	Ar^1	Ar^2	Yield of products[a] (%)		Yield increasment
			One-pot	Two steps [b]	
1	4-MeC_6H_4	Ph	37 (**3a**)	20	1.85
2	4-$MeOC_6H_4$	Ph	41(**3b**)	23	1.78
3	4-FC_6H_4	Ph	52 (**3c**)	28	1.86
4	4-BrC_6H_4	Ph	47 (**3d**)	39	1.21
5	3,5-$Cl_2C_6H_3$		49 (**3e**)	41	1.20
6	3-F,4-ClC_6H_3	Ph	57 (**3f**)	33	1.73
7	3-$O_2NC_6H_4$	Ph	69 (**3g**)	53	1.30
8	3,4-$Cl_2C_6H_3$	Ph	51 (**3h**)	41	1.24
9	3-BrC_6H_4	Ph	47 (**3i**)	–	–
10	3-ClC_6H_4	Ph	45 (**3j**)	–	–
11	4-ClC_6H_4	Ph	38 (**3k**)	–	–
12	3-ClC_6H_4	4-ClC_6H_4	48 (**3l+4l**)[c]	–	–
13	3,5-$Cl_2C_6H_3$	4-ClC_6H_4	53 (**3m+4m**)[c]	–	–

[a]Isolated yield. [b]Calculated, based on our previously published results [Ref. 31]. [c]Chromatographically inseparable mixture.



Scheme-I: Calculated reaction mechanism for the formation of **3**(**4**) and Gibbs free energies of the reagents, intermediates, transition states and products. All energies are given in kcal/mol

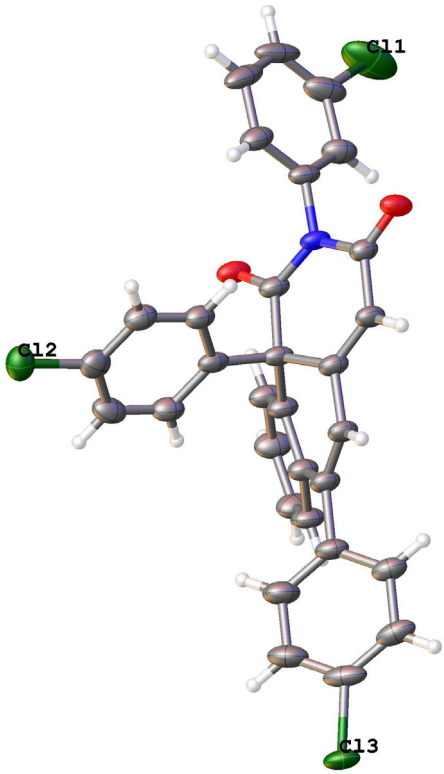


Fig. 1. ORTEP representation of co-crystallized **3l** and **4l** mixture

result of exo-orientation of reactants in the transition state [38]. The rearrangement of cycloadduct **5** starts with the formation of cation **6**. That further could transform *via* either the formation of intermediate alkenol **7** (pathway "a") or the formation of intermediate alkenol **11** (pathway "b"). Intermediate **7**, under acidic conditions, undergoes subsequent conversion into cation **9**. Followed 1,2-shift lead to intermediate **10**, which is converted into product **3(4)**. Intermediate **11** in his turn undergoes 1,2-shift to cation **12** firstly followed by subsequent conversion into cation **10a**, which is also converted into product **3(4)**. It should be noticed that the transformation of cation **7** to **8** as well as cation **12** to **13** proceeds as intramolecular 1,4-proton transfer with simultaneous C=C double bond formation. It is obvious from the calculations that pathway "a" (highlighted in green colour) is preferable: the excess of energy of 26.9 kcal/mol is satisfactory to reaction flow, while pathway "b" needs extra 17.7 kcal/mol.

Evaluation of cytotoxic activity: The antitumor activity of obtained compounds against human leukemia K562 cell line was evaluated *in vitro* by MTS assay. The results of these investigations are shown in Fig. 2. It was found that the most potent compound is **3i** bearing 3-bromophenyl substituent on benzo[*h*]isoquinoline moiety and its half maximal inhibitory concentration (IC_{50}) is 35.61± 0.06 μg/mL.

Conclusion

In conclusion, a facile source and time-saving synthetic method for construction of benzo[*h*]isoquinoline scaffold by one-pot synthesis from *N*-aryl itaconimides and 1,3-diarylisobenzofuran *via* strong acid induced cascade of cationic rearrangement reactions is developed. The reaction mechanism has been studied at M11/cc-pVDZ level of theory. It was found that

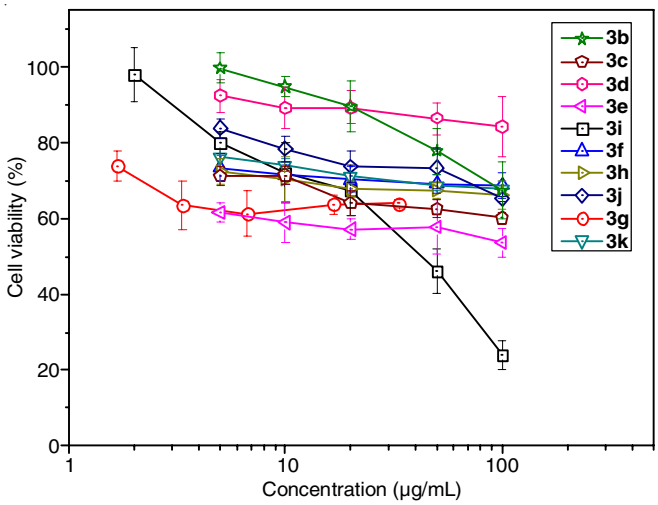


Fig. 2. Cytotoxicity of synthesized compounds against human leukemia K562 cell line

the formation of desired products proceeds through cascade of cationic rearrangement reactions including [1,2]-sigmatropic rearrangement (1,2-carbonyl migration) with ring expansion. Additionally, the antitumor activity of synthesized compounds was evaluated by MTS assay *in vitro* against human leukemia K562 cell line.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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