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A new synthesis of the linearly fused [1,2,4]triazolo[1,5-*b*]isoquinoline ring. Observation of an unexpected Dimroth rearrangement

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Dedicated to Professor Csaba Szántay on the occasion of his 80th birthday

Abstract

A new and general synthesis of the linearly fused [1,2,4]triazolo[1,5-*b*]isoquinoline ring system starting from 2,3-diaminoisoquinolinium salts has been elaborated. Starting compounds bearing an alkyl group in position 4 easily reacted with aldehydes to yield the cyclized products. In the case of a lack of electron donating group in position 4 (e.g., unsubstituted or 4-cyano substituted diamino derivatives) a Dimroth rearrangement took place under the same reaction conditions to yield 3-isoquinolylhydrazones. The mechanism of this unexpected transformation has been verified by isotope labelling experiments. Clarification of the reaction mechanism allowed finding proper reaction conditions to eliminate the rearrangement route, and thus, to perfect successful ring closure to the fused triazoles.

Keywords: Triazole; Hydrazone; Dimroth rearrangement; ^{15}N labelling

1. Introduction

In our earlier publications we have described a relatively facile access to fused [1,2,4]triazoles.[1] These compounds were obtained by treatment of 1,2-diaminopyridinium salts with various aldehydes in the presence of a base. During this transformation, a ring closure occurred followed by spontaneous oxidation of the primarily formed intermediate to give the heteroaromatic end product. This procedure allowed the synthesis of a set of [1,2,4]triazolo[1,5-*a*]pyridines and its angularly fused benzologues: [1,2,4]triazolo[1,5-*a*]quinolines and [1,2,4]triazolo[5,1-*a*]isoquinolines.

Based on some recent records on the valuable biological activity of some related fused [1,2,4]triazoles,[2] continuation of this synthetic activity seemed of interest and extension of the established procedure to the hitherto scarcely studied linearly fused benzologue of triazolopyridine: triazolo[1,5-*b*]isoquinoline has been decided. Literature survey revealed that only two derivatives of this tricyclic ring system obtained by a different approach have been reported earlier.[3]

2. Results and discussion

For the synthesis of the desired linearly fused triazoles, application of our earlier established protocol seemed the most straightforward procedure. Thus, 2,3-diaminoisoquinolinium salts (**2**) have been synthesized by direct N-amination of some substituted 3-aminoisoquinolines (**1**)[4] by *O*-tosyl-hydroxylamine (TSH)[5,6] (Scheme 1) and these compounds were reacted with aldehydes.

Thus, experiments for ring closure starting from the 4-substituted diaminium salts **2b–d** yielded the expected

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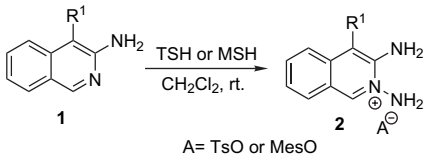


2	R^1	Yield (%)
a	H	85
b	CH_3	48
c	C_2H_5	66
d	CH_2Ph	72
e	CN	21

Scheme 1.

[1,2,4]triazoles **3a–j** in good yields. When, however, the 4-unsubstituted **2a** was treated under the same reaction conditions with various aldehydes, an unexpected product: the hydrazones **4a–d** were formed (Scheme 2).

The firm proof of the constitution of this hydrazone was provided by X-ray crystal structure determination (Fig. 1).

A two-fold rotation axis at {0,y,1/4} arranges two **4c** molecules into a dimeric assembly. Thus, the crystal structure displays only one symmetric pair of stronger intermolecular contacts, namely a *H*-bridge with donor—H···acceptor atoms of N(1′)—H(1N)···N(2) [−x,y,1/2−z]. The *H*-bridge donor–acceptor geometry is characterized by D–H=0.90 Å, H···A=2.18 Å, D···A=3.0735(14) Å and D–H···A=171°. No other productive contacts are visible within van der Waals radii sum, and the N2′ atom apparently does not play role in maintaining the crystal structure. Apart from two approaches that might perhaps be taken as indicative for weak C–H···π most other contacts appear to be weakly repulsive.

Although, upon the crystallographic analysis there was no doubt about the structure of **4c**,[8] preparative evidence has also been found in the case of one of the derivatives. Thus, 3-hydrazinoisoquinoline-*N*-oxide[9] (**5**) was reacted with 4-methylbenzaldehyde to yield the hydrazone-*N*-oxide **6**, which could be successfully reduced by elemental indium[10] to **4a** in acceptable

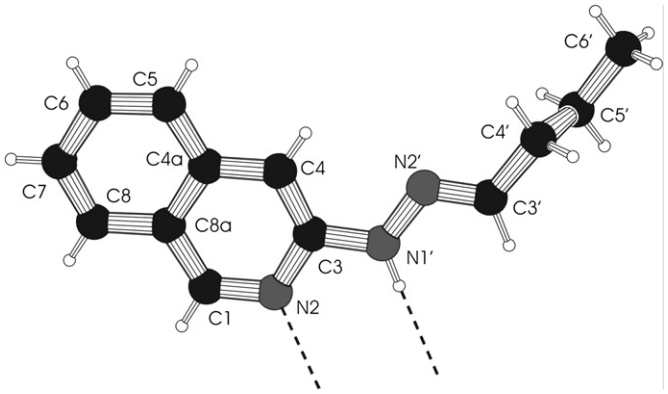
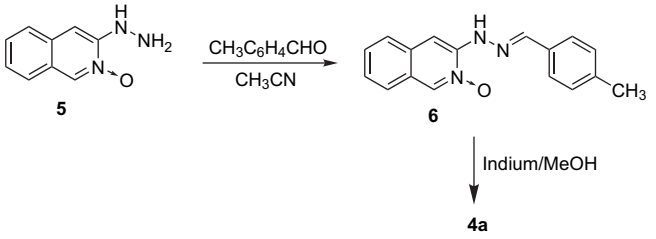


Figure 1. Molecular structure representation[7] of compound **4c** with the *H*-bridge attachments indicated by broken lines.

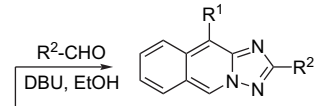
yield (Scheme 3). Physical data (mp, NMR, IR) of this product and those of the compound obtained as a result of the above mentioned route starting from **2** proved to be entirely identical.



Scheme 3.

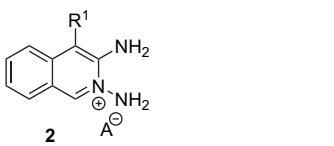
Formation of the hydrazone **4** could be rationalized in two ways (Fig. 2):

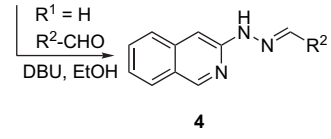
(i) Although many results were in agreement with our earlier structural assignment for **2**,[4] we now had to



3	R^1	R^2	Yield (%)
a	CH_3	4-CH_3-C_6H_4	55
b	CH_3	Ph	58
c	CH_3	C_3H_7	47
d	C_2H_5	4-CH_3-C_6H_4	42
e	C_2H_5	Ph	43
f	C_2H_5	CH_3	39

3	R^1	R^2	Yield (%)
g	CH_2Ph	4-CH_3-C_6H_4	61
h	CH_2Ph	Ph	60
i	CH_2Ph	C_3H_7	56
j	CH_2Ph	CH_3	37





4	R^2	Yield (%)
a	4-CH_3-C_6H_4	35
b	Ph	51
c	C_3H_7	36
d	CH_3	49

Scheme 2.

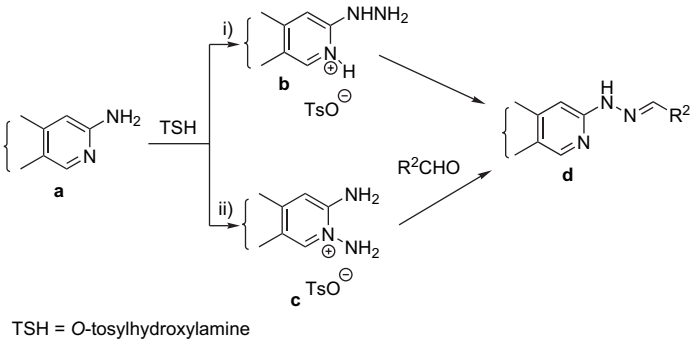


Figure 2. Alternative mechanisms for the formation of hydrazones (**d**) from amines (**a**).

question the exact structure of this compound, and had to consider that in the course of the N-amination of **1** it might be the *exo*-amino group that participates in the conversion to yield a hydrazine (i.e., in Fig. 2, amination of **a** would give **b** rather than **c**). In this case formation of a hydrazone (**d**) would be trivial.

(ii) An alternative mechanism would be formation of an *N*-amino salt (**c**) as originally assumed. This compound can undergo a ring transformation reaction during which the ring-nitrogen atom of the isoquinoline ring and the nitrogen atom of the amino group attached to position 3 would be exchanged to give the product (**d**). Such a conversion could be a Dimroth-type rearrangement[11] taking place via temporary ring opening of the pyridine moiety followed by a repeated ring closure.

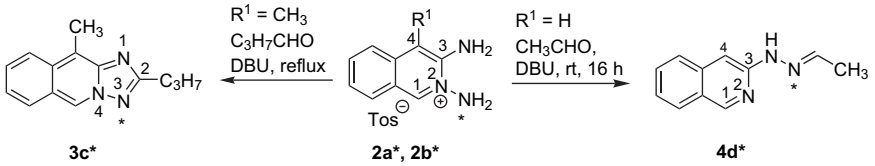
By the help of detailed NMR investigations, the structure of **2** could be verified unambiguously. For two selected derivatives (**2a** and **2b**), three nitrogen atoms have been observed at natural abundance by running $^{1}H-^{15}N$ correlation measurements. The amine nitrogen atoms in **2a** were identified by the H4–(C3)N2′ and H1–(N2)N1′ crosspeaks of the $^{1}H-^{15}N$ gHMQC spectrum (−324.5 and −306.0 ppm), while N2 appeared at −211.2 ppm, showing correlation to H4 and N2′H_2 protons (Scheme 4). Similar nitrogen shifts have been found for **2b** (−325.3, −304.8 and −212.0 ppm). Simultaneously, the amine nitrogen atoms were verified from the $^{1}H-^{15}N$ gHSQC experiment according to their direct NH couplings.

In order to prove the fact of selective amination of the isoquinoline ring nitrogen atom followed by a subsequent transformation to hydrazone **4** (i.e., **a**→**c**→**d** pathway, Fig 2) ^{15}N stable-isotope labelling was introduced. The ^{15}N labelled derivatives **2a*** and **2b*** have been prepared by reaction of **1a** and **1b** with ^{15}N labelled *O*-tosylhydroxylamine[4] (prepared from commercially available ^{15}N-hydroxylamine of 20% isotope excess). In the directly detected ^{15}N spectrum of **2a*** and **2b*** only signals of the N1′ amine nitrogen atoms (−306.0 and −304.8 ppm, respectively) appeared. Accordingly, structure **b** in Figure 2 can be ruled out.

Both **2a*** and **2b*** were then subjected to the above described reactions with aldehydes. The observed nitrogen chemical shifts of compound **4d** are indicative of the hydrazone structure. Selective labelling in compounds **3c*** and **4d*** was assessed by comparing the crosspeak intensities of the $^{1}H-^{15}N$ HMQC spectra with those of the corresponding unlabelled derivatives. Accordingly, labelled nitrogen atoms were found at −134.1 ppm in **3c*** and at −81.0 ppm in **4d***. Contrary to the triazole product **3c***, where the labelled nitrogen retains its original position, the hydrazone **4d*** contains the ^{15}N label in the side chain (N2′) (Scheme 4).

The proposed reaction mechanism is shown in Figure 3. Thus, the first step is the condensation reaction of **c** and an aldehyde to form an azomethinimine side chain (**e**), and this species would be attacked by a nucleophile to give the second intermediate (**f**). The role of the nucleophile can be fulfilled either by the solvent (alcohol, water) or another molecule of **c** bearing a basic nitrogen atom. In this stage of the events, an electrocyclic ring opening—with participation of three electron pairs as shown by the arrows—can occur to afford a ring-opened species (**g**), which can undergo a 180° turn along the bond between the two non-cyclic carbon atoms. The result of this motion is shown by the tautomeric form **h**. Finally, a subsequent electrocyclization to **i** and elimination of the protonated form of the nucleophile yields the hydrazone **d**.

This mechanism seemed to be in entire accordance with the result of the above mentioned isotope labelling since the *N*-amino nitrogen atom will move to the hydrazone-nitrogen position in the course of the reaction sequence. There is, however, another possibility for the change of these nitrogen atoms: if in intermediate **e** an N–N cleavage would happen and the resulting azomethine fragment would participate in



Scheme 4.

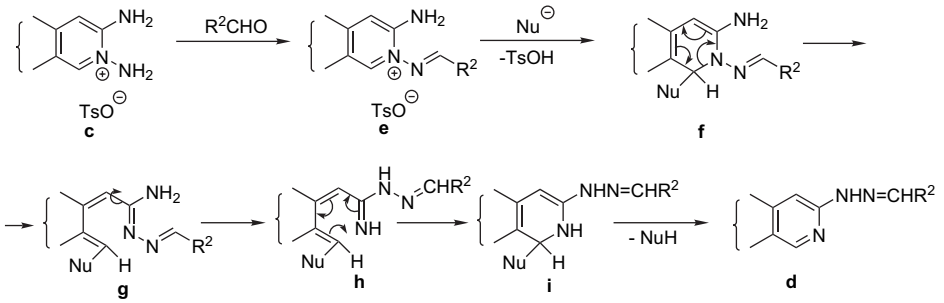
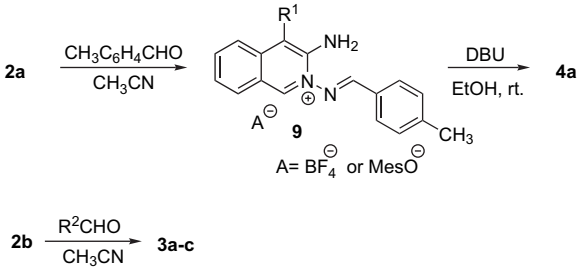


Figure 3. Proposed mechanism of the Dimroth rearrangement to isoquinolylhydrazones.

a [1,3] sigmatropic rearrangement, this would also result in the same product (**d**) and the *N*-amino nitrogen atom would get to the same position as it did in the Dimroth-type rearrangement.

In order to check this, another ^{15}N-labelled derivative containing the isotope N-atom in the 3-amino group (**1a**$^{\#}$) have been synthesized. The synthesis is outlined in Scheme 5. The location of the applied ^{15}N isotope label throughout this reaction pathway was followed by ^{1}H–^{15}N HMQC measurements. First 3-isoquinolyl triflate **7**[12] was subjected to a palladium catalyzed amination[13] by using ^{15}N-labelled formamide to yield 3-formamidoisoquinoline (**8**). The formyl group was removed by aqueous acidic hydrolysis to give 3-aminoisoquinoline (**1a**$^{\#}$; the labelled nitrogen at −334.5 ppm), which gave, upon N-amination, the labelled diamino salt **2a**$^{\#}$ (−322.0 ppm). Reaction of **2a**$^{\#}$ with 4-methylbenzaldehyde yielded the hydrazone **4a**$^{\#}$ (−116.8 ppm) in which the ^{15}N atom was found in the ring-nitrogen position. This finding, i.e., change of the position of the isotopic label, is in clear accordance with the proposed Dimroth-route, because in a sigmatropic transformation the position of the ^{15}N atom would not have changed.

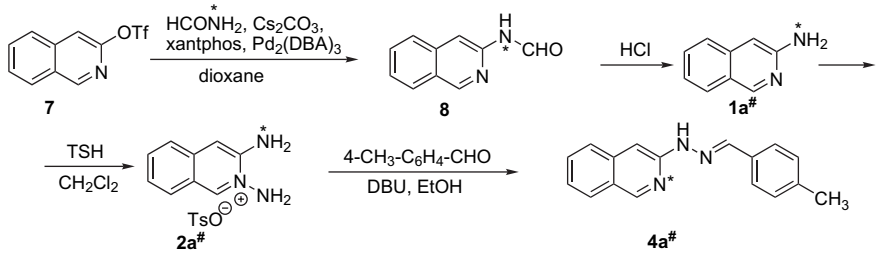
It is important to note that, in principle, the above discussed ring opening can also occur in an earlier stage of the reaction pathway and, thus, the diaminoisoquinolinium salt (Fig. 3, **c**) could also be subjected to this transformation. In this case, the condensation with the aldehyde would be the last step. In order to check this possibility **2a** was reacted with the aldehyde in the absence of base (i.e., in acetonitrile) in order to make difficulties for the rearrangement route. After a 5 h reflux the supposed intermediate **9** was obtained in considerable yield. Furthermore, treatment of this compound with DBU in ethanol afforded **4a** (Scheme 6). This finding reveals that the azomethine salt **9** is most probably an intermediate along the rearrangement of **2a** to **4a**.



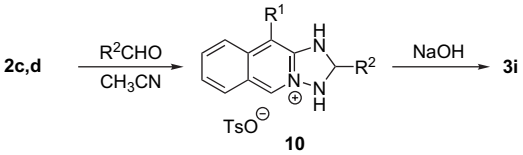
Scheme 6.

The successful isolation of the intermediate **9** raised the question if similar intermediates are also formed along the pathway to **3** starting from **2b–d**. Interestingly, reactions of **2b–d** with some selected aldehydes did not lead to isolation of the intermediates related to **9**. Instead, **2b** yielded the triazoles **3a–c**, whereas reaction of two other diaminoisoquinolinium salts (**2c**,**d**) allowed the isolation of another intermediate dihydrotriazolium salt **10e** in the form of a solid of very low solubility (Scheme 7). Intermediate **10e** when treated with a base easily underwent oxidation to the triazole (**3h**). The fact that intermediate **9**, which was obviously also formed along the reaction pathway, could not be isolated suggests that in these cases the cyclization to the dihydrotriazole is very fast. Furthermore, the interesting difference observed between **2b** and **2c**,**d** might be due to the bad solubility of the isolated **10a–f**.

All these findings suggested that the triazole synthesis might also be carried out with **2a** if any nucleophilic attack leading to ring transformation can be excluded. This supposition proved to be true: treatment of **2a** with some aldehydes in acetonitrile in the presence of molecular sieves[21] (in order to remove traces of the nucleophilic water) gave rise to the triazoles **3k**,**l**,**m** (Scheme 8) being unsubstituted in position 10 (i.e., in position 4 of the isoquinoline moiety).

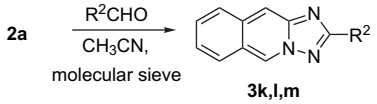


Scheme 5.



10	R^1	R^2	Y (%)
a	C_2H_5	4-CH_3-C_6H_4	90
b	C_2H_5	Ph	89
c	C_2H_5	C_3H_7	89
d	CH_2Ph	4-CH_3-C_6H_4	78
e	CH_2Ph	Ph	88
f	CH_2Ph	C_3H_7	53

Scheme 7.



3	R^2	Yield (%)
k	4-$CH_3C_6H_4$	54
l	Ph	47
m	C_3H_7	35

Scheme 8.

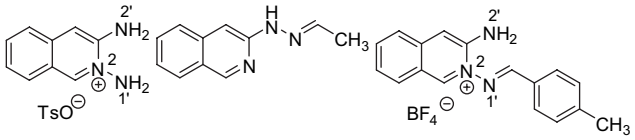
Nitrogen shifts, indicative of the different structures, are summerized in Table 1. The resonances of the amines (N-1′, N-2′ in **2a**, N-2′ in **9**, N-1, N-3 in **10d**) occur at relatively low frequencies. The amine type sp^3 N-atom in the hydrazone (N-1′ in **4d**) is shifted downfield about 50 ppm owing to the partial delocalization of the electron lone pair into the double bond system. The chemical shifts of the isoquinoline ring-nitrogen atoms lie between −120 and −220 ppm. The most deshielded nitrogen atoms appear in the C=N bond of the hydrazones (N-2′ in **4d** and N-1′ in **9**).

These results indicate that the outstanding behaviour of **2a** in comparison to **2b–d**, i.e., the fact that this compound undergoes Dimroth rearrangement rather than yielding triazoles, may well be due to the relatively enhanced positive charge and sensitivity towards nucleophilic attack in position 1 of the isoquinoline ring. This suggestion was satisfactorily supported by transformation of 2,3-diamino-4-cyanoisoquinolinium mesitylate (**2e**) where, because of the strongly electron withdrawing cyano group, an even higher preference for the rearrangement was experienced. Thus, while formation **4a** from **2a** took place in 24 h in 35% yield only, the corresponding cyano derivative **4e** was obtained from **2e** in 5 h in high (83%) yield (Scheme 9).

3. Conclusion

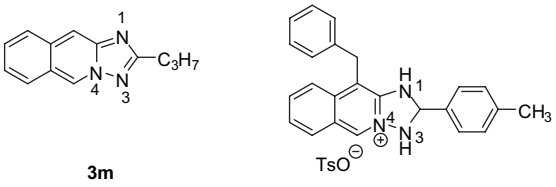
From the investigations described in this paper one can conclude that reaction of 2,3-diaminoisoquinolinium salts with aldehydes can follow two different pathways. In the case of isoquinolinium derivatives containing electron donating groups in position 4, ring closure to new linearly fused triazoloisoquinolines take place, whereas in other cases, due to the sensitivity of position 1 against nucleophiles, a Dimroth rearrangement occurs to yield new isoquinolylhydrazones. Clarification of the reaction mechanism of this unexpected rearrangement by the help of N-labelling also allowed finding proper reaction conditions to direct the reaction pathway to the originally intended triazole-formation route.

Table 1
^{15}N chemical shifts (ppm) of compound **2a**, **4d**, **9**, **3m** and **10d**



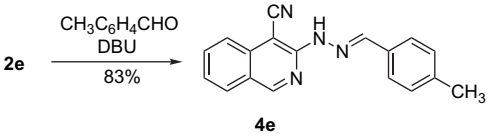
2a **4d** **9**

N-2	−211.2	−125.0	−186.5
N-1′	−306.0	−253.0	−91.2
N-2′	−324.5	−81.0	−323.5



3m **10d**

N-1	−179.3	−310.6
N-3	−134.1	−276.0
N-4	−154.6	−191.3



Scheme 9.

4. Experimental part

4.1. General methods

Melting points were determined by a Büchi apparatus and are uncorrected. The IR spectra were recorded on a Thermo Nicolet Avatar 320 FTIR spectrometer. Experiments were performed on Varian INOVA-200 or Varian INOVA-400 spectrometers equipped with a 5 mm inverse detection z-gradient probe. ^1H and ^{13}C NMR spectra were measured at rt (25 °C) in an appropriate solvent. ^1H and ^{13}C chemical shifts are

expressed in parts per million (δ) referenced to residual solvent signals, ^{15}N chemical shifts to the neat nitromethane. J values are given in hertz. The complete signal assignment was performed by running 2D heteronuclear ($^{1}H-^{13}C$ and $^{1}H-^{15}N$) gHSQC and gHMQC measurements. The pulse programs were taken from the Varian software library. The elemental analysis has been carried out with an Elementar Vario EL III apparatus. Chromatographic separations were carried out on Merck Kieselgel 60 (230–400 mesh). Reactions were monitored with Merck Kieselgel 60 F_{254}-precoated TLC plates (0.25 mm thickness). All the chemicals and solvents were used as supplied.

Syntheses of isoquinolin-3-amine (**1a**),[18] 4-methylisoquinolin-3-amine (**1b**),[19] 3-aminoisoquinoline-4-carbonitrile,[20] 2,3-diamino-isoquinolinium 4-methylbenzenesulfonate (**2a**)[4] and 2,3-diamino-4-methylisoquinolinium 4-methylbenzenesulfonate (**2b**)[4] have been published earlier. Novel derivatives (i.e., **1c**, **1d**, **2c**, **2d**) have been prepared according to these literature procedures.

4.2. General procedure for substituted 3-amino-isoquinolines

A mixture of 1-bromo-4-ethylisoquinolin-3-amine (0.27 mol), DMF (450 mL), TEA (40 mL) and palladium-charcoal catalyst (10%, 2 g) was subjected to catalytic hydrogenation under normal pressure for 4 h. The reaction mixture was filtered, the filtrate was evaporated to one fifth of the original volume, and the residue was poured onto ice-water (500 mL). The precipitated crystals were filtered off and recrystallized from toluene.

4.2.1. 4-Ethylisoquinolin-3-amine (*1c*)

This compound was obtained from 1-bromo-4-ethylisoquinolin-3-amine (67.8 g, 0.27 mol) to give the *title compound* **1c** (23.7 g, 51%) as orange crystals, mp 108–110 °C. IR (KBr) ν_{max}: 3477, 3304, 3168, 2963, 1633, 1580, 1377, 759 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.8 (1H, s, H1), 7.8 (2H, m, H5+H8), 7.57 (1H, t, J=8 Hz, H6), 7.21 (1H, t, J=8 Hz, H7), 4.5 (2H, br s, NH_2), 2.9 (2H, m, CH_2), 1.2 (3H, m, CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 12.8 (*C*H_3), 19.5 (*C*H_2), 111.2 (C4), 121.4 (C5), 122.6 (C6), 124.6 (C8a), 128.7 (C7), 130.4 (C8), 136.7 (C4a), 149.8 (C1), 151.9 (C3). Anal. Calcd for $C_{11}H_{12}N_2$ (172.23): C, 76.71; H, 7.02; N, 16.27. Found: C, 76.37; H, 6.87; N, 16.31.

4.2.2. 4-Benzylisoquinolin-3-amine (*1d*)

This compound was obtained from 4-benzyl-1-bromoisoquinolin-3-amine (84.5 g, 0.27 mol) to give the *title compound* **1d** (41.4 g, 72%) as orange crystals, 112–120 °C. IR (KBr) ν_{max}: 3373, 3330, 3187, 2677, 1623, 1584, 1460, 1452, 750, 733 cm^{-1}. ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 8.8 (1H, s, H1), 7.82 (1H, m, H8), 7.73 (2H, m, H5+H6), 7.40 (1H, t, H7), 7.10 (5H, m, Ph), 5.8 (2H, br s, NH_2), 4.2 (2H, s, CH_2). ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 31.1, 106.2, 122.0, 122.0, 123.7, 126.4, 128.8 (2C), 128.9 (2C), 129.0, 130.9, 137.6, 141.0, 150.8, 155.0. Anal. Calcd for $C_{16}H_{14}N_2$ (243.3): C, 82.02; H, 6.02; N, 11.96. Found: C, 82.00; H, 6.31; N, 12.02.

4.3. General procedure for N-amination of substituted 3-amino-isoquinolines

A solution of isoquinoline-3-amines (10 mmol) in CH_2Cl_2 was added to a solution of TSH reagent (15 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was stirred at rt for 1 h. The deposited yellow crystals were filtered off, and washed with ether. The product was recrystallized from 2-propanol.

4.3.1. 2,3-Diamino-4-ethylisoquinolinium 4-methylbenzenesulfonate (*2c*)

This compound was obtained from 4-ethylisoquinolin-3-amine (**1c**, 1.72 g, 10 mmol) to give the *title compound* **2c** (2.37 g, 66%) as yellow crystals, mp 133–137 °C. IR (KBr) ν_{max}: 3230, 3129, 2972, 1649, 1195, 1121, 1034, 1011, 814, 681, 597 cm^{-1}. ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 9.18 (1H, s, H1), 7.9 (1H, d, J=8.4 Hz, H8), 7.82 (1H, d, J=8.9 Hz, H5), 7.7 (1H, t, J=8.9 Hz, H6), 7.48 (2H, br s, C3–NH_2), 7.42 (2H, m, H3+H5(anion)), 7.32 (3H, m, H2+H6(anion)+H7), 2.9 (2H, q, J=7.0 Hz, CH_2), 2.2 (3H, s, CH_3(anion)), 1.05 (3H, t, J=7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 15.1, 20.8, 30.4, 114.3, 120.0, 122.2, 125.3, 125.5 (2C), 128.1 (2C), 128.5, 129.0, 134.7, 137.6, 138.2, 142.9, 148.3. Anal. Calcd for $C_{18}H_{21}N_3O_3S$ (359.44): C, 60.15; H, 5.89; N, 11.69; S, 8.92. Found: C, 60.03; H, 6.10; N, 11.44; S, 8.92.

4.3.2. 2,3-Diamino-4-benzylisoquinolinium 4-methylbenzenesulfonate (*2d*)

This compound was obtained from 4-benzylisoquinolin-3-amine (**1d**, 2.13 g, 10 mmol) to give the *title compound* **2d** (3.04 g, 72%) as yellow crystals, mp 200–206 °C. IR (KBr) ν_{max}: 3415, 3210, 3113, 1644, 1507, 1202, 1121, 1035, 1011, 684, 569 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 9.3 (1H, s, H1), 8.0 (1H, d, J=8.4 Hz, H8), 7.82 (1H, d, J=8 Hz, H5), 7.7 (1H, t, H6), 7.6 (2H, br s, C3–NH_2), 7.46 (2H, m, H3+H5(anion)), 7.4 (2H, br s, N–NH_2), 7.38 (1H, t, H7), 7.2 (2H, m, H2′+H6′), 7.15 (3H, m, H3′+H4′+H5′), 7.05 (2H, m, H2+H6(anion)), 4.4 (2H, s, CH'_2), 2.22 (3H, s, CH_3(anion)). ^{13}C NMR (DMSO-d_6) δ (ppm): 21.4 (*C*H_3 (anion)), 31.1 (*C*H_2′), 115.0 (C4), 120.7 (C1 (anion)), 122.9 (C5), 126.0 (C6), 126.1 (C3+C5 (anion)), 127.1(C7), 128.7 (C2+C6 (anion)), 128.8 (C2′+C6′), 129.2 (C3′+C5′), 129.7 (C4′), 135.4 (C8), 138.2 (C8a), 138.3 (C4a), 138.8 (C1′), 143.6 (C1), 146.3 (C4 (anion)), 149.0 (C3). Anal. Calcd for $C_{23}H_{23}N_3O_3S$ (421.51): C, 65.54; H, 5.50; N, 9.97. Found: C, 65.41; H, 5.39; N, 9.93.

4.3.3. 2,3-Diamino-4-cyanoisoquinolinium 2,4,6-trimethylbenzenesulfonate (*2e*)

The solution of 3-aminoisoquinoline-4-carbonitrile (**1e**, 0.563 g, 3.3 mmol) in CH_2Cl_2 was added to the solution of MSH reagent (1.419 g, 6.6 mmol) in CH_2Cl_2 (40 mL) at

0 °C. The reaction mixture was stirred at rt for 4.5 h. The deposited yellow crystals were filtered off, and washed with ether. The product was recrystallized from MeOH four times to give the *title compound* **2e** (0.267 g, 21%) as yellow crystals, mp 231–234 °C. IR (KBr) ν_{max}: 3308, 3141, 2219, 1662, 1161, 1086, 1012, 682 cm^{-1}. ^1H NMR (CD_3OD) δ (ppm): 2.18 (3H, s, CH_3(anion)); 2.56 (6H, s, 2×CH_3-(anion)), 6.78 (2H, s, H3′+H5′(anion)), 7.57 (1H, dd, J=7.9+7.3 Hz, H7), 7.87 (1H, d, J=8.7 Hz, H5), 8.01 (1H, dd, J=8.7+7.3 Hz, H6), 8.05 (1H, d, J=7.9 Hz, H8), 9.42 (1H, s, H1). ^{13}C NMR (CD_3OD) δ (ppm): 23.6, 26.0 (2C), 91.3, 116.6, 124.0, 125.9, 130.9, 131.6, 134.2, 134.4 (2C), 142.8, 142.9 (2C), 143.4, 144.4, 155.4, 155.6. For elemental analysis this compound was converted to perchlorate salt. Anal. Calcd for $C_{10}H_9ClN_4O_4$ (284.66): C, 42.19; H, 3.19; N, 19.68. Found: C, 41.88; H, 3.50; N, 19.56.

4.4. General procedure for preparation of [1,2,4]triazolo[1,5-b]isoquinolines (*3a–m*)

Method A: To the solution of **2b–d** (2 mmol) and aldehyde (20 mmol) in EtOH (30 mL) DBU (1.4 mL) was added, and the mixture was stirred at rt. The progress of the reaction was monitored by TLC. After disappearance of the starting material the reaction mixture was evaporated, water (50 mL) was added and the mixture was extracted with chloroform. The organic layer was dried over Na_2SO_4, and evaporated. The residue was flash chromatographed over silica, by using hexane–EtOAc 4:1 as eluent. The product was recrystallized from EtOAc.

Method B: To the solution of **2a** (0.993 g, 3 mmol) and aldehyde (30 mmol) in abs acetonitrile (40 mL) was added molecular sieves (3.0 g, FLUKA, UOP type, 4 Å) and the mixture was stirred at rt overnight. The progress of the reaction was monitored by TLC. The reaction mixture was filtered and evaporated, the residue was flash chromatographed over silica by using hexane–EtOAc 4:1 as eluent. The product was recrystallized from EtOAc.

4.4.1. 10-Methyl-2-p-tolyl-[1,2,4]triazolo[1,5-b]-isoquinoline (*3a*)

This compound was prepared by Method A from **2b** (0.690 g, 2 mmol) and 4-methylbenzaldehyde (2.4 g, 20 mmol) to give the *title compound* **3a** (0.300 g, 55%) as light yellow crystals, mp 218–220 °C. IR (KBr) ν_{max}: 3065, 3021, 2920, 1611, 1444, 1394, 1290, 1249, 1178, 768 cm^{-1}. ^1H NMR (DMSO-d_6+$CDCl_3$) δ (ppm): 9.74 (1H, s, H5), 8.22 (2H, m, H2′+H6′), 8.02 (2H, m, H6+H9), 7.60 (1H, t, J=8.0 Hz, H8), 7.42 (1H, t, J=7.5 Hz, H7), 7.38 (2H, m, H3′+H5′), 3.0 (3H, s, CH_3), 2.40 (3H, s, CH_3'). ^{13}C NMR (DMSO-d_6+$CDCl_3$) δ (ppm): 13.3, 21.8, 118.8, 122.8, 123.8, 125.5, 125.8, 127.6 (2C), 127.8, 128.7, 128.9, 130.0 (2C), 131.2, 140.6, 150.6, 165.1. Anal. Calcd for $C_{18}H_{15}N_3$ (273.33): C, 79.10; H, 5.33; N, 15.37. Found: C, 78.70; H, 5.51; N, 15.32.

4.4.2. 10-Methyl-2-phenyl-[1,2,4]triazolo[1,5-b]-isoquinoline (*3b*)

This compound was prepared by Method A from **2b** (0.690 g, 2 mmol) and benzaldehyde (2.12 g, 20 mmol) to give the *title compound* **3b** (0.303 g, 58%) as light yellow crystals, mp 196–199 °C. IR (KBr) ν_{max}: 3063, 1630, 1610, 1460, 1439, 1393, 1286, 1250, 714 cm^{-1}. ^1H NMR (DMSO-d_6) δ (ppm): 9.8 (1H, s, H5), 8.38 (2H, m, H2′+H6′), 8.06 (2H, m, H6+H9), 7.40–7.65 (5H, m, H3′+H4′+H5′+H7+H8), 2.98 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6) δ (ppm): 13.4, 119.1, 122.9, 124.0, 125.9, 126.1, 127.7, 127.9 (2C), 129.0, 129.6 (2C), 131.1, 131.3, 131.6, 150.6, 165.0. Anal. Calcd for $C_{17}H_{13}N_3$ (259.31): C, 78.74; H, 5.05; N, 16.20. Found: C, 78.45; H, 5.01; N, 16.18.

4.4.3. 10-Methyl-2-propyl-[1,2,4]triazolo[1,5-b]-isoquinoline (*3c*)

This compound was prepared by Method A from **2b** (0.690 g, 2 mmol) and butyraldehyde (1.44 g, 20 mmol) to give the *title compound* **3c** (0.210 g, 47%) as light yellow crystals, mp 108–110 °C. IR (KBr) ν_{max}: 3063, 2962, 2929, 2872, 1609, 1480, 1468, 1392, 1258, 743 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 9.62 (1H, s, H5), 7.98 (1H, dd, J=8+2.5 Hz, H6), 7.96 (1H, dd, J=8.2+3 Hz, H9), 7.51 (1H, ddd, J=8.2+8+2.5 Hz, H8), 7.38 (1H, ddd, J=8+8+3 Hz, H7), 2.85 (3H, s, CH_3), 2.84 (2H, m, C1′H_2), 1.82 (2H, m, C2′H_2), 0.95 (3H, m, C3′H_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.2 (CH_3), 14.8 (C3′), 22.3 (C2′), 31.0 (C1′), 118.2 (C10), 122.3 (C5a), 124.0 (C6), 125.4 (C7), 125.6 (C5), 127.6 (C9), 128.7 (C8), 130.8 (C9a), 150.0 (C10a), 169.0 (C2). ^{15}N NMR ($CDCl_3$) δ (ppm): −132.0 (N3), −176.0 (N1). Anal. Calcd for $C_{14}H_{15}N_3$ (225.29): C, 74.64; H, 6.71; N, 18.65. Found: C, 74.27; H, 6.76; N, 18.50.

4.4.4. 10-Ethyl-2-p-tolyl-[1,2,4]triazolo[1,5-b]-isoquinoline (*3d*)

This compound was prepared by Method A from **2c** (0.718 g, 2 mmol) and 4-methylbenzaldehyde (2.4 g, 20 mmol) to give the *title compound* **3d** (0.360 g, 42%) as light yellow crystals, mp 202–204 °C. IR (KBr) ν_{max}: 3059, 2969, 1611, 1453, 1392, 1323, 1286, 1177, 739 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 9.2 (1H, s, H5), 8.32 (2H, m, H2′+H6′), 8.0 (1H, d, J=8 Hz, H6), 7.8 (1H, d, J=8.5 Hz, H9), 7.2–7.5 (4H, m, H3′+H5′+H7+H8), 3.6 (2H, q, J=7.5 Hz, CH_2), 2.42 (3H, s, CH_3'), 1.44 (3H, t, J=7.5 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.5, 20.7, 21.5, 122.7, 123.1, 123.9, 125.1, 125.5, 126.8, 127.6, 127.7 (2C), 128.5, 129.4 (2C), 130.2, 140.2, 150.1, 165.7. Anal. Calcd for $C_{19}H_{17}N_3$ (287.36): C, 79.41; H, 5.96; N, 14.62. Found: C, 79.17; H, 5.98; N, 14.52.

4.4.5. 10-Ethyl-2-phenyl-[1,2,4]triazolo[1,5-b]-isoquinoline (*3e*)

This compound was prepared by Method A from **2c** (0.718 g, 2 mmol) and benzaldehyde (2.12 g, 20 mmol) to give the *title compound* **3a** (0.350 g, 43%) as light yellow crystals, mp 198–200 °C. IR (KBr) ν_{max}: 3063, 2966, 2931, 1609,

1460, 1393, 1326, 1287, 712 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 9.22 (1H, s, H5), 8.40 (2H, m, H2′+H6′), 8.03 (1H, d, J=8 Hz, H6), 7.8 (1H, d, J=8 Hz, H9), 7.20–7.60 (5H, m, H3′+H4′+H5′+H7+H8), 3.55 (2H, q, J=7.5 Hz, CH_2), 1.47 (3H, t, J=7.5 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.5, 21.2, 122.7, 123.1, 124.0, 125.2, 125.7, 126.8, 127.7, 127.8 (2C), 128.6 (2C), 130.1, 130.3, 131.4, 150.1, 165.6. Anal. Calcd for $C_{18}H_{15}N_3$ (273.33): C, 79.10; H, 5.53; N, 15.37. Found: C, 79.10; H, 5.65; N, 15.32.

*4.4.6. 10-Ethyl-2-methyl-[1,2,4]triazolo[1,5-b]-isoquinoline (**3f**)*

This compound was prepared by Method A from **2c** (0.718 g, 2 mmol) and acetaldehyde (0.88 g, 20 mmol) to give the *title compound* **3f** (0.250 g, 39%) as light yellow crystals, mp 80–88 °C. IR (KBr) ν_{max}: 3212, 2972, 1770, 1738, 1552, 1331, 1285, 1057, 951 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 9.18 (1H, s, H5), 8.0 (1H, d, J=8.5 Hz, H6), 7.80 (1H, d, J=8.5 Hz, H9), 7.44 (1H, dd, J=8.5+7.6 Hz, H8), 7.35 (1H, dd, J=8.5+7.6 Hz, H7), 3.50 (2H, q, J=7.8 Hz, CH_2), 2.71 (3H, s, CH_3'), 1.40 (3H, t, J=7.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.6, 15.1, 20.9, 122.6, 123.3, 124.0, 125.0, 125.4, 127.0, 128.1, 130.4, 149.8, 165.9. Anal. Calcd for $C_{13}H_{13}N_3$ (211.26): C, 73.91; H, 6.20; N, 19.89. Found: C, 73.53; H, 6.17; N, 19.58.

*4.4.7. 10-Benzyl-2-p-tolyl-[1,2,4]triazolo[1,5-b]-isoquinoline (**3g**)*

This compound was prepared by Method A from **2d** (0.870 g, 2 mmol) and 4-methylbenzaldehyde (2.4 g, 20 mmol) to give the *title compound* **3g** (0.640 g, 61%) as light yellow crystals, mp 238–239 °C. IR (KBr) ν_{max}: 3074, 3058, 3032, 2919, 1609, 1455, 1436, 1392, 741, 696 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$+TFA) δ (ppm): 9.6 (1H, s, H5), 8.22 (2H, m, H2′+H6′), 8.08 (2H, m, H6+H9), 7.74–7.96 (2H, m, H7+H8), 7.4 (2H, m, H3′+H5′), 7.03–7.22 (5H, m, Ph), 4.95 (2H, s, CH_2), 2.4 (3H, s, CH_3'). ^{13}C NMR ($CDCl_3$+TFA) δ (ppm): 21.6, 32.3, 119.0, 119.8, 123.9, 124.8, 127.4, 127.7 (2C), 128.0, 128.2 (2C), 129.1 (2C), 129.2, 130.4 (2C), 133.8, 135.8, 136.0, 145.4, 158.3, 159.6. Anal. Calcd for $C_{24}H_{19}N_3$ (349.43): C, 82.49; H, 5.48; N, 12.03. Found: C, 82.10; H, 5.34; N, 11.90.

*4.4.8. 10-Benzyl-2-phenyl-[1,2,4]triazolo[1,5-b]-isoquinoline (**3h**)*

This compound was prepared by Method A from **2d** (0.870 g, 2 mmol) and benzaldehyde (2.12 g, 20 mmol) to give the *title compound* **3h** (0.600 g, 60%) as light yellow crystals, mp 193–195 °C. IR (KBr) ν_{max}: 3071, 3026, 1630, 1608, 1459, 1452, 1433, 1395, 1286, 707 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$+TFA) δ (ppm): 9.6 (1H, s, H5), 8.2 (4H, m, H2′+H6′+H6+H9), 7.51–7.95 (5H, m, H3′+H4′+H5′+H7+H8), 7.20–7.0 (5H, m, Ph), 5.0 (2H, s, CH_2). ^{13}C NMR ($CDCl_3$+TFA) δ (ppm): 32.3, 119.3, 122.8, 123.9, 124.8, 127.3, 127.8 (2C), 128.3 (2C), 129.0 (2C), 129.2, 129.6 (2C), 133.8, 134.0, 135.9, 136.0, 139.8, 158.3, 160.4. Anal. Calcd for $C_{23}H_{17}N_3$ (335.40): C, 82.36; H, 5.11; N, 12.53. Found: C, 82.10; H, 5.13; N, 12.45.

*4.4.9. 10-Benzyl-2-propyl-[1,2,4]triazolo[1,5-b]-isoquinoline (**3i**)*

This compound was prepared by Method A from **2d** (0.870 g, 2 mmol) and butyraldehyde (1.44 g, 20 mmol) to give *title compound* **3i** (0.504 g, 56%) as white crystals, mp 134–137 °C. IR (KBr) ν_{max}: 3049, 2960, 2870, 1608, 1495, 1424, 1328, 742 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 9.2 (1H, s, H5), 8.0 (1H, d, J=9 Hz, H6), 7.8 (1H, d, J=8.4 Hz, H9), 7.0–7.5 (7H, m, H7+H8+Ph), 4.90 (2H, s, CH_2), 3.0 (2H, t, J=7.3 Hz, C1–H_2'), 2.0 (2H, m, C2–H_2'), 1.05 (3H, t, J=7.3 Hz, CH_3'). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.1, 22.0, 31.3, 33.0, 121.1, 122.3, 123.6, 124.7, 125.1, 126.3, 126.8, 128.2, 128.4 (2C), 128.5 (2C), 130.9, 139.6, 150.6, 169.9. Anal. Calcd for $C_{20}H_{19}N_3$ (301.38): C, 79.70; H, 6.35; N, 13.94. Found: C, 79.63; H, 6.41; N, 13.93.

*4.4.10. 10-Benzyl-2-methyl-[1,2,4]triazolo[1,5-b]-isoquinoline (**3j**)*

This compound was prepared by Method A from **2d** (0.870 g, 2 mmol) and acetaldehyde (0.88 g, 20 mmol) to give the *title compound* **3j** (0.311 g, 38%) as white crystals, mp 142–150 °C. IR (KBr) ν_{max}: 3523, 3062, 2928, 1736, 1497, 1453, 1306, 701 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 9.2 (1H, s, H5), 8.0 (1H, d, J=8.2 Hz, H6), 7.8 (1H, d, J=7.8 Hz, H9), 7.0–7.5 (7H, m, H7+H8+Ph), 4.85 (2H, s, CH_2), 2.7 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.9, 32.9, 120.8, 122.3, 123.6, 124.6, 125.2, 126.2, 126.8, 128.2, 128.3 (2C), 128.5 (2C), 131.0, 139.4, 150.6, 166.1. Anal. Calcd for $C_{18}H_{15}N_3$ (273.33): C, 79.10; H, 5.53; N, 15.37. Found: C, 79.15; H, 5.75; N, 15.24.

*4.4.11. 2-p-Tolyl-[1,2,4]triazolo[1,5-b]isoquinoline (**3k**)*

This compound was prepared by Method B from **2a** (0.993 g, 3 mmol) and 4-methylbenzaldehyde (3.6 g, 30 mmol) to give the *title compound* **3k** (0.420 g, 54%) as yellow crystals, mp 286–289 °C. IR (KBr) ν_{max}: 3050, 3020, 1642, 1613, 1437, 1328, 1282, 827, 739 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 9.38 (1H, s, H5), 8.30 (2H, m, H2′+H6′), 8.18 (1H, s, H10), 7.80 (2H, m, H6+H9), 7.47 (1H, t, J=8.0 Hz, H8), 7.38 (1H, t, J=8.0 Hz, H7), 7.30 (2H, m, H3′+H5′), 2.41 (3H, s, CH_3'). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.7, 110.6, 122.5, 125.9, 126.1, 126.5, 127.1, 127.9 (2C), 128.4, 128.6, 129.6 (2C), 133.9, 140.8, 150.9, 166.7. HRMS (EI): M^+, found: 259.1117. $C_{17}H_{13}N_3$ requires: 259.1110. Anal. Calcd for $C_{17}H_{13}N_3$ (259.31): C, 78.74; H, 5.05; N, 16.20. Found: C, 78.37; H, 4.95; N, 16.01.

*4.4.12. 2-Phenyl-[1,2,4]triazolo[1,5-b]isoquinoline (**3l**)*

This compound was prepared by Method B from **2a** (0.993 g, 3 mmol) and benzaldehyde (3.18 g, 30 mmol) to give the *title compound* **3l** (0.350 g, 57%) as yellow crystals, mp 288–290 °C. IR (KBr) ν_{max}: 3051, 1639, 1457, 1400, 1331, 1283, 1256, 712 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 9.36 (1H, s, H5), 8.40 (2H, m, H2′+H6′), 8.18 (1H, s, H10), 7.82 (2H, m, H6+H9), 7.42–7.55 (4H, m, H3′+H4′+H5′+H8),

7.36 (1H, t, J=7.5 Hz, H7). ^{13}C NMR ($CDCl_3$) δ (ppm): 110.8, 122.6, 126.0, 126.1, 126.5, 127.1, 128.0 (2C), 128.6, 128.9 (2C), 129.2, 130.0, 130.6, 131.2, 134.0. HRMS (EI): M^+, found: 245.0950. $C_{16}H_{11}N_3$ requires: 245.0953. Anal. Calcd for $C_{16}H_{11}N_3$ (245.28): C, 78.35; H, 4.52; N, 17.13. Found: C, 78.05; H, 4.62; N, 16.94.

4.4.13. 2-Propyl-[1,2,4]triazolo[1,5-b]isoquinoline (**3m**)

This compound was prepared by Method B from **2a** (0.993 g, 3 mmol) and butyraldehyde (2.16 g, 30 mmol) to give the *title compound* **3m** (0.220 g, 35%) as yellow crystals, mp 118–121 °C. IR (KBr) ν_{max}: 3047, 2959, 2870, 1641, 1612, 1470, 1324, 1255, 746 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 9.30 (1H, s, H5), 8.10 (1H, s, H10), 7.81 (1H, dd, J=8.2+2.2 Hz, H6), 7.78 (1H, dd, J=8+2 Hz, H9), 7.47 (1H, ddd, J=8+7.8+2.2 Hz, H8), 7.37 (1H, ddd, J=8.2+7.8+2 Hz, H7), 3.0 (2H, m, CH_2), 1.92 (2H, m, CH_2), 1.05 (3H, m, CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.2 (C3′), 22.0 (C2′), 31.4 (C1′), 110.2 (C10), 122.1 (C5a), 125.8 (C6), 126.2 (C7), 126.3 (C5), 127.1 (C9), 128.5 (C8), 133.7 (C9a), 150.3 (C10a), 170.4 (C2). ^{15}N NMR ($CDCl_3$), δ (ppm): −134.1 (N3), −154.6 (N4), −179.3 (N1). Anal. Calcd for $C_{13}H_{13}N_3$ (211.26): C, 73.91; H, 6.20; N, 19.89. Found: C, 73.68; H, 6.16; N, 19.70.

4.5. General procedure for substituted 3-methylidene-hydrazinyl-isoquinolines (**4a–d**)

To the solution of **2a**,**e** (2 mmol) and aldehyde (20 mmol) in EtOH (30 mL) was added DBU (1.4 mL), and the mixture was stirred at rt. The progress of the reaction was monitored by TLC. After disappearance of the starting material the reaction mixture was evaporated, water (50 mL) was added, and the mixture was extracted with chloroform. The organic layer was dried over Na_2SO_4, and evaporated. The residue was flash chromatographed over silica by using hexane–EtOAc 4:1 as eluent.

4.5.1. (*E*)-3-(2-(4-Methylbenzylidene)hydrazinyl)-isoquinoline (**4a**)

This compound was prepared from **2a** (0.663 g, 2 mmol) and 4-methylbenzaldehyde (2.4 g, 20 mmol) to give the *title compound* **4a** (0.180 g, 35%) as orange crystals, mp 213–215 °C. IR (KBr) ν_{max}: 3188, 3031, 2981, 1626, 1593, 1454, 1134, 741, 465 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.8 (1H, s, N1H'), 8.95 (1H, s, H1), 8.04 (1H, s, N=CH), 7.88 (1H, d, J=8.2 Hz, H8), 7.75 (1H, d, J=8.7 Hz, H5), 7.54–7.58 (3H, m, H6+H2′+H6′), 7.38 (1H, s, H4), 7.27 (1H, m, H7), 7.21 (2H, m, H3′+H5′), 2.30 (3H, s, CH_3′). ^{13}C NMR (DMSO-d_6) δ (ppm): 21.6, 97.6, 123.7, 124.8, 125.9, 126.6 (2C), 128.4, 130.0 (2C), 131.2, 133.5, 138.7, 139.0, 139.9, 152.1, 154.1. Anal. Calcd for $C_{17}H_{15}N_3$ (261.32): C, 78.13; H, 5.79; N, 16.08. Found: C, 77.76; H, 5.74; N, 16.07.

4.5.2. (*E*)-3-(2-Benzylidenehydrazinyl)isoquinoline (**4b**)

This compound was prepared from **2a** (0.663 g, 2 mmol) and benzaldehyde (2.12 g, 20 mmol) to give the *title compound* **4b** (0.250 g, 51%) as orange crystals, mp 179–183 °C. IR (KBr) ν_{max}: 3187, 2981, 1629, 1593, 1566, 1438, 1229, 1136, 865, 749 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.9 (1H, s, H1), 8.53 (1H, s, N1H'), 7.82 (2H, m, H8+H5), 7.72–7.48 (5H, m, Ph), 7.42 (2H, m, H4+H6), 7.30 (2H, m, N=CH+H7). ^{13}C NMR ($CDCl_3$) δ (ppm): 99.2, 123.8, 125.3, 125.9, 126.7 (2C), 128.0, 128.9 (2C), 129.1, 130.9, 135.3, 139.1, 139.4, 151.5, 152.8. HRMS (EI): M^+, found: 247.1105. $C_{16}H_{13}N_3$ requires: 247.1110. Anal. Calcd for $C_{16}H_{13}N_3$ (247.29): C, 77.71; H, 5.30; N, 16.99. Found: C, 77.53; H, 5.17; N, 16.67.

4.5.3. (*E*)-3-(2-Butylidenehydrazinyl)isoquinoline (**4c**)

This compound was prepared from **2a** (0.663 g, 2 mmol) and butyraldehyde (1.44 g, 20 mmol) to give the *title compound* **4c** (0.310 g, 36%) as orange crystals, mp 94–96 °C. IR (KBr) ν_{max}: 3192, 2954, 1627, 1591, 1434, 1219, 863 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.84 (1H, s, H1), 8.04 (1H, s, N1H'), 7.78 (1H, d, J=8.5 Hz, H8), 7.64 (1H, d, J=8.3 Hz, H5), 7.51 (1H, dd, J=8.5+8.0 Hz, H6), 7.34 (1H, s, H4), 7.26 (1H, dd, J=8.5+8.0 Hz, H7), 7.20 (1H, t, J=7.5 Hz, N=CH), 2.4 (2H, m, C4–H_2'), 1.6 (2H, m, C5–H_2'), 1.0 (3H, m, CH_3′). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.0, 20.6, 34.5, 98.6, 123.4, 125.0, 125.7, 127.9, 130.7, 139.2, 143.6, 151.5, 153.4. HRMS (EI): M^+, found: 213.1257. $C_{13}H_{15}N_3$ requires: 213.1266. Anal. Calcd for $C_{13}H_{15}N_3$ (213.28): C, 73.21; H, 7.09; N, 19.70. Found: C, 73.03; H, 6.88; N, 19.31.

4.5.4. (*E*)-3-(2-Ethylidenehydrazinyl)isoquinoline (**4d**)

This compound was prepared from **2a** (0.663 g, 2 mmol) and acetaldehyde (0.88 g, 20 mmol) to give the *title compound* **4d** (0.180 g, 49%) as orange crystals, mp 128–133 °C. IR (KBr) ν_{max}: 3189, 3032, 2975, 1629, 1591, 1358, 1130, 747 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.84 (1H, s, H1), 8.2 (1H, N1′H), 7.78 (1H, dd, J=8+3 Hz, H8), 7.64 (1H, dd, J=8.1+3 Hz, H5), 7.50 (1H, ddd, J=8.1+7.5+3 Hz, H6), 7.34 (1H, s, H4), 7.20–7.28 (2H, m, H7+N2′=CH), 2.1 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 18.4 (CH_3), 98.5 (C4), 123.5 (C7), 125.0 (C4a), 125.7 (C5), 128.0 (C8), 130.7 (C6), 139.2 (C8a), 139.6 (N2′=CH), 151.5 (C1), 153.4 (C3). ^{15}N NMR ($CDCl_3$) δ (ppm): −81.0 (N2′), −125.0 (N2), −253.0 (N1′). Anal. Calcd for $C_{11}H_{11}N_3$ (213.28): C, 71.33; H, 5.99; N, 22.69. Found: C, 71.27; H, 6.00; N, 22.32.

4.5.5. (*E*)-3-(2-(4-Methylbenzylidene)hydrazinyl)-isoquinoline-4-carbonitrile (**4e**)

This compound was prepared from **2e** (0.768 g, 2 mmol) and 4-methylbenzaldehyde (2.4 g, 20 mmol) to give the *title compound* **4e** (0.477 g, 83%) as brown crystals, mp 128–133 °C. IR (KBr) ν_{max}: 3232, 3048, 2965, 2202, 1620, 1587, 1578, 1556, 1510, 1417 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.97 (1H, s, H1), 8.74 (1H, s, N1′H), 8.12 (1H, dd, J=8.5+1.1 Hz, H5), 7.86 (1H, dd, J=8.5+1.2 Hz, H8), 7.82 (1H, s, N2′=CH), 7.77 (1H, ddd, J=8.5+7+1.2 Hz, H6), 7.75 (2H, m, H2′+H6′), 7.44 (1H, ddd, J=8.5+7+1.1 Hz, H7), 7.24 (2H, m, H3′+H5′), 2.38 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.7 (CH_3), 82.3 (C4), 116.9 (CN), 123.4

(C5), 123.9 (C8a), 125.3 (C7), 127.6 (C2′+C6′), 128.8 (C8), 129.8 (C3′+C5′), 131.7 (C1′), 133.5 (C6), 138.7 (C4a), 140.3 (C4′), 142.8 (N2′=*C*H), 153.9 (C3), 156.2 (C1). Anal. Calcd for $C_{18}H_{14}N_4$ (286.33): C, 75.50; H, 4.93; N, 19.57. Found: C, 75.60; H, 4.85; N, 19.60.

4.6. (*E*)-3-(2-(4-Methylbenzylidene)hydrazinyl)-isoquinoline 2-oxide (**6**)

To the solution of 3-hydrazinylisoquinoline-2-oxide[9] (**5**) (0.350 g, 2 mmol) in acetonitrile (30 mL), 4-methylbenzaldehyde (3 mL) was added, and the mixture was refluxed for 4 h. Upon cooling, the product was precipitated, filtered off, and recrystallized from acetonitrile to yield *title compound* **6** (0.420 g, 76%) as orange crystals, mp 195–200 °C. IR (KBr) ν_{max}: 3163, 3019, 2920, 1644, 1531, 1510, 1218, 856, 739 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 9.9 (1H, br s, N1′*H*), 8.76 (1H, s, H1), 8.0 (1H, s, N2′=C*H*), 7.70 (1H, d, *J*=8 Hz, H5), 7.65 (1H, s, H4), 7.64 (2H, m, H2′+H6′), 7.62 (1H, d, *J*=7.9 Hz, H8), 7.50 (1H, dd, *J*=7.9+7.7 Hz, H7), 7.34 (1H, dd, *J*=8+7.7 Hz, H6), 7.23 (2H, m, H3′+H5′), 2.42 (3H, s, C*H*$_3$). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.7 (*C*H$_3$), 101.4 (C4), 122.8 (C4a), 125.3 (C6), 125.4 (C5), 125.5 (C8), 127.1 (C2′+C6′), 129.6 (C7), 129.7 (C3′+C5′), 131.8 (C8a), 132.0 (C1′), 135.5 (C1), 140.2 (C4′), 144.2 (N2′=*C*H), 145.6 (C3). Anal. Calcd for $C_{17}H_{15}N_3O$ (277.32): C, 73.63; H, 5.45; N, 15.15. Found: C, 73.37; H, 5.07; N, 15.06.

4.6.1. Reduction of **6** to **4a**

To a solution of **6** (0.277 g, 1 mmol) in saturated NH_4Cl (3 mL) and MeOH (5 mL), indium (0.137 g) was added and refluxed for 1 h. The reaction mixture was diluted with MeOH (15 mL) and refluxed for an additional 7 h. After neutralization with saturated $NaHCO_3$ and extraction with chloroform, the organic layer was dried over Na_2SO_4 and evaporated. The residue was subjected to flash chromatography over *silica* by using hexane–EtOAc 2:1 as eluent. Yield: 0.063 g (24%). Physical and spectroscopic data (mp, IR, NMR) of this product were identical with **4a**, which was earlier isolated from **2a** and 4-methylbenzaldehyde.

4.7. *N*-(Isoquinolin-3-yl)formamide (**8**)

$Pd_2(DBA)_3CHCl_3$ (0.206 g, 0.2 mmol), Cs_2CO_3 (2.608 g, 8 mmol) and xantphos (0.347 g) were placed in a two necked round bottom flask. Dioxane (20 mL) was added to the mixture, and heated at 100 °C under Ar atmosphere. Isoquinolin-3-yl trifluoromethanesulfonate[12] (**7**) (1.108 g, 4 mmol) and formamide (0.360 mg, 8 mmol, containing 20% excess of ^{15}N-labelled formamide) was dissolved in dioxane (5 mL), and the solution was added to the reaction mixture. It was stirred for 4 h. The progress of the reaction was monitored by TLC. After disappearance of the starting material the reaction mixture was filtered on Celite and evaporated. The residue was subjected to flash chromatography over *silica* by using hexane–EtOAc 4:1 as eluent to give the *title compound* **8** (0.406 g, 59%) as white crystals, mp 134–136 °C (lit.[2] 138 °C). In the NMR spectrum two signal sets of the amide rotamers are present. ^1H NMR ($CDCl_3$) δ (ppm): 9.4+9.8 (1H, CON*H*), 8.6+9.45 (1H, s, C*H*O), 9.1 (1H, s, H1), 8.4+7.26 (1H, s, H4), 7.91 (1H, d, H8), 7.85+7.75 (1H, d, H5), 7.68 (1H, t, H7), 7.50 (1H, t, H6). ^{13}C NMR ($CDCl_3$) δ (ppm): 109.1+103.9 (C4), 125.8+126.0 (C8), 126.2 (C8a), 126.6+126.8 (C5), 127.5+127.8 (C6), 131.0+131.3 (C7), 137.9 (C4a), 145.4+146.3 (C3), 150.9+152.1 (C1), 159.2+162.9 (CHO). *m/z* (ES ionization) 174 (MH^+ ^{15}N), 173 (MH^+), 146 (MH^+ ^{15}N–28), 145 (MH^+–28).

4.8. ^{15}N-Labelled isoquinolin-3-amine (**1a#**)

N-(Isoquinolin-3-yl)formamide (**8**, 1.8 g, 10.5 mmol) was heated in 10% HCl (120 mL) at boiling point. The solution was cooled at rt, and it was neutralized with 10% NaOH. The mixture was extracted with chloroform (3×30 mL), the organic layer was dried over Na_2SO_4, evaporated and the residue was recrystallized from toluene to yield 0.910 g (61%) of product as yellow crystals. Physical and spectroscopic data of this product (mp, IR, NMR) were identical with those of the earlier isolated compound.

4.9. (*E*)-3-Amino-2-(4-methylbenzylideneamino)-isoquinolinium tetrafluoroborate (**9**)

A solution of **2a** (0.662 g, 2 mmol) and 4-methylbenzaldehyde (2.4 g, 20 mmol) in abs acetonitrile (30 mL) was refluxed for 5 h. The progress of the reaction was monitored by TLC. After disappearance of the starting material the reaction mixture was evaporated and then acetonitrile (5 mL) and tetrafluoroboric acid (50%, 1 mL) was added. Upon addition of ether the product separated as an orange solid, it was filtered off and recrystallized from acetonitrile to give the *title compound* **9** (0.405 g, 58%) as orange crystal, mp 214–217 °C. IR (KBr) ν_{max}: 3466, 3359, 1659, 1599, 1035, 877, 817, 749 cm^{-1}. ^1H NMR (DMSO-d_6) δ (ppm): 9.70 (1H, s, H1), 9.16 (1H, s, N1′=C*H*), 8.04 (2H, m, H2′+H6′), 7.92 (1H, dd, *J*=8+2.3 Hz, H8), 7.87 (2H, s, N2′H_2), 7.82 (1H, dd, *J*=8+2.5 Hz, H5), 7.73 (1H, ddd, *J*=8+7.7+2.3 Hz, H6), 7.46 (2H, m, H3′+H5′), 7.42 (1H, ddd, *J*=8+7.7+2.5 Hz, H7), 7.36 (1H, s, H4), 2.43 (3H, s, C*H*$_3$). ^{13}C NMR (DMSO-d_6) δ (ppm): 22.1 (*C*H$_3$), 105.7 (C4), 121.2 (C8a), 125.5 (C5), 126.5 (C7), 129.1 (C8), 129.3 (C1′), 130.5 (C3′+C5′), 131.3 (C2′+C6′), 135.5 (C6), 138.2 (C1), 140.9 (C4a), 145.6 (C4′), 148.3 (C3), 169.3 (N1′=*C*H). ^{15}N NMR (DMSO-d_6) δ (ppm): −91.2 (N1′), −186.5 (N2′), −323.5 (NH_2). Anal. Calcd for $C_{17}H_{16}BF_4N_3$ (349.13): C, 58.48; H, 4.62; N, 12.04. Found: C, 58.25; H, 4.30; N, 11.97.

4.10. General procedure for 2,3-dihydro-1H-[1,2,4]triazolo[1,5-b]isoquinolin-4-ium 4-methylbenzenesulfonates (**10a–f**)

A solution of **2c**,**d** (3 mmol) and the appropriate aldehyde (30 mmol) in abs acetonitrile (45 mL) was refluxed for 6 h. The progress of the reaction was monitored by TLC. After

disappearance of the starting material the reaction mixture was cooled down to rt, the deposited yellow crystals were filtered off, and washed with ether. The product was boiled in hot EtOAc, filtered off and washed with EtOAc.

*4.10.1. 10-Ethyl-2-p-tolyl-2,3-dihydro-1H-[1,2,4]-triazolo[1,5-b]isoquinolin-4-ium 4-methyl-benzenesulfonate (**10a**)*

This compound was prepared from **2c** (1.077 g, 3 mmol) and 4-methylbenzaldehyde (3.6 g 30 mmol) to give the *title compound* **10a** (1.25 g, 90%) as yellow crystals, mp 170–172 °C. IR (KBr) ν_{max}: 3095, 1648, 1473, 1444, 1216, 1176, 1034, 1011, 814 cm^{-1}. ^1H NMR (DMSO-d_6) δ (ppm): 9.42 (1H, s, H5), 9.3 (1H, s, H1), 9.25 (1H, d, J=9.2 Hz, H3), 8.1 (1H, d, J=8.0 Hz, H6), 8.0 (1H, d, J=8.0 Hz, H9), 7.82 (1H, t, J=8.0 Hz, H8), 7.5 (1H, t, J=8.0 Hz, H7), 7.4 (4H, m, H3+H5(anion)+H2′+H6′), 7.22 (2H, m, H3′+H5′), 7.04 (2H, m, H2+H6(anion)), 6.4 (1H, d, J=9.2 Hz, H2), 3.0 (2H, m, CH_2″), 2.3 (3H, s, CH_3′), 2.22 (3H, s, CH_3(anion)), 1.2 (3H,m, CH_3″). ^{13}C NMR (DMSO-d_6) δ (ppm): 13.7, 19.8, 21.4, 21.5, 75.8, 114.4, 122.7, 126.2 (2C), 126.6, 127.8 (2C), 128.7 (2C), 130.0 (2C), 130.4, 135.0 (2C), 135.1, 135.4, 137.6, 138.3, 139.9, 144.5, 146.4. HRMS (EI): M^+, found: 290.1642. $C_{19}H_{20}N_3$ requires: 290.1652. Anal. Calcd for $C_{26}H_{27}N_3O_3S$ (461.58): C, 67.65; H, 5.90; N, 9.10; S, 6.95. Found: C, 67.43; H, 6.10; N, 9.09; S, 7.22.

*4.10.2. 10-Ethyl-2-phenyl-2,3-dihydro-1H-[1,2,4]-triazolo[1,5-b]isoquinolin-4-ium 4-methyl-benzenesulfonate (**10b**)*

This compound was prepared from **2c** (1.077 g, 3 mmol) and benzaldehyde (3.18 g, 30 mmol) to give the *title compound* **10b** (1.21 g, 89%) as yellow crystals, mp 168–175 °C. IR (KBr) ν_{max}: 3095, 1650, 1446, 1203, 1159, 1121, 1031, 1008, 682 cm^{-1}. ^1H NMR (DMSO-d_6) δ (ppm): 9.5 (1H, s, H5), 9.4 (1H, d, J=9.0 Hz, H3), 9.35 (1H, s, H1), 8.1 (1H, d, J=8.5 Hz, H6), 8.0 (1H, d, J=8.5 Hz, H9), 7.85 (1H, t, J=8.5 Hz, H8), 7.4 (2H, m, H3+H5(anion)), 7.35 (1H, t, J=8.5 Hz, H7), 7.4–7.45 (5H, m, Ph), 7.02 (2H, m, H2+H6(anion), 6.45 (1H, d, J=9.0 Hz, H2), 3.0 (2H, m, CH_2″), 2.2 (3H, s, CH_3(anion)), 1.2 (3H, m, CH_3″). ^{13}C NMR (DMSO-d_6) δ (ppm): 13.7, 19.8, 21.4, 75.9, 114.5, 122.7, 122.8, 126.1 (2C), 126.6, 127.8 (2C), 128.7 (2C), 129.5 (2C), 130.3, 130.4, 135.0, 135.1, 137.6, 138.3, 138.5, 144.4, 146.3. HRMS (EI): M^+, found: 276.1490. $C_{18}H_{18}N_3$ requires: 276.1495. Anal. Calcd for $C_{25}H_{25}N_3O_3S$ (447.55): C, 67.09; H, 5.63; N, 9.39; S, 7.16. Found: C, 66.81; H, 5.42; N, 9.36; S, 7.36.

*4.10.3. 10-Ethyl-2-propyl-2,3-dihydro-1H-[1,2,4]-triazolo[1,5-b]isoquinolin-4-ium 4-methyl-benzenesulfonate (**10c**)*

This compound was prepared from **2c** (1.077 g, 3 mmol) and butyraldehyde (2.16 g 30 mmol) to give the *title compound* **10c** (1.12 g, 89%) as yellow crystals, mp 151–156 °C. IR (KBr) ν_{max}: 3116, 2953, 1651, 1495, 1217, 1171, 1124, 1033, 1010, 684, 595 cm^{-1}. ^1H NMR (DMSO-d_6) δ (ppm): 9.4 (1H, s, H5), 9.0 (1H, d, J=8.7 Hz, H3), 8.8 (1H, s, H1), 8.03 (1H, dd, J=9+2 Hz, H6), 7.97 (1H, dd, J=8.7+2 Hz, H9), 7.8 (1H, ddd, J=8.7+8+2 Hz, H8), 7.5 (1H, ddd, J=9+8+2 Hz, H7), 7.4 (2H, m, H3+H5(anion)), 7.02 (2H, m, H2+H6(anion)), 5.4 (1H, m, H2), 2.95 (2H, m, CH_2″), 2.22 (3H, s, CH_3(anion)), 1.8 (2H, m, CH_2′), 1.4 (2H, m, CH_2′), 1.2 (3H, m, CH_3″), 0.92 (3H, m, CH_3′). ^{13}C NMR (DMSO-d_6) δ (ppm): 13.6 (C3′), 14.3 (C2″), 17.5 (C2′), 19.7 (CH_3(anion)), 21.4 (C1″), 37.6 (C1′), 74.5 (C2), 114.4 (C10), 122.5 (C5a), 122.6 (C9), 126.1 (C3+C5(anion)), 126.5 (C8), 128.7 (C2+C6(anion)), 130.2 (C7), 135.0 (C6), 135.5 (C5), 137.5 (C9a), 138.3 (C1(anion)), 144.9 (C4(anion)), 146.3 (C10a). Anal. Calcd for $C_{22}H_{27}N_3O_3S$ (413.53): C, 63.90; H, 6.58; N, 10.16; S, 7.75. Found: C, 63.78; H, 6.57; N, 10.16; S, 8.02.

*4.10.4. 10-Benzyl-2-p-tolyl-2,3-dihydro-1H-[1,2,4]-triazolo[1,5-b]isoquinolin-4-ium 4-methyl-benzenesulfonate (**10d**)*

This compound was prepared from **2d** (1.305 g, 3 mmol) and 4-methylbenzaldehyde (3.6 g, 30 mmol) to give the *title compound* **10d** (1.23 g, 78%) as yellow crystals, mp 202–204 °C. IR (KBr) ν_{max}: 3170, 3056, 1651, 1510, 1232, 1181, 1170, 1121, 1033, 1010, 679 cm^{-1}. ^1H NMR (DMSO-d_6) δ (ppm): 9.6 (2H, s, H1+H5), 9.38 (1H, d, J=9.0 Hz, H3), 8.10 (1H, d, J=8.3 Hz, H6), 7.90 (1H, d, J=8.0 Hz, H9), 7.80 (1H, t, J=8.0 Hz, H8), 7.50 (1H, t, J=8.0 Hz, H7), 7.45 (4H, m, H3+H5(anion)+H2′+H6′), 7.25 (6H, H3′+H5′+H2″+H3″+H5″+H6″), 7.18 (1H, m, H4″), 7.05 (2H, m, H2+H6 (anion), 6.46 (1H, d, J=9.0 Hz, H2), 4.40 (2H, m, CH_2″), 2.30 (3H, s, CH_3′), 2.22 (3H, s, CH_3(anion)). ^{13}C NMR (DMSO-d_6) δ (ppm): 21.4, 21.5, 31.6, 75.8, 110.9, 122.7, 123.2, 126.2 (2C), 126.6, 127.2, 127.8 (2C), 128.7 (2C), 128.8 (2C), 129.3 (2C), 130.0 (2C), 130.5, 135.3, 135.5, 136.2, 138.2, 138.4, 138.8, 139.9, 145.5, 146.3. ^{15}N NMR (DMSO-d_6) δ (ppm): −191.3 (N4), −276.0 (N3), −310.6 (N1). HRMS (EI): M^+, found: 352.1807. $C_{24}H_{22}N_3$ requires: 352.1808. Anal. Calcd for $C_{31}H_{29}N_3O_3S$ (523.19): C, 71.10; H, 5.58; N, 8.02; S, 6.12. Found: C, 70.88; H, 5.32; N, 8.11; S, 6.32.

*4.10.5. 10-Benzyl-2-phenyl-2,3-dihydro-1H-[1,2,4]-triazolo[1,5-b]isoquinolin-4-ium 4-methyl-benzenesulfonate (**10e**)*

This compound was prepared from **2d** (1.305 g, 3 mmol) and benzaldehyde (3.18 g, 30 mmol) to give the *title compound* **10e** (1.35 g, 88%) as yellow crystals, mp 198–200 °C. IR (KBr) ν_{max}: 3094, 3051, 1701, 1650, 1220, 1171, 1122, 1034, 1011, 681 cm^{-1}. ^1H NMR (DMSO-d_6) δ (ppm): 9.56 (2H, s, H1+H5), 9.40, (1H, d, J=9.0 Hz, H3), 8.11 (1H, d, J=8.0 Hz, H6), 7.90 (1H, d, J=8.0 Hz, H9), 7.80 (1H, t, J=8.0 Hz, H8), 7.57 (2H, m, H2′+H6′), 7.50 (1H, t, J=8.0 Hz, H7), 7.46 (5H, m, H3+H5(anion)+H3′+H4′+H5′), 7.14–7.30 (5H, m, Ph″), 7.08 (2H, m, H2+H6(anion)), 6.50 (1H, d, J=9.0 Hz, H2), 4.40 (2H, m, CH_2″), 2.24 (3H, s, CH_3(anion)). ^{13}C NMR (DMSO-d_6) δ (ppm): 21.4, 31.6, 75.8, 110.9, 122.7, 123.2, 126.2 (2C), 126.7, 127.2, 127.8 (2C), 128.7 (2C), 128.8 (2C), 19.3 (2C), 129.5 (2C), 129.8, 130.2,

130.3, 130.5, 135.3, 136.2, 138.2, 138.8, 145.4, 146.3. HRMS (EI): M^+, found: 338.1649. $C_{23}H_{20}N_3$ requires: 338.1652. Anal. Calcd for $C_{30}H_{27}N_3O_3S$ (509.62): C, 70.70; H, 5.34; N, 8.25; S, 6.29. Found: 70.42; H, 5.52; N, 8.28; S, 6.24.

*4.10.6. 10-Benzyl-2-propyl-2,3-dihydro-1H-[1,2,4]-triazolo[1,5-b]isoquinolin-4-ium 4-methyl-benzenesulfonate (**10f**)*

This compound was prepared from **2d** (1.305 g, 3 mmol) and butyraldehyde (2.16 g, 30 mmol) to give the *title compound* **10f** (0.76 g, 53%) as yellow crystals, mp 161–164 °C. IR (KBr) ν_{max}: 3062, 2962, 1783, 1650, 1455, 1170, 1122, 1033, 1010, 682 cm^{-1}. ^1H NMR (DMSO-d_6) δ (ppm): 9.52 (1H, s, H5), 9.05 (1H, s, H1), 8.97 (1H, d, J=7 Hz, H3), 8.07 (1H, dd, J=8.2+3 Hz, H6), 7.84 (1H, dd, J=8+2 Hz, H9), 7.75 (1H, ddd, J=8+7.8+3 Hz, H8), 7.47 (1H, ddd, J=8.2+7.8+2 Hz, H7), 7.43 (2H, m, H3+H5(anion), 7.30–7.10 (5H, m, Ph″), 7.05 (2H, m, H2+H6(anion), 5.40 (1H, m, q, J=7 Hz, H2), 4.34 (2H, s, CH_2″), 2.2 (3H, s, CH_3(anion)), 1.72 (2H, m, C1–H_2′), 1.40 (2H, m, C2–H_2′), 0.91 (3H, t, J=7 Hz, CH_3′). ^{13}C NMR (DMSO-d_6) δ (ppm): 14.3, 17.5, 21.4, 31.6, 37.5, 74.5, 110.8, 122.5, 123.0, 126.1 (2C), 126.5, 127.2, 128.7 (2C), 128.8 (2C), 129.3 (2C), 130.4, 135.3, 136.5, 138.2, 138.3, 138.9, 146.0, 146.2. Anal. Calcd for $C_{27}H_{29}N_3O_3S$ (475.60): C, 68.18; H, 6.15; N, 8.84; S, 6.74. Found: C, 68.02; H, 6.16; N, 8.84; S, 7.07.

*4.11. General procedure for reaction of 4-methyl-2,3-diamino-isoquinolinium 4-methylbenzenesulfonate (**2b**) with aldehydes without the presence of DBU*

A solution of **2b** (690 mg, 2 mmol) and the appropriate aldehyde (20 mmol) in abs acetonitrile (30 mL) was refluxed for the period specified below. The progress of the reaction was monitored by TLC. After disappearance of the starting material the reaction mixture was evaporated, 50 mL of 10% Na_2CO_3 was added, and the mixture was extracted with chloroform. The organic layer was dried over Na_2SO_4 and then it was evaporated. Ether was added to the residue, whereupon a crystalline solid separated. The product was filtered off and recrystallized from EtOAc to yield **3a** (0.202 g, 37%) or **3c** (0.200 g, 47%). All physical and spectroscopic data of these products were identical with those of the products obtained from **2b** and aldehyde under basic conditions.

*4.12. Oxidation of 10-benzyl-2-phenyl-2,3-dihydro-1H-[1,2,4]triazolo[1,5-b]isoquinolin-4-ium 4-methyl-benzenesulfonate (**10e**) under basic conditions*

The suspension of **10e** (0.255 g, 0.5 mmol) in 10% NaOH (20 mL) was heated until boiling. After cooling the mixture was extracted with chloroform. The organic layer was dried over Na_2SO_4, evaporated and the residue was recrystallized from EtOAc to yield 0.153 g (91%) of product. All physical and spectroscopic data of this product **3h** were identical with those of the earlier isolated compound obtained from **2d** and benzaldehyde.

*4.13. Transformation of (E)-3-amino-2-(4-methylbenzylideneamino)isoquinolinium tetrafluoroborate (**9**) into (E)-3-(2-(4-methylbenzylidene)hydrazinyl)-isoquinoline (**4a**) under basic conditions*

To the solution of **9** (0.200 g, 0.57 mmol) in EtOH (20 mL) was added DBU (1.4 mL), and the mixture was stirred at rt. The progress of the reaction was monitored by TLC. After disappearance of the starting material the reaction mixture was evaporated. The residue was subjected to flash chromatography over *silica* by using hexane–EtOAc 2:1 as eluent, to give **4a** (0.101 g, 67%) as yellow crystals. All physical and spectroscopic data of this product (**4a**) were identical with those of the earlier isolated compound obtained from **2a** and 4-methylbenzaldehyde.

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Supplementary data

^1H–^{15}N gHMQC spectra of compounds **2a** and **4d**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.10.103.

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8. A crystal of **4c** ($C_{13}H_{15}N_3$, Mr=213.28, pale yellow block, size: 0.60×0.45×0.25 mm) was mounted on a glass fibre. Cell parameters were determined by least-squares fitting of the setting angles of 25 ($36.97 \leq \theta \leq 39.86°$) reflections. Monoclinic, space group *C*2/*c*, a=16.258(1) Å, b=7.444(1) Å, c=19.484(1) Å, α=90.00°, β=93.76(1)°, γ=90.00°, V=2353.0(4) $Å^3$, T=296(2) K, Z=8, $F(000)$=912, D_x=1.204 Mg/m^3, μ=0.577 mm^{-1}. Intensity data were collected on an Enraf-Nonius CAD4 four-circle diffractometer (graphite monochromator;

Cu Kα radiation, λ=1.54180 Å) at 296(2) K in the range $4.55 \leq \theta \leq 74.83^{\circ}$ using $\omega/2\theta$ scans. Backgrounds were measured 1/2 the total time of the peak scans. The intensities of three standard reflections were monitored regularly (every 60 min). The intensities of the standard reflections indicated a crystal decay of 1% (the data were corrected for decay). A total of 5132 reflections were collected of which 2401 were unique [R(int)=0.0112, $R(\sigma)$=0.0113]; intensities of 2049 reflections were greater than $2\sigma(I)$.[14] Completeness to θ=0.988. An empirical absorption correction[15] was applied to the data (the minimum and maximum transmission factors were 0.723 and 0.869). The initial structure model was provided by direct methods[16] (and subsequent difference syntheses). Anisotropic full-matrix least-squares refinement on F^2 for all non-hydrogen atoms[17] yielded the final model (R_1=0.0389 and wR_2=0.1245 for 2049 [$I>2\sigma(I)$] and R_1=0.0433 and wR_2=0.1288 for all (2401) intensity data, GOF=1.064). The maximum and minimum residual electron density in the final difference map was 0.17 and −0.15 e Å^{-3}. Hydrogen atomic positions, calculated from assumed geometries, were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the U(eq) value of the atom to which they were bonded.[22]

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22. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographyc Data Centre as supplementary publication number CCDC 656158. Copies of the data can be obtained, free of charge, on application to CCCD, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).