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SYNTHESIS OF LINEARLY FUSED TETRACYCLIC HETEROCYCLES THROUGH A NOVEL BASE CATALYZED INTRAMOLECULAR REARRANGEMENT INVOLVING SCISSION OF N-N BOND

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ABSTRACT : Synthesis of s-triazolothiadiazepinoquinolines **4a-f** and the base catalyzed intramolecular facile rearrangement of **4a-f** to s-triazolothi-azinoquinolines **5a-f** involving scission of N-N bond is reported.

In continuation of our earlier studies on the synthesis of condensed quinoline heterocycles[1,2,3], employing 2-chloro-3-formylquinoline[4] **1a**, 3-methyl-4-amino-5-mercapto-1:2:4 triazole[5,6], triazole **2a** was condensed with **1a**. The reaction was carried out at room temperature using isopropanol as solvent. Condensation took place involving only the aldehydic group and resulted in the formation of 4–(2^1–chloro–3^1-azomethinylquinoline)– 3-methyl – 5-mercapto-1:2:4 triazole **3a.** The structure of **3a** was confirmed by spectral and analytical data.

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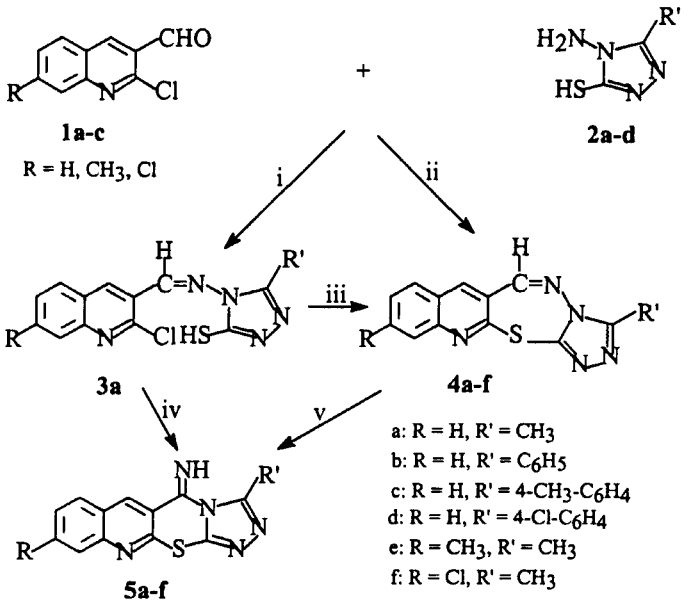
The mass spectrum showed a molecular ion peak at m/z 303, IR spectrum showed the absence of an aldehydic carbonyl group and the presence of a weak band at 2666 cm^{-1} attributable to SH group and the NMR spectrum showed a sharp singlet at δ 8.85 ppm and a broad singlet at δ 3.75 ppm corresponding to one proton each attributable to CH=N and SH groups respectively. Compound **3a** underwent smooth cyclization when treated with (1:1) methanolic potassium hydroxide solution at room temperature to afford s-triazolothiadiazepinoquinoline **4a**. The structure of **4a** was confirmed by spectral and analytical data.

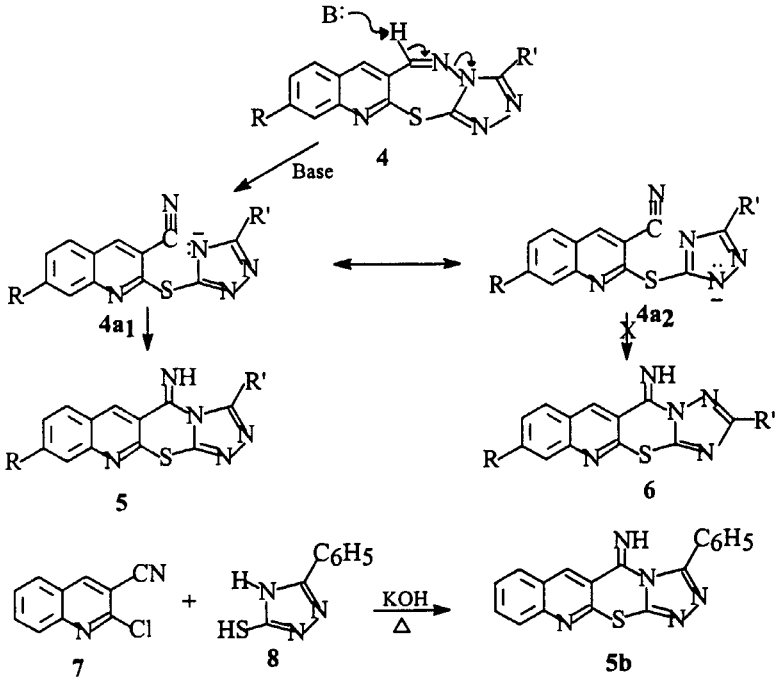


Scheme -1

Reagents and conditions: i) Isopropanol, R.T., 15 h (94 %) ii) Isopropanol, conc. HCl, reflux, 0.5 h (82.4-93.7 %), iii) CH_3OH-aq.KOH, 1 eq. R.T., 2 h (92.8 %)

iv) CH_3OH-aq.KOH, 2 eq., reflux, 2 h (85 %), v) CH_3OH-KOH, 1 eq., reflux, 1-8 h. (89.2-98 %).

Base catalyzed intramolecular rearrangement involving scission of N-N bond or N-O bond and formation of a nitrile group is wellknown in the literature[7]. Close observation of the structure of **4a** reveals that it contains a CH=N-N system. Therefore, diazepino compound **4a** was treated with hot (1:1) methanolic KOH solution. When rearrangement took place, a new isomeric product s-triazolothiazinoquinoline **5a** was obtained (**Scheme–1**). The compound **5a** was also obtained directly from **3a** under reflux using 1:2 equivalents of methanolic KOH solution. The NMR spectrum of **5a** showed the absence of the azomethine proton, IR spectrum contained a broad band at 3350-3260 cm^{-1} attributed to NH group, but no nitrile band and mass spectrum showed a molecular peak at m/z 267. Comparison of ^{13}C NMR spectrum showed that the doublet due to the azomethine group, CH=N-N at δ 152 ppm in **4a** was found absent in the spectrum of **5a**. Instead a singlet at δ 162 ppm attributed to N-CH=NH was seen in the spectrum of **5a**. The course of the reaction from **4a** to **5a** can be rationalized. Abstraction of the azomethine proton by base and subsequent scission of the N-N bond leads to a nitrile, which undergoes facile intramolecular ring closure to give **5a** (**Scheme-2**). The intermediate nitrile formed by the cleavage of N-N bond could lead to the formation of s-triazolothiazinoquinoline **5** or **6**. However, that the compound formed was **5** and not **6** was proved by an unambiguous synthesis of **5b** by the base-catalyzed condensation of 2-chloro-3-cyanoquinoline[4] **7** with 3-phenyl-5-mercapto-s-triazole[9] **8**. It was also observed that the s-triazolothiadiaze-



Scheme 2

pinoquinoline **4a** could be obtained directly from **1a** without isolating the intermediate compound **3a**.Carrying out the condensation reaction of **1a** and **2a** in isopropanol under reflux using a few drops of concentrated HCl as catalyst gave compound **4a**, found identical with the one obtained by the cyclization of the intermediate compound **3a.**

In order to study the generality of the rearrangement, s-triazolothia-diazepinoquinolines **4b-f** were prepared from respective chloroaldehydes **1a-c** and 3-substituted–5-mercapto-s-triazoles **2b-d** and subjected to base-catalyzed intramolecular facile rearrangement. The desired rearrangement products **5b-f** were obtained.

In summary, we have demonstrated that 2-chloro-3-formylquinolines **1** can be used as excellent starting materials for the synthesis of s-triazolothiazino-quinolines **5**. Condensing 3-substituted-4-amino-5-mercapto-1:2:4 triazoles **2** with appropriate formylquinolines **1** and then subjecting the diazepino compounds **4** to base-catalyzed novel intramolecular rearrangement involving the scission of **N-N** bond affords quinolines **5**.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tube using Thomas-Hoover apparatus and were uncorrected. The **IR** spectra in nujol were determined on a perkin–Elmer 1000 spectrophotometer , ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 or DMSO–d_6 + CF_3COOH on a varian A-60 or OBFRQ 400 MHz spectrometer using TMS as an internal standard (δ units), ^{13} C NMR spectra were determined in $CDCl_3$, and mass spectra (EI) on a Jeol D-300 spectrometer. Analytical TLC was performed on Merck 60F-254 silica gel plates.

4(2^1-Chloro-3^1-azomethinylquinoline)-3-methyl-5-mercapto-1:2:4 triazole 3a: A mixture of 2-chloro-3-formylquinoline **1a** (0.005 mol, 0.96 g) and 3-methyl-4-amino-5-mercapto-1:2:4 triazole **2a** (0.005 mol, 0.73 g) in isopropanol (75 mL) was stirred at room temperature for 15 h. The reaction mixture was then poured into ice-water (150 mL) and stirred for 0.5 h. The yellow product obtained was collected by filtration, washed with water, dried and purified by column chromatography using benzene-acetone (7:3) as eluent to afford **3a** in 94 % yield; **m.p** 179-180 °C ; **IR** (nujol) : 1577, 1613, 1688(s) and 2666(w) cm^{-1}; **^{1}H NMR**

(DMSO–d_6): δ (ppm) 2.25 (s,3H,CH_3), 3.75 (bs, 1H, SH), 7.55 - 8.25 (m,4H, H-Aromatic), 8.85 (s,1H, CH=N), 9.05 (s, 1H, H-4); **EIMS:** M^+ (m/z) 303. Calcd.mass for $C_{13}H_{10}N_5ClS$: 303.50. **Anal. calcd:** C: 51.44, H: 3.32, N: 23.08, S: 10.56. **Found:** C: 51.39, H: 3.40, N: 23.02, S: 10.52.

3-Methyl-(1:2:4) triazolo [3,4-b] (1,3,4) thiadiazepino (6,7-3,2) quinoline 4a: (method A). A mixture of **3a** (0.005 mol, 1.53 g) in methanol (40 mL) and aqueous KOH (0.5 g in 5 mL) was stirred at room temperature for 2 h. The product that obtained after pouring the reaction mixture into cold water (75 mL) was collected by filtration, washed with water, dried and recrystallized from DMF to afford **4a** in 92.8 % yield (1.41 g) as a white micro needle shaped solid, **m.p** 280-181 °C; **IR** (nujol) : 1611 and 1535 cm^{-1}; **^{1}H NMR** (DMSO+TFA) : δ (ppm) 2.54 (s, 3H, CH_3), 7.65-7.90 (m, 4H, H-Aromatic), 8.25 (s, 1H, CH=N), 8.36 (s, 1H, H-4); **EIMS :** M^+ (m/z) 267. Calcd. mass for $C_{13}H_9N_5S$: 267. 3811. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ (ppm) 10.86, 126.02, 127.12, 128.42, 128.83, 129.37, 133.24, 141.50, 149.04, 151.91, 152.88, 153.49. **Anal. calcd:** C: 58.28, H: 3.38, N: 26.14, S: 11.99. **Found:** C: 58.22, H: 3.25, N: 26.15, S: 11.97.

General procedure for the preparation of 3-and 10-disubstituted-(1:2:4) triazolo [3,4-b] (1,3,4) thiadiazepino [6,7-3,2] quinolines 4a-f:

A mixture of appropriately 7-substituted-2-chloro-3-formylquinoline (**1a-c**, 0.005 mol) and 3-substituted–4-amino–5-mercapto-1:2:4 triazole (**2a-d**, 0.005 mol) in isopropanol (40-75 mL) containing 2-3 drops of conc. HCl was heated under reflux on a steam bath for 0.5 h. The product that obtained was collected by filtration, washed with water, dried and recrystallized from DMF solvent to afford **4a-f** in high yield (82.4 – 93.7 %).

3-Methyl-(1:2:4) triazolo [3,4-b] (1,3,4) thiadiazepino (6,7-3,2) quinoline 4a: (Method B) was obtained in 83.3 % yield (1.4 g); IR, NMR and M.P were same as the compound prepared by the cyclization of intermediate **3a.**

3-Phenyl-(1:2:4) triazolo [3,4-b] (1,3,4) thiadiazepino (6,7-3,2) quinoline 4b: was obtained in 93.7 % yield (1.8 g) as white micro needles, m.p 251-252 °C; IR (nujol): 1617 and 1548 cm^{-1}; EIMS: M^+ (m/z) 329. Calcd.mass for $C_8H_{11}N_5S$: 329.2859, N: 21.22, requires N:21.26.

3(4^1 – Methylphenyl)- (1:2:4) triazolo [3,4-b] (1,3,4) thiadiazepino (6,7-3,2) quinoline 4c: was obtained in 85.4 % yield (1.70 g) as soft white micro crystals, **m.p** 263-264 °C; **IR** (nujol): 1609 and 1552 cm^{-1}; **EIMS** : M^+ (m/z) 343. Calcd.mass for $C_{19}H_{13}N_5S$: 343.445. **N:** 20.32, requires **N:** 20.39.

3(4^1 – Chlorophenyl)-(1:2:4) triazolo [3,4-b] (1,3,4) thiadiazepino (6,7-3,2) quinoline 4d: was obtained in 93 % yield (1.95 g) as white flakes, **m.p** 283-284 °C; **IR** (nujol): 1609, 1557 and 1661 cm^{-1}; **EIMS:** M^+ (m/z) 363. Calcd. mass for $C_{18}H_{10}N_5SCl$: 363.268, **N:** 19.19, requires **N:** 19.25.

3,10-Dimethyl-(1:2:4) triazolo [3,4-b] (1,3,4) thiadiazepino (6,7-3,2) quinoline 4e: was obtained in 82.4 % yield (1.45 g) as white micro crystalline solid, **m.p** 259-260 °C; **IR** (nujol): 1616 and 1513 cm^{-1} ; **EIMS** : M^+ (m/z) 281. Calcd mass for $C_{14}H_{11}N_5S$: 281.177, **N:** 24.82, requires **N:**24.90.

10-Chloro-3-methyl-(1:2:4) triazolo [3,4-b] (1,3,4) thiadiazepino (6,7-3,2) quinoline 4f: was obtained in 86.2 % yield (1.59 g) as pale yellow micro needles, **m.p** 284-286 °C; **IR** (nujol): 1603 and 1574 cm^{-1}; **EIMS:** M^+(m/z) 301. Calcd. mass for $C_{13}H_8N_5SCl$: 302.3811. **N:** 23.14, requires **N:** 23.16.

General procedure for the preparation of 3- and 9-disubstituted-5-imino-5H-(1:2:4) triazolo [3,4-b]-1,3 thiazino (5,6-3,2) quinolines 5a-f:

An equimolar (0.0033 mol) mixture of appropriate s-triazolothiadiazepinoquinoline in methanol (**4a-f**, in 100-150 mL) and KOH was heated under reflux on a steam bath for 1-8 h. The solvent was then evaporated under reduced pressure to afford a solid residue, which was treated with cold water (30 mL), filtered, washed with ethanol (2x10 mL), dried and recrystallized from methanol or THF or dioxan to afford **5a-f** in 89.2 – 98 % yield.

3-Methyl-5-imino-5H-(1:2:4) triazolo [3,4-b] -1,3- thiazino (5,6-3,2) quinoline 5a: Reaction time; 1.5 h, was obtained in 94.5 % yield (0.85 g) as a pale yellow crystalline solid , **m.p** 252-253 °C (CH_3OH); **IR** (nujol) : 3267, 1648, and 1580 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ (ppm) 2.55 (s, 3H, CH_3), 7.60-8.06 (m, 4H, H-Aromatic), 9.52 (s, 1H, H-4), 9.56 (s, 1H, NH); **EIMS :** M^+(m/z) 267. Calcd. mass for $C_{13}H_9N_5S$: 267.4811. **^{13}C NMR** ($CDCl_3$, 100 MHz): δ (ppm) 14.23, 126.13, 127.66, 127.73, 128.03, 129.17, 133.23, 139.12, 147.30, 14.975, 149.35, 149.59, 153.96, 163.26. **Anal. cacld:** C: 58.38, H: 3.38 , N: 26.14, S: 11.97. **Found:** C: 58.24, H: 3.39, N: 26.11, S: 11.89.

3-Phenyl-5-imino-5H-(1:2:4) triazolo [3,4-b]-1,3- thiazino (5,6-3,2) quinoline, 5b: Reaction time; 3 h, was obtained in 92 % (0.937 g) as white micro needles, **m.p** 283-284 °C (CH_3OH); **IR** (nujol): 3268, 1647, 1581 and 1612 cm^{-1}; **EIMS:** M^+ (m/z) 329. Calcd. mass for $C_{18}H_{11}N_5S$: 329.3859. **Anal. calcd:** C: 65.63 , H: 3.36, N: 21.26. **Found:** C: 65.58, H: 3.32, N: 21.18.

3(4-Methylphenyl)-5-imino-5H-(1:2:4) triazolo [3,4-b]-1,3- thiazino (5,6-3,2) quinoline, 5c: Reaction time; 1 h, was obtained in 90 % yield (1 g) as pale yellow

micro needles, **m.p** 287-288 °C (THF); **IR** (nujol): 3271, 1635, 1580 and 1605 cm^{-1}; **EIMS :** M^+(m/z) 343. Calcd. mass for $C_{19}H_{13}N_5S$: 343.445, **Anal. Calcd:** C: 66.44, H: 3.36, N: 21.26, **Found:** C: 65.58, H: 3.32, N: 21.18.

3(4-Chlorophenyl)-5-*imino*-5H-(1:2:4) triazolo [3,4-b]-1,3-thiazino (5,6-3,2) quinoline 5d: Reaction time; 8 h, was obtained in 98 % yield (0.55 g) as pale yellow micro silky needles, **m.p** 289-290 °C (dioxan); **IR** (nujol): 3290, 1642, 1582, and 1613 cm^{-1}; **EIMS:** M^+ (m/z) 363. Calcd. mass for $C_{18}H_{10}N_5SCl$: 363.368. **Anal. calcd:** C: 59.41, H: 2.77, N : 19.24. **Found:** C: 59.39, H: 2.71, N: 19.21.

3,9-Dimethyl-5-imino-5H-(1:2:4) triazolo [3,4-b]-1,3- thiazino (5,6-3,2) quinoline, 5e: Reaction time; 2.5 h, was obtained as a white soft solid, **m.p** 234-235 °C (CH_3OH); **IR** (nujol): 3421, 1650, 1550 and 3261 cm^{-1}; **EIMS:** M^+ (m/z) 281. Calcd. mass for $C_{14}H_{11}N_5S$: 281.177. **Anal. calcd:** C: 69.76, H: 3.94, N: 24.9, **Found:** C: 69.73, H: 3.91, N: 24.91.

3-Methyl-9-chloro-5-imino-5H-(1:2:4) triazolo [3,4-b]-1,3- thiazino (5,6-3,2) quinoline, 5f: Reaction time; 2 h, was obtained in 98 % yield (0.85 g) as pale yellow silky needles, **m.p** 288-289 °C (THF); **IR** (nujol): 3282, 3053, 1645 and 1611 cm^{-1}; **EIMS:** M^+ (m/z) 301. Calcd. mass for $C_{13}H_8N_5SCl$: 302.380, **Anal. calcd:** C: 51.63, H: 2.66, N: 23.16. **Found:** C: 51.60, H: 2.62, N: 23.13.

Preparation of 3-methyl-5-*imino*-5H-(1:2:4) triazolo [3,4-b]-1,3-thiazino (5,6-3,2) quinoline 5a from 3a:

A mixture of 4 (2^1 -chloro-3^1 –azomethinylequinoline) –3-methyl-5-mercapto-1:2:4 triazole **3a** (0.005 mol, 1.53 g) in methanol (75 mL) and KOH (0.01 mol,

0.56 g) in water (5 mL) was heated with stirring on a steam bath for 2 h. After complete reaction (TLC), the mixture was concentrated by rotary evaporation and poured in to cold water (50 mL). The product that obtained was collected by filtration, washed with water, dried and recrystallized from methanol to afford 3a in 85 % yield (1.3 g).

Preparation of 3-phenyl-5-imino-5H-(1:2:4) triazolo [3,4-b]-1,3- thiazino (5,6-3,2) quinoline 5b from 7 and 8:

A mixture of 2-chloro-3-cyanoquinoline **7** (0.01 mol, 1.88 g) and 3-phenyl-5-mercapto-s-triazole **8** (0.01 mol; 1.7 g) containing methanolic KOH (1.12 g in 75 mL) was refluxed on a steam bath for 2.5 h. After complete reaction (TLC), the reaction mixture was concentrated by rotary evaporation, poured in to ice-cold water (60 mL) and neutralized with acetic acid. The product that obtained was collected by filtration, washed thoroughly with water, dried and recrystallized from methanol to afford **5b** in 78 % yield (2.79 g).

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