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Studies in pyrimidine-annulated heterocycles: unusual formation of spiroheterocyclic compounds from acid catalyzed reaction of enol ether

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Abstract—A number of spiroheterocycles are synthesized in moderate yield by treating 5-aryloxymethylene-6,7,8-trihydropyrido[2,3-*d*]pyrimidines-2,4(1*H*,3*H*)diones with H_2SO_4 in chloroform–methanol–water. These spiroheterocycles are also regioselectively synthesized by tri-*n*-butyltin hydride induced radical cyclization of 5-(*o*-bromoaryloxymethylene)-6,7,8-trihydropyrido[2,3-*d*]pyrimidines-2,4(1*H*,3*H*)diones.

Pyrimidine derivatives are well-known[1,2] for their biological activity. Numerous pyrimidine and uracil based compounds have found application in medicine and therapeutics e.g. some are used in the chemotherapy of cancer[3] and some are used against HIV and viral[4] diseases. Usually functionalization of uracil at the C-5 and C-6 positions leads to biologically interesting molecules. In continuation of our work on pyrimidine annulated heterocycles[5] we have recently reported[6] the synthesis of 5-aryloxymethylene-6,7,8-tri-hydropyrido[2,3-*d*]pyrimidine-2,4-diones (**1**). We have now turned our attention to the synthesis of spiroheterocycles from the earlier obtained products of [3,3] sigmatropic rearrangement. Here we report the results of this investigation.

The starting materials for the synthesis of spiroheterocycles were synthesized according to our earlier published procedure.[6] The substrate **1** was refluxed with a catalytic amount of H_2SO_4 in chloroform–methanol–water mixture for 4 h in an attempt to cleave the enol ether. Three different products, a spiroheterocycle (**2**) (mp 192°C, 8%), and two products **3** (mp 162°C, 12%) and **4** (mp 144°C, 45%) were obtained (Scheme 1).

Formation of products **2**–**4** from the substrates **1** by acid catalysis may be explained by the initial protonation of the enol ether double bond of **1** to form a latent carbonium ion **5**. The protonation of a vinyl ether normally occurs at the remote position relative to the oxygen function. But here the more basic nitrogen function of the diene unit is controlling the site of protonation. This carbonium ion **5** may undergo nucleophilic attack by the aromatic double bond ('pathway a') to give a resonance stabilized carbocation **6** which may then lose a proton to give spiroheterocyclic compounds **2**, or nucleophilic attack by water followed by deprotonation and elimination of anisole to give **9**, which may then undergo double group transfer reaction[7] with **1** to give **3** and **4** (Scheme 2). The group transfer reaction is thermally symmetry-allowed.[8] Removal of anisole is demonstrated by GC analysis of the crude reaction mixture after usual work up (compared with a standard sample of anisole).

Aryl radical cyclization has recently emerged as a valuable tool for organic synthesis.[9] The generation and subsequent reactions of radicals formed from aryl halides using tri-*n*-butyltin hydride and azobisisobutyronitrile (AIBN) is now well-established[9] and a wide range of natural product synthesis based on aryl radical cyclizations have been reported.[10] However, the literature reveals only a few examples of heteroaryl radicals.[11] We have, therefore, explored the possibility whether the spiroheterocyclic system (**2**) can be synthesized by tri-*n*-butyltin hydride initiated radical cyclization of appropriate substrates (**1i**,**j**). The substrates **1i**,**j** were refluxed in dry benzene with sodium cyanoborohydride and tri-*n*-butyltin chloride in the presence of 0.5–0.6 mol equiv. of azobisisobutyronitrile (AIBN) for 4 h to give spiroheterocycles **2a** and **2e** in 55 and 52% yield, respectively (Scheme 3).

The formation of the products **2a**,**e** from **1i**,**j** may be explained by the formation of aryl radical **10** followed by '5-*endo*' trig cyclization to give spirocyclic radical **11**,

Keywords: enol ethers; radicals and radical reactions; spiro compounds; group transfer reaction; pyrimidines/pyrimidinones.

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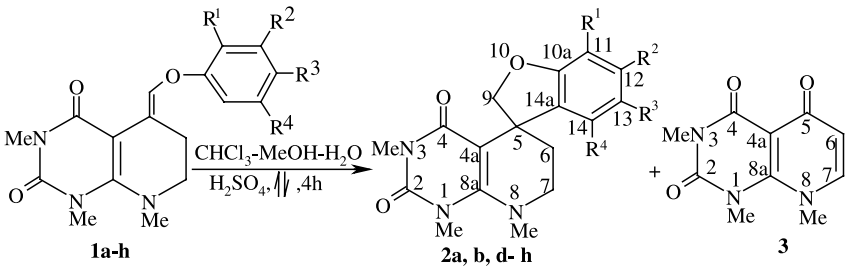
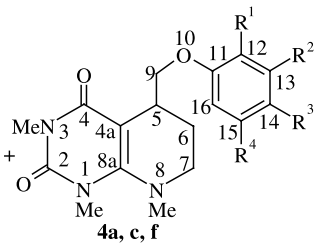
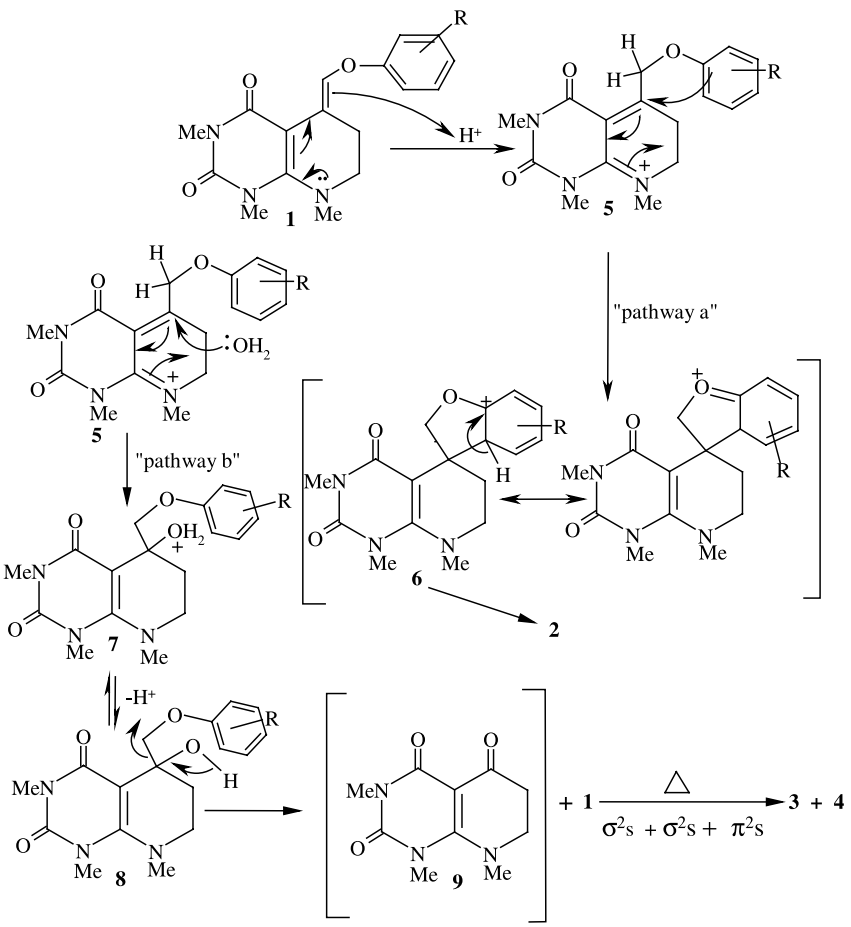


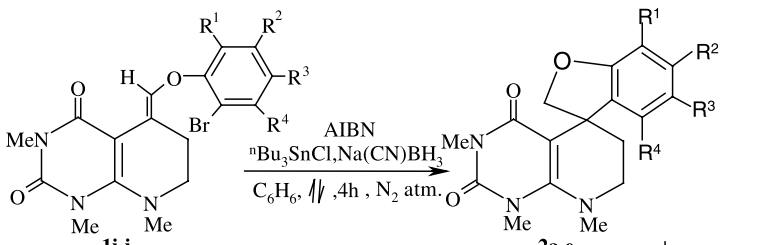
1	2 Yield(%)	3 Yield(%)	4 Yield(%)
a. R^1= R^2= R^3= R^4= H	8	12	45
b. R^1=Me, R^2=R^3=R^4=H	40	-	-
c. R^3=Me, R^1=R^3=R^4=H	-	6	42
d. R^2= R^4= Me, R^1= R^3= H	50	-	-
e. R^1=R^3=Me, R^2=R^3=H	42	-	-
f. R^1= Cl, R^4= R^2= R^3= H	6	9	47
g. R^1=R^4= Me, R^2 = R^3=H	50	-	-
h. R^1= R^2= Me, R^3= R^4= H	48	-	-



Scheme 1.

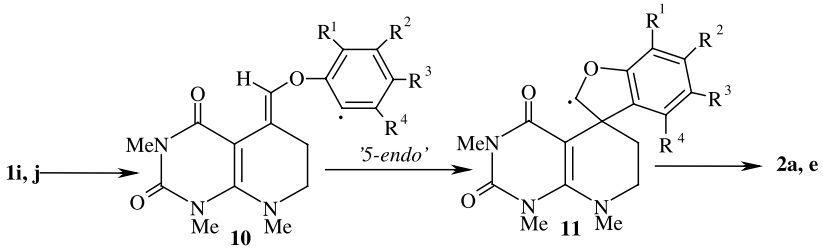


Scheme 2.



1	2 Yield(%)
i. $R^1=R^2=R^3=R^4=H$	2a 52
j. $R^1=R^3=Me$, $R^2=R^4=H$	2e 55

Scheme 3.



Scheme 4.

which may then give the final spiroheterocycles **2a**,**e** (Scheme 4).

The options here are (i) a '4-*exo*' *trig* versus '5-*endo*' *trig* onto the alkenyl part of the diene and (ii) '6-*exo*' *trig* versus '7-*endo*' *trig* onto the ene-amine part of the diene. Recently, it has been shown that the '5-*endo*' *trig* cyclization is preferred[12] over a '4-*exo*' if the radical stabilization is unfavored. Therefore, the results reported here are interesting. '5-*endo*' cyclization of intermediate radical **10** gave spiroheterocyclic compounds as the only isolable products in the cases studied so far.

In conclusion the conditions under which the spiroheterocycles are formed is normally the usual ones for enol ether cleavage. From the aforesaid results it is clear that the substituents on the aromatic ring seem to have a pronounced effect on the course of the reaction. The regioselective synthesis of spiroheterocycles has also been achieved by tri-*n*-butyltin hydride initiated radical cyclization of 5-(*o*-bromoaryloxymethylene)-6,7,8-trihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)diones.

1. Experimental

1.1. General

Melting points were determined in a open capillary and are uncorrected. UV absorption spectra were recorded in EtOH on a Shimadzu UV-2401 PC spectrophotometer (λ_{max} in nm) and IR spectra in KBr discs on a Perkin–Elmer L 120-000A apparatus (ν_{max} in cm^{-1}). ^1H NMR and ^{13}C NMR spectra were run in $CDCl_3$ with TMS as an internal standard on a Bruker DPX-300 MHz and 75.5 MHz instrument at the Indian Institute of Chemical Biology, Kolkata (chemical shifts in δ ppm). Elemental analyses and mass spectra were recorded by RSIC (CDRI), Lucknow on a JEOL D-300 (E1) instrument. GC analysis was performed at IICB, Kolkata on a Hewlett–Packard 6890 plus fitted with FID. Silica gel (60–120 mesh) was obtained from Spectrochem, India. Extracts were dried over anhydrous sodium sulfate. Petroleum ether refers to the fraction boiling between 60 and 80°C.

The starting materials (**1a**–**h**) for this study were prepared according to our earlier published procedure.[6] The substrates **1g**–**j** were newly prepared from the amines 6-[*N*-4-(2′,5′-dimethylphenoxybut-2-ynyl)-*N*-methylamino]-1,3-dimethyl-uracil, 6-[*N*-4-(2′,3′-dimethylphenoxy-but-2-ynyl)-*N*-methylamino]-1,3-dimethyl-uracil, 6-[*N*-4-(2′-bromophenoxybut-2-ynyl)-*N*-methylamino]-1,3-dimethyl-uracil and 6-[*N*-4-(2′-bromo 4′,6′-dimethylphenoxybut-2-ynyl)-*N*-methylamino]-1,3-dimethyl-uracil for which characterization data are given as follows.

1.1.1. 6-[*N*-4-(2′,5′-Dimethylphenoxybut-2-ynyl)-*N*-methylamino]-1,3-dimethyl-uracil. Yield 76%, viscous liquid; UV (EtOH): λ_{max} 216 and 276 nm; IR (neat): ν_{max} 2960, 1705, 1640 and 1285 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, $-CH_3$), 2.30 (s, 3H, $-CH_3$), 2.74 (s, 3H, $-NCH_3$), 3.28 (s, 3H, $-NCH_3$), 3.35 (s, 3H, $-NCH_3$), 3.71 (s, 2H, $-NCH_2$), 4.63 (s, 2H, $-OCH_2$), 5.41 (s, 1H, vinylic *H*) 6.79–6.86 (m, 3H, Ar*H*); *m*/*z* 341 (M^+). Anal. calcd for $C_{19}H_{23}N_3O_3$: C, 66.86; H, 6.74; N, 12.31%; found C, 66.91; H, 6.69; N, 12.20%.

1.1.2. 6,7,8-Trihydro-1,3,8-trimethyl-5-(2′,5′-dimethylphenoxymethylene)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)diones (1g). Yield 72%, white solid, mp 164°C; UV (EtOH): λ_{max} 210, 268, 318 nm; IR (KBr): ν_{max} 2900, 1680, 1635 and 1280 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, $-CH_3$), 2.33 (s, 3H, $-CH_3$), 2.78 (t, J=6 Hz, 2H, $-NCH_2CH_2$), 2.83 (s, 3H, $-NCH_3$), 3.12 (t, J=6 Hz, 2H, $-NCH_2$), 3.44 (s, 3H, $-NCH_3$), 3.47 (s, 3H, $-NCH_3$), 6.72–6.76 (m, 3H, Ar*H*), 8.25 (s, 1H, =C*H*); *m*/*z* 341 (M^+). Anal. calcd for $C_{19}H_{23}N_3O_3$: C, 66.86; H, 6.74; N, 12.31%; found C, 66.91; H, 6.74; N, 12.22%.

1.1.3. 6-[*N*-4-(2′,3′-Dimethylphenoxybut-2-ynyl)-*N*-methylamino]-1,3-dimethyl-uracil. Yield 78%, viscous liquid; UV (EtOH): λ_{max} 212 and 278 nm; IR (neat): ν_{max} 2960, 1690, 1640 and 1285 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, $-CH_3$), 2.33 (s, 1H, $-CH_3$), 2.71 (s, 3H, $-NCH_3$), 3.30 (s, 3H, $-NCH_3$), 3.39 (s, 3H, $-NCH_3$), 3.76 (s, 2H, $-NCH_2$), 4.65 (s, 2H, $-OCH_2$), 5.43 (s, 1H, vinylic *H*) 6.88–7.19 (m, 3H, Ar*H*); *m*/*z* 341 (M^+). Anal. calcd for $C_{19}H_{23}N_3O_3$: C, 66.86; H, 6.74; N, 12.31%; found C, 66.73; H, 6.81; N, 12.36%.

1.1.4. 6,7,8-Trihydro-1,3,8-trimethyl-5-(2′,3′-dimethylphenoxymethylene)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)diones (1h). Yield 75%, white solid, mp 134°C; UV (EtOH): λ_{max} 209, 266 and 316 nm; IR (KBr): ν_{max} 2900, 1680, 1620 and 1280 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H, $-CH_3$), 2.35 (s, 3H,$-CH_3$), 2.77 (t, J=6 Hz, 2H, $-NCH_2CH_2$), 2.87 (s, 3H, $-NCH_3$), 3.23 (t, J=6 Hz, 2H, $-NCH_2$), 3.46 (s, 3H, $-NCH_3$), 3.49 (s, 3H, $-NCH_3$), 6.71–6.79 (m, 3H, Ar*H*), 8.19 (s, 1H, =C*H*); *m*/*z* 341 (M^+). Anal. calcd for $C_{19}H_{23}N_3O_3$: C, 66.86; H, 6.74; N, 12.31%; found C, 66.66; H, 6.83; N, 12.21%.

1.1.5. 6-[*N*-4-(2′-Bromophenoxybut-2-ynyl)-*N*-methylamino]-1,3-dimethyl-uracil. Yield 75%, viscous liquid; UV (EtOH): λ_{max} 216 and 283 nm; IR (neat): ν_{max} 2960, 1710 1640, 1250, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.72 (s, 3H, $-NCH_3$), 3.29 (s, 3H, $-NCH_3$), 3.35 (s, 3H, $-NCH_3$), 3.85 (s, 2H, $-NCH_2$), 4.77 (s, 2H, $-OCH_2$), 5.36 (s, 1H, vinylic *H*) 7.16–7.28 (m, 4H, Ar*H*); *m*/*z* 391, 393 (M^+). Anal. calcd for $C_{17}H_{18}N_3O_3Br$: C, 52.05; H, 4.59; N, 10.72%; found C, 52.11; H, 4.44; N, 10.85%.

1.1.6. 6,7,8-Trihydro-1,3,8-trimethyl-5-(2′-bromophenoxymethylene)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)diones (1i). Yield 75%, white solid, mp 190°C; UV (EtOH): λ_{max} 219, 258 and 318 nm; IR (KBr): ν_{max} 2910, 1690, 1610, 1280 and 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.80 (t, J=6 Hz, 2H, $-NCH_2CH_2$), 2.88 (s, 3H, $-NCH_3$), 3.29 (t, J=6 Hz, 2H, $-NCH_2$), 3.47 (s, 3H, $-NCH_3$), 3.49 (s, 3H, $-NCH_3$), 6.87–6.91 (m, 4H, Ar*H*), 8.31 (s, 1H, =C*H*); *m*/*z* 391, 401 (M^+). Anal. calcd for $C_{17}H_{18}N_3O_3Br$: C, 52.05; H, 4.59; N, 10.72%; found C, 52.19; H, 4.50; N, 10.69%.

1.1.7. 6-[*N*-4-(2′-Bromo-4′,6′-dimethylphenoxybut-2-ynyl)-*N*-methylamino]-1,3-dimethyl-uracil. Yield 79%, viscous liquid; UV (EtOH): λ_{max} 219, 267 nm; IR (neat): ν_{max} 2955, 1710, 1650, 1220, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, $-CH_3$), 2.37 (s, 3H, $-CH_3$), 2.81 (s, 3H, $-NCH_3$), 3.33 (s, 3H, $-NCH_3$), 3.40 (s, 3H, $-NCH_3$), 3.82 (s, 2H, $-NCH_2$), 4.78 (s, 2H, $-NCH_2$), 5.41 (s, 1H, vinylic *H*) 7.11 (s, 1H, Ar*H*), 7.19 (s, 1H, Ar*H*); *m*/*z* 419, 421 (M^+). Anal. calcd for $C_{19}H_{22}N_3O_3Br$: C, 54.29; H, 5.24; N, 10.00%; found C, 54.13; H, 5.33; N, 9.92%.

1.1.8. 6,7,8-Trihydro-1,3,8-trimethyl-5-(2′-bromo-4′,6′-dimethylphenoxymethylene)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)diones (1j). Yield 73%, white solid, mp 188°C; UV (EtOH): λ_{max} 220, 265 and 317 nm; IR (KBr): ν_{max} 2920, 1680, 1620, 1205 and 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, $-CH_3$), 2.41 (s, 3H, $-CH_3$), 2.78 (t, J=6 Hz, 2H, $-NCH_2CH_2$), 2.85 (s, 3H, $-NCH_3$), 3.26 (t, J=6 Hz, 2H, $-NCH_2$), 3.45 (s, 3H, $-NCH_3$), 3.47 (s, 3H, $-NCH_3$), 6.88 (s, 1H, Ar*H*), 6.93 (s, 1H, Ar*H*), 8.27 (s, 1H, =C*H*); *m*/*z* 419, 421 (M^+). Anal. calcd for $C_{19}H_{22}N_3O_3Br$: C, 54.29; H, 5.24; N, 10.00%; found C, 54.23; H, 5.29; N, 10.08%.

1.2. General procedure for the acid catalyzed reaction of compound 1a–h

Compound **1a–h** (1 mmol) was dissolved in chloroform (8.4 mL). Water (3 mL), methanol (13.5 mL) and sulfuric acid (2.3 mL) were added to this solution. The reaction mixture was refluxed on a water bath for 4 h. It was then cooled and extracted with chloroform (3×20 mL) and the combined extract was washed with sodium bicarbonate solution (3×20 mL), water (3×15 mL) and dried over Na_2SO_4. After removal of chloroform the crude mass was chromatographed over silica gel. The compounds were successively eluted out with pet-ether/ethylacetate (9:1).

1.2.1. 5-{3′-Benzo(2′,3′-dihydro)furo}-6,7,8-trihydro-1,3,8-trimethyl-pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2a). Yield 8%, white solid, mp192°C; UV (EtOH): λ_{max} 213 and 285 nm; IR (KBr): ν_{max} 2920, 1700, 1640 and 1210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.88–1.98 (m, 2H, $-NCH_2CH_2$), 2.84 (s, 3H, $-NCH_3$), 3.09–3.18 (m, 2H, $-NCH_2$), 3.22 (s, 3H, $-NCH_3$), 3.44 (s, 3H, $-NCH_3$), 4.19 (d, J=8.1 Hz, 1H, $-OCH_2$), 4.79 (d, J=8.1 Hz, 1H, $-OCH_2$), 6.80–6.84 (m, 3H, Ar*H*), 7.10–7.12 (m, 1H, Ar*H*); δ 28.14 (CH_3), 30.51 (C_6), 33.58 (CH_3), 39.07 (N_8-CH_3), 46.67 (C_5), 48.83 (C_7), 79.57 (C_9), 97.41 (C_{4a}), 109.60 (C_{11}), 124.71 (C_{13}), 127.56 (C_{14}), 132.82 (C_{14a}), 138.78 (C_{12}), 153.18 (C_2), 155.87 (C_{8a}), 160.44 (C_{10a}), 160.93 (C_4). *m*/*z* 313 (M^+). Anal. calcd for $C_{17}H_{19}N_3O_3$: C, 65.17; H, 6.07; N, 13.41%; found C, 65.32; H, 5.96; N, 13.34%.

1.2.2. 5-{3′-Benzo(2′,3′-dihydro-7′-methyl)furo}-6,7,8-trihydro-1,3,8-trimethyl-pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (2b). Yield 40%, white solid, mp 216°C; UV (EtOH): λ_{max} 213 and 285 nm; IR (KBr): ν_{max} 2920, 1700, 1640 and 1190 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.84–1.89 (m, 2H, $-NCH_2CH_2$), 2.25 (s, 3H, CH_3), 2.83 (s, 3H, $-NCH_3$), 3.07–3.19 (m, 2H, $-NCH_2$), 3.22 (s, 3H, $-NCH_3$), 3.44 (s, 3H, $-NCH_3$), 4.19 (d, J=8 Hz, 1H, $-OCH_2$), 4.80 (d, J=8 Hz, 1H, $-OCH_2$), 6.66–6.74 (m, 2H, Ar*H*), 6.94 (m, 1H, Ar*H*); *m*/*z* 327 (M^+). Anal. calcd for $C_{18}H_{21}N_3O_3$: C, 66.05; H, 6.42; N, 12.84%; found C, 66.14; H, 6.37; N, 12.79%.

1.2.3. 5-{3′-Benzo(2′,3′-dihydro-4′,6′-dimethyl)furo}-6,7,8-trihydro-1,3,8-trimethyl-pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (2d). Yield 50%, white solid, mp 226°C; UV (EtOH): λ_{max} 214 and 288 nm; IR (KBr): ν_{max} 2940, 1690, 1620 and 1300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.83–1.89 (m, 2H, $-NCH_2CH_2$), 2.07 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.85 (s, 3H, $-NCH_3$), 3.12–3.16 (m, 2H, $-NCH_2$), 3.24 (s, 3H, $-NCH_3$), 3.43 (s, 3H, $-NCH_3$), 4.10 (d, J=8.1 Hz, 1H, $-OCH_2$), 4.64 (d, J=8.1 Hz, 1H, $-OCH_2$), 6.38 (s, 1H, Ar*H*), 6.51 (s, 1H, Ar*H*); ^{13}C NMR (300 MHz): δ 17.77 ($C_{14}-CH_3$), 21.87 ($C_{12}-CH_3$), 28.23 (CH_3), 30.56 (C_6), 33.78 (CH_3), 41.07 (N_8-CH_3), 46.55 (C_5), 48.60 (C_7), 80.81 (C_9), 97.51 (C_{4a}), 108.77 (C_{11}), 124.01 (C_{13}), 127.73 (C_{14}), 132.12 (C_{14a}), 138.22 (C_{12}), 153.11 (C_2), 156.17 (C_{8a}), 160.63 (C_{10a}), 161.46 (C_4); *m/z* 341 (M^+). Anal. calcd for $C_{19}H_{23}N_3O_3$: C, 66.86; H, 6.74; N, 12.31%; found C, 66.98; H, 6.67; N, 12.27%.

1.2.4. 5-{3′-Benzo(2′,3′-dihydro-5′,7′-dimethyl)furo}-6,7,8-trihydro-1,3,8-trimethyl-pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (2e). Yield 42%, white solid, mp 240°C; UV (EtOH): λ_{max} 218 and 285 nm; IR (KBr): ν_{max} 2940, 1680, 1615 and 1290 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.78–1.86 (m, 2H, $-NCH_2CH_2$), 2.09 (s, 3H, $-CH_3$), 2.22 (s, 3H, $-CH_3$), 2.76 (s, 3H, $-NCH_3$), 2.96–3.07 (m, 2H, $-NCH_2$), 3.15 (s, 3H, $-NCH_3$), 3.36 (s, 3H, $-NCH_3$), 4.09 (d, J=8.1 Hz, 1H, $-OCH_2$), 4.72 (d, J=8.1 Hz, 1H, $-OCH_2$), 6.49 (s, 1H, Ar*H*), 6.71 (s, 1H, Ar*H*); *m/z* 341 (M^+). Anal. calcd for $C_{19}H_{23}N_3O_3$: C, 66.86; H, 6.74; N, 12.31%; found C, 66.98; H, 6.82; N, 12.37%.

1.2.5. 5-{3′-Benzo(2′,3′-dihydro-7′-chloro)furo}-6,7,8-trihydro-1,3,8-trimethyl-pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (2f). Yield 6%, white solid, mp 212°C; UV (EtOH): λ_{max} 218 and 285 nm; IR (KBr): ν_{max} 2940, 1700, 1640 and 1290 cm^{-1};^1H NMR (300 MHz, $CDCl_3$): δ 1.76–1.94 (m, 2H, $-NCH_2CH_2$), 2.78 (s, 3H, $-NCH_3$), 3.04–3.06 (m, 2H, $-NCH_2$), 3.15 (s, 3H, $-NCH_3$), 3.47 (s, 3H, $-NCH_3$), 4.02 (d, J=8.1 Hz, 1H, $-OCH_2$), 4.54 (d, J=8.1 Hz, 1H, $-OCH_2$), 6.29–6.51 (m, 3H, Ar*H*); *m/z* 347, 349 (M^+). Anal. calcd for $C_{17}H_{18}ClN_3O_3$: C, 58.78; H, 5.18; N, 12.10%; found C, 58.87 H, 5.11; N, 12.04%.

1.2.6. 5-{3′-Benzo(2′,3′-dihydro-4′,7′-dimethyl)furo}-6,7,8-trihydro-1,3,8-trimethyl-pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (2g). Yield 50%, white solid, mp 252°C; UV (EtOH): λ_{max} 218 and 285 nm; IR (KBr): ν_{max} 2940, 1680, 1615 and 1290 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.78–1.86 (m, 2H, $-NCH_2CH_2$), 2.01 (s, 3H, $-CH_3$), 2.22 (s, 3H, $-CH_3$), 2.76 (s, 3H, $-NCH_3$), 2.96–3.07 (m, 2H, $-NCH_2$), 3.15 (s, 3H, $-NCH_3$), 3.36 (s, 3H, $-NCH_3$), 4.09 (d, J=8.1 Hz, 1H, $-OCH_2$), 4.72 (d, J=8.1 Hz, 1H, $-OCH_2$), 6.49–6.61 (m, 2H, Ar*H*); *m/z* 341 (M^+). Anal. calcd for $C_{19}H_{23}N_3O_3$: C, 66.86; H, 6.74; N, 12.31%; found C, 66.98; H, 6.82; N, 12.37%.

1.2.7. 5-{3′-Benzo(2′,3′-dihydro-6′,7′-dimethyl)furo}-6,7,8-trihydro-1,3,8-trimethyl-pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (2h). Yield 48%, white solid, mp 224°C; UV (EtOH): λ_{max} 217 and 290 nm; IR (KBr): ν_{max} 2900, 1710, 1645 and 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.80–1.87 (m, 2H, $-NCH_2CH_2$), 2.12 (s, 3H, $-CH_3$), 2.18 (s, 3H, $-CH_3$), 2.81 (s, 3H, $-NCH_3$), 3.01–3.17 (m, 2H, $-NCH_2$), 3.25 (s, 3H, $-NCH_3$), 3.36 (s, 3H, $-NCH_3$), 4.10 (d, J=8.1 Hz, 1H, $-OCH_2$), 4.72 (d, J=8.1 Hz, 1H, $-OCH_2$), 6.53–6,65 (m, 2H, Ar*H*); *m/z* 341 (M^+). Anal. calcd for $C_{19}H_{23}N_3O_3$: C, 66.86; H, 6.74; N, 12.31%; found C, 66.71; H, 6.65; N, 12.27%.

1.2.8. 6,7,8-Trihydro-1,3,8-trimethylpyrido[2,3-*d*]pyrimidine-2,4,5(1*H*,3*H*)trione (3). White solid, mp 162°C; UV (EtOH): λ_{max} 220, 249 and 307 nm; IR (KBr): ν_{max} 2920, 1680, 1630 and 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.83 (s, 3H, $-NCH_3$), 3.46 (s, 3H, $-NCH_3$), 3.71 (s, 3H, $-NCH_3$), 6.97 (d, J=5.1 Hz, 1H, $=CH$), 8.43 (d, J=5.1 Hz, 1H, $-CH=CH$); ^{13}C NMR (300 MHz): δ 22.41 (N_8-CH_3), 28.32 (CH_3), 30.05 (CH_3), 109.46 (C_{4a}), 122.26 (C_6), 151.32 (C_5), 152.01 (C_7), 153.42 ($C_{2,8a}$), 162.04 (C_4); *m/z* 221 (M^+). Anal. calcd for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 4.97; N, 19.00%; found C, 54.35; H, 4.99; N, 19.06%.

1.2.9. 6,7,8-Trihydro-1,3,8-trimethyl-5-{phenoxy(5,9-dihydro)methylene}pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (4a). Yield 45%, white solid, mp144°C; UV (EtOH): λ_{max} 215 and 285 nm; IR (KBr):ν_{max} 2920, 1690, 1630 and 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.71–1.73 (m, 1H, $-NCH_2CH_2$), 2.03–2.06 (m, 1H, $-NCH_2CH_2$), 2.74 (s, 3H, $-NCH_3$), 3.02–3.06 (m, 1H, $-CH_2CH$), 3.20–3.25 (m, 2H, $-NCH_2$), 3.33 (s, 3H, $-NCH_3$), 3.37 (s, 3H, $-NCH_3$), 3.79 (t, J=9.5 Hz, 1H, $-OCH_2$), 4.32–4.35 (dd, J=9.5, 3.0 Hz, 1H, $-OCH_2$), 6.88–6.91 (m, 1H, Ar*H*), 7.00–7.01 (m, 2H, Ar*H*), 7.24–7.27 (m, 2H, Ar*H*); ^{13}C NMR (300 MHz): δ 19.34 (C_6), 27.76 (CH_3), 30.52 (C_5), 33.52 (CH_3), 41.58 (N_8-CH_3), 47.75 (C_7), 67.83 (C_9), 94.55 (C_{4a}), 114.58 (C_{12}, C_{16}), 120.44 (C_{14}), 129.35 (C_{13}, C_{15}), 152.58 (C_2), 156.10 (C_{8a}), 158.56 (C_{11}), 162.71 (C_4); *m/z* 315 (M^+). Anal. calcd for $C_{17}H_{21}N_3O_3$: C, 64.76; H, 6.66; N, 13.33%; found C, 64.88; H, 6.54; N, 13.28%.

1.2.10. 6,7,8-Trihydro-1,3,8-trimethyl-5-{4′-methylphenoxy(5,9-dihydro)methylene}pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (4c). Yield 42%, white solid, mp 125°C; UV (EtOH): λ_{max} 213 and 286 nm; IR (KBr): ν_{max} 2920, 1690, 1630 and 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.66–1.76 (m, 1H, $-NCH_2CH_2$), 2.04–2.08 (m, 1H, $-NCH_2CH_2$), 2.27 (s, 3H, $-CH_3$), 2.76 (s, 3H, $-NCH_3$), 3.03–3.07 (m, 1H, $-CH_2CH$), 3.20–3.28 (m, 2H, $-NCH_2$), 3.34 (s, 3H, $-NCH_3$), 3.39 (s, 3H, $-NCH_3$), 3.78 (t, J=9.5 Hz, 1H, $-OCH_2$), 4.39–4.44 (dd, J=9.5, 3.0 Hz, 1H, $-OCH_2$), 6.91 (d, J=8.1 Hz, 2H, Ar*H*), 7.07 (d, J=8.1 Hz, 2H, Ar*H*); *m/z* 329 (M^+). Anal. calcd for $C_{18}H_{23}N_3O_3$: C, 65.65; H, 6.99; N, 12.76%; found C, 65.76; H, 7.11; N, 12.71%.

1.2.11. 6,7,8-Trihydro-1,3,8-trimethyl-5-{2′-chlorophenoxy(5,9-dihydro)methylene}pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (4f). Yield 47%, white solid, mp 148°C; UV (EtOH): λ_{max} 213 and 284 nm; IR (KBr): ν_{max} 2920, 1630 and 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.67–1.72 (m, 1H, $-NCH_2CH_2$), 2.09–2.12 (m, 1H, $-NCH_2CH_2$), 2.71 (s, 3H, $-NCH_3$), 2.99–3.03 (m, 1H, $-CH_2CH$), 3.18–3.21 (m, 2H, $-NCH_2$), 3.27 (s, 3H, $-NCH_3$), 3.33 (s, 3H, $-NCH_3$), 3.93 (t, J=9.5 Hz, 1H, $-OCH_2$), 4.35–4.39 (dd, J=9.5, 3.0 Hz, 1H, $-OCH_2$), 6.77–6.81 (m, 1H, Ar*H*), 7.13–7.19 (m, 2H, Ar*H*),

7.24–7.26 (m, 1H, Ar*H*); *m/z* 351, 349 (M^+). Anal. calcd for $C_{17}H_{20}ClN_3O_3$: C, 58.45; H, 5.73; N, 12.03%; found C, 58.59; H, 5.81; N, 11.96%.

1.3. GC analysis

The crude reaction mixture of **1a** after usual work up was injected into the column (oven temperature 40°-5-12C/mim-240-18). RT (min) of the standard sample of anisole was 2.762 whereas, the reaction mixture gave a peak at 2.812.

1.4. General procedure for the preparation of 2a,e by radical cyclization

A suspension of the compounds **1i**,**j** (0.5 mmol), ^{n}Bu$_3$SnCl (0.075 mL), Na(CN)BH$_3$ (1 mmol) and AIBN (0.5–0.6 mol equiv.) in 7 mL of dry benzene were refluxed for 4–5 h under N_2 atmosphere. Solvent was evaporated under reduced pressure and the residue was taken in 10 mL of water and was extracted with $CHCl_3$ (3×10 mL). The combined organic extract was washed with 1% aqueous NH_4OH (2×10 mL) and brine, and dried (Na_2SO_4). Evaporation of the solvent furnished the residual mass which was then magnetically stirred with saturated solution of potassium fluoride (5 mL) for 24 h. It was then extracted with $CHCl_3$ (3×10 mL) and was washed with water for several times and dried (Na_2SO_4). The residual mass after removal of the solvent ($CHCl_3$), was subjected to column chromatography using pet-ether/ethylacetate (3:1) as eluant to give cyclized products **2a**,**e** which were then recrystallized from chloroform–petroleum ether was characterized by comparing with products obtained from acid-catalyzed reaction of enolethers **1a**,**e**.

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References

1. (a) Lunt, E. *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon: Oxford, 1974; Vol. 4, p 493. (b) Brown, J. D. *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 3, p 57. (c) Sasaki, T.; Minamoto, K.; Suzuki, T.; Yam-ashita, S. *Tetrahedron* **1980**, *36*, 865, and references cited therein. (d) Bradshow, T. K.; Hutchison, D. W. *Chem. Soc. Rev.* **1977**, *6*, 43.
2. (a) Marumato, R.; Farukawa, Y. *Chem. Pharm. Bull.* **1977**, *25*, 2974. (b) Cheng, C. C.; Roth, B. *Prog. Med. Chem.* **1971**, *8*, 61. (c) Jones, A. S.; Swgers, J. R.; Walker, R. T.; Clercq, E. D. *J. Med. Chem.* **1988**, *31*, 268. (d) Griengl, H.; Wanck, E.; Schwarz, W.; Streicher, W.; Rosenwirth, B.; Clercq, E. D. *J. Med. Chem.* **1987**, *30*, 1199. (e) Clercq, E. D.; Benaerts, R. *J. Biol. Chem.* **1987**, *262*, 14905.
3. Heidelberger, In *Pyrimidine and Pyrimidine Antimetabolites in Cancer Medicine*; Holland, J. F., Frei, E., Eds.; Lea and Febiger: Philadelphia, 1984; p 801.
4. (a) DeClercq, E.; Descamps, J.; Somer, P. De; Barr, P. J.; Jones, A. S.; Walker, R. T. *Proc. Natl Acad. Sci. USA* **1979**, *76*, 2947. (b) Gallo, R. C. *Sci. Am.* **1986**, *255*, 78. (c) Gallo, R. C. *Sci. Am.* **1987**, *256*, 46. (d) Miyasaka, T.; Tanaka, H.; Baba, M.; Hayakawa, H.; Walker, R. T.; Balzarini, J.; DeClercq, E. *J. Med. Chem.* **1989**, *32*, 2507. (e) Baba, M.; Tanaka, H.; DeClercq, E.; Pauwels, R.; Balzarini, J.; Schols, D.; Nakashima, H.; Perno, C. F.; Walker, R. T.; Miyasaka, T. *Biochem. Biophys. Res. Commun.* **1989**, *165*, 1375. (f) DeClercq, E. *Med. Res. Rev.* **1993**, *13*, 229.
5. (a) Majumdar, K. C.; Das, U.; Jana, N. K. *J. Org. Chem.* **1998**, *63*, 3550. (b) Majumdar, K. C.; Das, U. *J. Org. Chem.* **1998**, *63*, 9997.
6. Majumdar, K. C.; Bhattacharrya, T. *Synthesis* **2001**, 1568.
7. Woodward, R. B.; Hoffman, R. *The Conservation of Orbital Symmetry*; Academic: New York, 1970.
8. (a) Hunig, S.; Muller, H. R.; Their, W. *Angew. Chem. Int. Ed.* **1965**, *4*, 271. (b) Doering Von, E.; Rosenthal, J. W. *J. Am. Chem. Soc.* **1967**, *89*, 4535.
9. (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: New York, 1986. (b) Curran, D. P. *Synthesis* **1988**, *417*, 489. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (d) Majumdar, K. C.; Basu, P. K. *Heterocycles* **2002**, *57*, 2413.
10. (a) Shankaran, K.; Solan, C. P.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 6001. (b) Solan, C. P.; Cuevas, J. C.; Quesnelle, C.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 4685. (c) Parker, K. A.; Spero, D. M.; Inman, K. C. *Tetrahedron Lett.* **1986**, *27*, 2833. (d) Jones, K.; Willkinson, J. A. *J. Chem. Soc. Chem. Commun.* **1992**, 1767.
11. (a) Shankaran, K.; Solan, C. P.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 6001. (b) Solan, C. P.; Cuevas, J. C.; Quesnelle, C.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 4685. (c) Snieckus, V. *Bull. Soc. Chim. Fr.* **1988**, 67. (d) Harrowven, D. C. *Tetrahedron Lett.* **1993**, *34*, 5653. (e) Harrowven, D. C.; Browne, R. *Tetrahedron Lett.* **1994**, *35*, 5301.
12. (a) Ikeda, M.; Ohtani, S.; Yamamoto, T.; Sato, T.; Ishibashi, H. *J. Chem. Soc. Perkin Trans. 1* **1998**, 1763. (b) Santhosh, K. C.; Gopalsamy, A.; Balasubramanian, K. K. *Eur. J. Org. Chem.* **2001**, 3461.