Sanjay K. Gautam,^a Hardesh K. Maurya,^b Ramendra Pratap,^c Brijesh Kumar,^d Abhinav Kumar,^a Vishnu K. Tandon,^{a*} and Vishnu Ji Ram^{a*}

^aDepartment of Chemistry, Lucknow University, Lucknow 226007, India

^bMedicinal Chemistry Department, CSIR-Central Institute of Aromatic Plants, Kukrail Road, Lucknow 226015, India

^cDepartment of Chemistry, Delhi University, North Campus, New Delhi 1100074, India

^dDivision of SAIF, Central Drug Research Institute, Lucknow 226001, India

*E-mail: vishnutandon@yahoo.co.in; vjiram@yahoo.com

Received May 26, 2014 DOI 10.1002/jhet.2342

Published online 16 September 2016 in Wiley Online Library (wileyonlinelibrary.com).



A concise and efficient base-induced synthesis of stair-shaped, 4-methylthio-2-oxo-5,6-dihydro-2*H*-naphtho[1,2-b]pyran[2,3-*d*]oxepine-3-carbonitriles (**3**) has been delineated by the reaction of 3,4-dihydronaphtho [1,2-b]oxepin-5(2*H*)-one (**1**) and methyl 2-cyano-3,3-dimethylthioacrylate in DMSO using powdered KOH as a base at room temperature. Amination of **3** has been achieved by reaction with secondary amine in ethanol at reflux temperature to yield 4-*sec*-amino-2-oxo-5,6-dihydro-2*H*-naphtho[1,2-*b*]pyran[2,3-*d*]oxepine-3-carbonitriles (**4**). Reaction of **3** with aryl methyl ketone (**5**) in DMSO at room temperature using powdered KOH as a base produced stair-shaped 5-aryl-7,8-dihydro-1,4-dioxa-2,3-dioxodinaphtho[1,2-*b*,*d*]oxepine (**6**) in good yields. However, reaction of 6-aryl-2*H*-pyran-2-one-3-carbonitrile (**8**) with 3,4-dihydronaphtho[1,2-*b*]pyran-5(2*H*)-one (**1**) did not give similar product, but in lieu 4-aryl-5,6-dihydronaphtho[1,2-*b*]oxepino[4,5-*b*]pyran-2-ylidene)acetonitrile (**9**) was isolated and characterized.

J. Heterocyclic Chem., 53, 2070 (2016).

INTRODUCTION

2*H*-pyran-2-one ring system is widely present in various natural products derived from marine organism, animals and plant kingdom in the form of either isolated or substructure. Natural products (**I**, **IIa–c**) of naphthoxepine skeleton display diverse pharmacological activities. Luffalactone (**I**) [1] isolated from *Liffariella variabilis* and various other chiral naphthoxepine derivatives (**IIa–c**) isolated from *Sinningia aggregate* display anti-inflammatory, phospholipase A₂ inhibitory [2] and antimicrobial [3] activities (Fig. 1).

Despite diverse pharmacological activities, they are also useful as synthon for the construction of newer entities to generate molecular diversity through ring transformation and stated framework rearrangement.

Although the chemistry of 2-pyranone is well developed and plenty of literature is available [4], the synthesis and ring transformation studies of partially reduced suitably functionalized benzo[b]oxepine (III) [5,6] and naphtho[*b*]oxepine (**IV**) (Fig. 1) [6] fused 2-pyranone system are meagerly developed. However, extensive literature survey revealed that the chemistry of 2-oxo-5,6-dihydro-2*H*-naphtho [1,2-*b*]pyrano[2,3-*d*]oxepine-5-carbonitrile (**IV**) is not developed so far. Dibenzoxepine [7] fused with heterocyclic system is known to display diverse pharmacological activities, and some of them are highly effective in the treatment of anxiety, depression and schizophrenia [8,9]. The therapeutic importance of this ring system aroused considerable interest to develop the chemistry of 2-pyranone fused naphtho[1,2-*b*] oxepine and other heterocyclic ring system through basecatalyzed ring transformation and framework rearrangement.

RESULTS AND DISCUSSION

Herein, we report an elegant regioselective approach to the synthesis of stair-shaped tetracyclic and pentacyclic heteroarenes. Our primary strategy to synthesize stair-shaped

November 2016 A Concise and an Efficient Base Induced Synthesis of Stair Shaped 5,6-Dihydronaphtho[1,2-b]oxepino 2071 [4,5-b]pyran, Dioxodinaphtho[1,2-b,d]oxepine and Naphtho[1,2-b]pyran[2,3-d]oxepine has been Reported



Figure 1. Naturally occurring naphthoxepine (I, II) analogs and synthetic analogs (III, IV).

oxa-aza- and oxa-aza-thia-heterocycles is based on the selection of right precursor. For this purpose, we selected 3,4-dihydro-2*H*-naphtho[1,2-*b*]oxepin-5-one (1) [10] as a substrate which on reaction with methyl 2-cyano-3,3-dimethylthioacrylate (2) [11] in DMSO in the presence of powdered KOH at room temperature provided 4-methylthio-2-oxo-5,6-diydro-2*H*-naphtho[1,2-*b*] pyrano[2,3-*d*]oxepine-3-carbonitrile (3) and was aminated with *sec*-amine in boiling ethanol to yield 4-*sec*-amino-2-oxo-5,6-diydro-2*H*-naphtho[1,2-*b*]pyrano[2,3-*d*]oxepine-3-carbonitrile (4) (Scheme 1). Numerous compounds prepared are listed in Table 1.

The intermediate **3** was used as a precursor for the carbanion-induced ring transformation and framework rearrangement. Thus, a base-induced ring transformation of **3** by *in situ* generated carbanion from aryl methyl ketone (**5**) at room temperature in DMSO led to provide regioselective stair-shaped 5-aryl-7,8-dihydro-1,4-dioxa-2,3-dioxodinaphtho [1,2-b,d]oxepine (**6**) following path A. Mechanistically, there is also a possibility for the formation of (2-aryl-5,6-dihydronaphtho[1,2-*b*]oxepino[4,5-*c*]pyran-2-ylidene)acetoni-trile (**7**). However, this reaction regioselectively gave product **6** only. The regioselectivity of product **6** over **7** is possibly because of steric hindrance at bridged carbon adjacent to ring oxygen of lactone (**3**) and also the presence of a better leaving group (SMe), and charge density calculation at C-4 position of

Scheme 1. Synthesis of naphtho[1,2-b]pyrano[2,3-d]oxepines (3,4) (Table 1).



 Table 1

 Structure, Mp and yields of naphtho[1,2-b]pyrano[2,3-d]oxepines



Journal of Heterocyclic Chemistry DOI 1

3 favors nucleophilic attack and directs the reaction to follow path A to give product **6** (Scheme 2). The reaction is initiated through substitution at C-4 followed by cyclization and hydrolysis of imine intermediate to yield **6**. All the compounds thus prepared are listed in Table 2.

It was conspicuous that when similar reaction was carried out using 6-aryl-4-methylthio-2H-pyran-2-one-3acetonitriles (8), an isolated lactone with 3,4-dihydro-2Hnaphtho[1,2-b]oxepin-5-one (1) as a source of carbanion in DMSO using powdered KOH as a base at room temperature did not follow the path B (Scheme 3) to give 6. However, the reaction product isolated and characterized was 4-aryl-5,6dihydronaphtho[1,2-b]oxepino[4,5-b]pyran-2-ylidene) acetonitrile (9). The chemical shift for CH-CN proton in ¹H NMR of **9** and ortep diagram from X-ray diffraction of a analogous compound reported [5c,12] earlier revealed that the compound 9 exists as a Z isomer. The formation of this product is only possible if reaction follows path A (Scheme 3). The reaction is possibly initiated by Michael addition of 3,4-dihydro-2H-naphtho[1,2-b]oxepin-5-one (1) [10] to the 6-aryl-2*H*-pyran-2-one-3-carbonitrile $(8)^{4,11}$ by attacking at C-6 followed by elimination of carbon dioxide and recyclization with liberation of methylmercaptan to yield **9** (Scheme 3).

All the compounds prepared are listed in Table 3. It is noteworthy that the precursor 6-aryl-2*H*-pyran-2-one-3carbonitrile (**8**) were synthesized from the reaction of methyl 2-cyano-3,3-dimethylthioacrylate (**2**) with aryl methyl ketone (**5**) in the presence of base (KOH or NaOH) at room temperature in DMSO [4,11].

In order to ascertain the nature of the reactive orbitals involved in reaction, density functional theory (DFT) calculations were performed of the representative compounds **5** and **8**. Optimized molecular geometries were calculated using the B3LYP [13] exchange-correlation functional. The spin-restricted DFT method was employed to model the closed shell-oxidized species. The 6-31G** basis set was used for all the atoms. The optimized structures of the compounds were used for molecular orbital analyses. Atomic charges were calculated using natural population analyses (NPA) [14] as implemented in Gaussian 03 program [15]. The natural charges over various atoms of interest are displayed in Figure 2. The natural charges on methyl carbon in **5** and unsaturated carbon center attached to phenyl ring in

Scheme 2. Synthesis and proposed mechanism of 5-aryl-7,8-dihydro-1,4-dioxa-2,3-dioxodinaphtho[1,2-b,d]oxepine (6) (Table 2).



Journal of Heterocyclic Chemistry DOI 10.1002/jhet

November 2016	A Concise and an Efficient Base Induced Synthesis of Stair Shaped 5,6-Dihydronaphtho[1,2-b]oxepino 2	073
	[4,5-b]pyran, Dioxodinaphtho[1,2-b,d]oxepine and Naphtho[1,2-b]pyran[2,3-d]oxepine has been Reported	





8 that are -0.77989 and +0.41418 esu respectively indicates that the nature of both the carbon centers is different and therefore their reactivity towards electrophiles and nucleophiles also differs.

CONCLUSION

A concise and efficient base-induced synthesis of stairshaped, 4-methylthio-2-oxo-5,6-dihydro-2*H*-naphtho[1,2-*b*] pyran[2,3-d] oxepine-3-carbonitriles (3) has been delineated by the reaction of 3,4-dihydronaphtho[1,2-b]oxepin-5(2H)one (1) and methyl 2-cyano-3,3-dimethylthioacrylate in DMSO using powdered KOH as a base at room temperature. Amination of 3 has been achieved by reaction with secondary amine in ethanol at reflux temperature to yield 4-sec-amino-2oxo-5,6-dihydro-2H-naphtho[1,2-b]pyran[2,3-d]oxepine-3-carbonitriles (4). Reaction of 3 with aryl methyl ketone in DMSO at room temperature using powdered KOH as a base produced stair-shaped 5-aryl-7,8-dihydro-1,4dioxa-2,3-dioxodinaphtho[1,2-b,d]oxepine (6) in good yields. However, reaction of 6-aryl-2H-pyran-2-one-3carbonitrile (8) with 3,4-dihydronaphtho[1,2-b]oxepin-5 (2H)-one (1) did not give analogous product, but in lieu 4-aryl-5,6-dihydronaphtho[1,2-b]oxepino[4,5-b]pyran-2ylidene)acetonitrile (9) was isolated and characterized.

EXPERIMENTAL

Materials and equipments. The reagents and the solvents used in this study were of analytical grade and were used without further purification. The melting points were determined on an electrically heated Townson Mercer melting point apparatus and are uncorrected. Commercial reagents were used without purification. ¹H and ¹³C NMR spectra were measured on a Bruker WM-300 (300 MHz)/Jeol-400, using CDCl₃ and

(Continued)

Vol 53



Scheme 3. Synthesis and proposed mechanism of (z) 4-aryl-5,6-dihydronaphtho[1,2-*b*]oxepino[4,5-*b*]pyran-2-ylidene)acetonitrile (**9**) (Table 3).

 Table 3

 Structure, Mp and yields of 4-aryl-5,6-dihydro-naphtho[1,2-b]oxepino

 [4,5-b]pyran-2-ylidene)acetonitrile (9) (Scheme 3).

Comp.	Structure	Mp (°C)	Yield (%)
9a	NC O	280–282	67
9b		266–268	87

Table 3 (Continued) Comp. Structure Mp (°C) Yield (%) 9c 278-280 85 NC 290–292 9d 75 NC 9e 248-250 62 CH 3 NC 9f 216-218 68 OCH3 NC 9 g 268-270 56 NC 9 h 242-244 58 NC 9i 252-254 52 NC

(Continued)

November 2016 A Concise and an Efficient Base Induced Synthesis of Stair Shaped 5,6-Dihydronaphtho[1,2-b]oxepino 2075 [4,5-b]pyran, Dioxodinaphtho[1,2-b,d]oxepine and Naphtho[1,2-b]pyran[2,3-d]oxepine has been Reported



Figure 2. Electrostatic potentials surfaces for the compounds 5 and 8 calculated at the B3LYP level of theory (red/green/blue denotes areas of high/medium/low charge densities) and computed natural charges on atom centers of interest. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

DMSO-d₆ as the solvents. Chemical shift are reported in parts per million shift (δ value) from Me₄Si (δ 0 ppm for ¹H NMR) or based on the middle peak of the solvent (CDCl₃), δ 77.00 ppm for ¹³C NMR) as the internal standard. Signal patterns are indicated as s, singlet; bs, broad singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; bh, broad hump. Coupling constant (J) are given in hertz. Infrared (IR) spectra were recorded on a Perkin-Elmer AX-1 spectrophotometer in KBr disc and reported in wave number (cm⁻¹). Electrospray ionization mass spectrometry spectrometers were used for mass spectra analysis. ¹³C NMR spectra of compounds could not be reported because of their very poor solubility in deuterated solvents (DMSO-d₆ and CDCl₃) used.

Synthesis and characterization

General procedure for the synthesis of 6-oxo-4-methylthio-3,6dihydro-2*H*-naphtho[1,2-*b*]pyrano[2,3-*d*]oxepine-5-carbonitriles (3). A mixture of 3,4-dihydro-2H-naphtho[1,2-b]oxepin-5-one (1, 212 mg, 1 mmol), methyl 2-cyano-3,3-dimethylthioacrylate (2, 203 mg, 1 mmol) and powdered KOH (84 mg, 1.5 mmol) in 20 mL DMSO stirred at room temperature for 2.5 h. Thereafter, the reaction mixture was poured onto crushed ice with vigorous stirring for 1 h. The pale yellow colored solid was filtered, dried and crystallized with CHCl3-hexane as 4-methylthio-2-oxo-5,6divdro-2H-naphtho[1,2-b]pyrano[2,3-d]oxepine-3-carbonitrile (3) as needles, yield 302 mg (90%); Mp 148-150°C; IR (KBr): 2213 (CN); 1701 (C=O); 1578; 1285; 1205; 1118; 1063; 969; 892; 808; 753; 562 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+ DMSO-d6): δ 1.57 (s, 3H, CH₃), 3.03 (t, 2H, CH₂), 4.76 (t, 2H, OCH₂), 7.59 (m, 3H, Ar-H), 7.83 (d, 1H, Ar-H), 7.92 (d, 1H, Ar-H), 8.31 (d, 1H, Ar-H); HRMS (ESI) calcd for C19H13NO3S: 336.0616 (MH⁺), found: 336.0610; Anal. Calcd. for C₁₉H₁₃NO₃S: C, 68.04; H, 3.91; N, 4.18. Found: C, 67.91; H, 3.89; N, 4.06.

General procedure for the synthesis of 6-oxo-4-(sec-amino)-3,6dihydro-2*H*-naphtho[1,2-*b*]pyrano[2,3-*d*]oxepine-5-carbonitriles (4). A mixture of 4-(methylthio)-6-oxo-3,6-dihydro-2*H*-naphtho [1,2-b]-pyrano-[2,3-d]-oxepine-5-carbonitrile (3, 1 mmol) and secondary amines (1.2 mmol) in methanol (40 mL) was refluxed for 5 h. The resulting solid was filtered and washed with EtOH. The product was purified by silica gel (60–120 mesh) column chromatography using CHCl₃–MeOH as eluent (if required).

6-Oxo-4-(piperidin-1-yl)-3,6-dihydro-2*H***-naphtho[1,2-***b***]-pyrano [2,3-***d***]oxepine-5-carbonitrile (4a). Pale yellow solid; yield: 52%; Mp 254–256°C; IR (KBr): 2250 (CN); 1691 (C=O); 1467, 1216, 1099, 909 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): \delta 2.53 (m, 6H, 3×CH₂), 2.74 (m, 4H, 2×CH₂), 3.63 (t, 2H, CH₂), 4.84 (t, 2H, OCH₂), 7.32 (s, 1H, Ar-H), 7.66 (m, 2H, Ar-H), 7.72 (s, 1H, Ar-H), 7.95 (d, 1H, Ar-H), 8.24 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₃H₂₀N₂O₃: 372.1474 (M⁺), Found: 372.1463;** *Anal.* **Calcd. for C₂₃H₂₀N₂O₃: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.29; H, 5.39; N, 7.48.**

6-Oxo-4-(pyrrolidin-1-yl)-3,6-dihydro-2*H***-naphtho[1,2-***b***]-pyrano [2,3-***d***]oxepine-5-carbonitrile (4b). Light cream-colored solid; yield 63%; Mp 306–308°C; IR (KBr): 2239 (CN); 1702 (C=O), 1452, 1221, 1113, 1026, 765 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): \delta 2.49 (m, 4H, 2×CH₂), 2.74 (m, 4H, 2×CH₂), 3.63 (t, 2H, CH₂), 4.84 (t, 2H, OCH₂), 7.64 (m, 4H, Ar-H), 7.94 (d, 1H, Ar-H), 8.23 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₂H₁₈N₂O₃: 358.1317 (M⁺), Found: 358.1309;** *Anal.* **Calcd. for C₂₂H₁₈N₂O₃: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.54; H, 5.01; N, 7.78.**

4-Morpholino-6-oxo-3,6-dihydro-2*H***-naphtho[1,2-***b***]pyrano-[2,3-***d***]oxepine-5-carbonitrile (4c). Pale yellow crystalline solid; yield 53%; Mp 310–312 °C; IR (KBr): 2221 (CN), 1709 (C=O), 1460, 1021, 763 cm⁻¹; ¹HNMR (400 MHz, DMSO-d₆): \delta 2.65 (m, 4H, 2xNCH₂), 3.47 (t, 2H, CH₂), 3.53 (m, 4H, 2xOCH₂); 4.76 (t, 2H, OCH₂), 7.25 (s, 1H, Ar-H), 7.64 (m, 3H, Ar-H), 7.86 (d, 1H, Ar-H), 8.19 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₂H₁₈N₂O₄: 375.1267 (MH⁺), Found: 375.1256;** *Anal.* **Calcd. for C₂₂H₁₈N₂O₄: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.40; H, 4.81: N, 7.43.**

4-(4-Methylpipridin-1-yl)-6-oxo-3,6-dihydro-2*H*-naphtho[1,2-*b*] pyrano[2,3-*d*]oxepine-5-carbonitrile (4d). Brown-colored powder; yield 61%; Mp 130–132°C; IR (KBr): 2235 (CN), 1698 (C=O), 1451, 1113, 1026, 765 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 1.20 (s, 3H, CH₃), 2.55 (m, 4H, CH₂), 2.74 (t, 2H, CH₂), 3.63 (m, 4H, 2xCH₂), 4.84 (t, 2H, OCH₂), 7.65 (m, 4H, Ar-H), 7.95 (d, 1H, Ar-H), 8.24 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₄H₂₂N₂O₃: 386.1630 (M⁺), Found: 386.1621; *Anal.* Calcd. for C₂₄H₂₂N₂O₃: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.42; H, 5.69; N, 7.20.

4-(4-Benzylpiperazin-1-yl)-6-oxo-3,6-dihydro-2H-naphtho[**1,2-b**] **pyrano**[**2,3-d**]**oxepine-5-carbonitrile (4e**). Light buff-colored solid; yield 53%; Mp 138–140°C; IR (KBr): 2216 (CN), 1697 (C=O), 1113, 1021, 763, 686, 643 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 2.41 (bs, 4H, 2×NCH₂), 2.49 (bs, 4H, 2×CH₂), 3.47 (t, 2H, CH₂), 3.53 (t, 2H, CH₂), 4.76 (t, 2H, OCH₂), 7.25 (m, 6H, Ar-H), 7.64 (m, 3H, Ar-H), 7.86 (d, 1H, Ar-H), 8.18 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₉H₂₅N₃O₃: 464.1974 (MH⁺), Found: 464.1964; *Anal.* Calcd. for C₂₉H₂₅N₃O₃: C, 75.14; H, 5.44; N, 9.07. Found: C, 75.28; H, 5.41; N, 7.16.

4-(4-Methylpiprazin-1-yl)-6-oxo-3,4-dihydro-2*H***-naphtho[1,2-***b***] pyrano**[2,3-*d*]**oxepine-5-carbonitrile (4f**). Yellow-colored powder; yield 65%; Mp 228–230°C; IR (KBr): 2228 (CN), 1709 (C=O), 1450, 1200, 1121, 1026, 765 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 2.23 (s, 4H, 2×CH₂), 2.49 (s, 3H, NCH₃), 2.73 (t, 4H, 2×CH₂), 3.59 (t, 2H, CH₂), 4.84 (t, 2H, OCH₂), 7.64 (m, 4H, Ar-H), 7.95 (d, 1H, Ar-H), 8.25 (d, 1H, Ar-H), HRMS (ESI) calcd for $C_{23}H_{21}N_3O_3$: 388.1661 (MH⁺), Found: 388.1653; *Anal.* Calcd. for $C_{23}H_{21}N_3O_3$: C, 71.30; H, 5.46; N, 10.85. Found: C, 71.11; H, 5.41; N, 10.79.

6-Oxo-4(4-methylpiprazin-1-yl)-3,6-dihydro-2*H***-naphtho[1,2-***b***] pyrano**[2,3-*d*]**oxepine-5-carbonitrile (4g**). Buff-colored powder; yield 70%; Mp 262–264°C; IR (KBr): 2242 (CN), 1707 (C=O), 1113, 1021, 763 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 2.88 (m, 8H, 4×CH₂), 3.75 (t, 2H, CH₂), 4.86 (t, 2H, OCH₂), 7.00 (d, 2H, Ar-H), 7.27 (d, 2H, Ar-H), 7.66 (m, 3H, Ar-H), 7.74 (d, 1H, Ar-H), 7.96 (d, 1H, Ar-H), 8.27 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₈H₂₂ClN₃O₃: 484.1428 (MH⁺), Found: 484.1417; *Anal.* Calcd. for C₂₈H₂₂ClN₃O₃: C, 69.49; H, 4.58; N, 8.68. Found: C, 69.38; H, 4.54; N, 8.67.

General procedure for the synthesis of 5-aryl-7,8-dihydro-1,4,9-trioxa-2,3-dioxonaphtho[b]oxepin[4,5-b]naphthalene (6). A mixiture of 4-methylthio-2-oxo-5,6-dihydro-2*H*-naphtho[1,2b]pyran[2,3-d]oxepine-3-carbonitriles (3, 1 mmol), aryl methyl ketone (5, 1 mmol) and powdered KOH (1.2 mmol) in DMSO (10 mL) was stirred at room temperature for 3 h. The reaction mixture was poured onto crushed ice and neutralized with 5% aqueous HCl with stirring at room temperature. The resulting solution was filtered, washed with water and dried. The product was purified by silica gel (60–120 mesh) column chromatography using EtOAc-hexane as eluent.

5-Phenyl-7,8-dihydro-1,4,9-trioxa-2,3-dioxonaphtho[b]oxepin [4,5-b]naphthalene (6a). Yellow powder, yield 42%; Mp 300–302°C; IR (KBr): 1775 (C=O), 1718, 1575, 1496, 1404, 1257, 1104, 1003, 814, 796, 718, 673 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.16 (t, 2H, CH₂), 4.78 (t, 2H, OCH₂), 6.87 (s, 1H, CH), 7.58 (m, 6H, Ar-H), 7.84 (d, 1H, Ar-H), 7.98 (d, 2H, Ar-H), 8.18 (d, 1H, Ar-H), 8.34 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₆H₁₆O₅: 408.0998 (M⁺), Found: 408.0988; *Anal.* Calcd. for C₂₆H₁₆O₅: C, 76.46; H, 3.95. Found: C, 76.30; H, 3.91.

5-(4-Chlorophenyl)-7,8-dihydro-1,4,9-trioxa-2,3-dioxanaphtho [*b*]oxepine[4,5-*b*]naphthalene (6b). Pale yellow powder; yield 59%; Mp 309–311°C; IR (KBr): 1775 (C=O), 1718, 1572, 1496, 1404, 1257, 1104, 1003, 814, 769, 718, 673 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+DMSO-d₆): δ 3.14 (t, 2H, CH₂), 4.78 (t, 2H, OCH₂), 6.54 (s, 1H, CH), 7.58 (m, 6H, Ar-H), 7.81 (d, 1H, Ar-H), 7.89 (d, 1H, Ar-H), 7.92 (d, 2H, Ar-H), 8.34 (d, 1H, Ar-H); HRMS (ESI) calcd for $C_{26}H_{15}CIO_5$: 442.0608 (M⁺); Found: 442.0599; *Anal.* Calcd. for $C_{26}H_{15}CIO_5$: C, 75.52; H, 3.41. Found: C, 75.31; H, 3.29.

5-Pyridyl-7,8-dihydro-1,4,9-trioxa-2,3-dioxanaphtho[b]oxepine [4,5-b]naphthalene (6c). Light brown powder; yield 58%; Mp 305–307°C; IR (KBr): 1765 (C=O), 1708, 1630, 1575, 1490, 1402, 1257, 1104, 1003, 879, 813, 769, 718, 673 cm^{-1} ; ¹H NMR (300 MHz, CDCl₃): δ 3.16 (t, 2H, CH₂); 4.78 (t, 2H, OCH₂); 6.87 (s, 1H, CH); 7.58 (m, 6H, Ar-H); 7.82 (d, 1H, Ar-H); 7.97 (d, 1H, Ar-H); 8.18 (d, 1H, Ar-H); 8.34 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₅H₁₅NO₅ 410.0950 (MH⁺); Found: 410.0940; *Anal.* Calcd. for C₂₅H₁₅NO₅: C, 73.35; H, 3.69; N, 3.42. Found: C, 73.19; H, 3.62; N, 3.39.

5(4-Methoxyphenyl)-7,8-dihydro-1,4,9-trioxa-2,3-dioxa naphtho [*b*]oxepine[4,5-*b*]naphthalene (6d). Brown-colored solid; yield 47%; Mp 162–164°C; IR (KBr): 1775 (C=O), 1718, 1680, 1572, 1496, 1404, 1257, 1104, 1003, 879, 814, 769, 718, 673 cm⁻¹; ¹H NMR: (300 MHz, CDCl₃): δ 3.00 (t, 2H, CH₂), 3.86 (s, 3H, CH), 4.46 (t, 2H, OCH₂), 6.86 (s, 1H, CH), 7.56 (m, 6H, Ar-H), 7.81 (d, 2H, Ar-H), 8.38 (d, 2H, Ar-H); HRMS (ESI) calcd for C₂₇H₁₈O₆: 438.1103 (M⁺), Found: 438.1097; *Anal.* Calcd. for C₂₇H₁₈O₆: C, 73.97; H, 4.14. Found: C, 73.79; H, 4.02.

5-(1-Naphthyl)-7,8-dihydro-1,4,9-trioxa-2,3-dioxanaphtho[b]oxepine[4,5-b]naphthalene (6e). Light reddish brown solid; yield 48%; Mp 214–216°C; IR (KBr): 1765 (C=O), 1699, 1625, 1575, 1490, 1334, 1111, 1001, 767, 683, 484 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.16 (t, 2H, CH₂), 4.78 (t, 2H, OCH₂), 7.11 (s, 1H, CH), 7.70 (m, 7H, Ar-H), 7.90 (d, 2H, Ar-H), 8.30 (m, 3H, Ar-H), 8.28 (d, 1H, Ar-H), HRMS (ESI) calcd for C₃₀H₁₈O₅: 458.1154 (M⁺), Found: 458.1142; *Anal.* Calcd. for C₃₀H₁₈O₅: C, 78.59; H, 3.96. Found: C, 78.40; H, 3.75.

5-(4-Methylphenyl)-7,8-dihydro-1,4,9-trioxa-2,3-dioxa naphtho [*b*]oxepine[4,5-*b*]naphthalene (6f). Brown solid; yield 64%; Mp 144–146°C; IR (KBr): 1775 (C=O), 1704, 1580, 1490, 1437, 1341, 1251, 1094, 1012, 956, 911, 823, 774, 670, 625, 507 cm⁻¹; ¹H NMR: (300 MHz, CDCl₃+DMSO-d₆): δ 2.19 (s, 3H, CH₃), 3.14 (t, 2H, CH₂), 4.78 (t, 2H, OCH₂), 6.54 (s, 1H, CH), 7.58 (m, 6H, Ar-H), 7.85 (dd, 2H, Ar-H), 7.92 (d, 1H, Ar-H), 8.35 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₇H₁₈O₅: 422.1154 (M⁺), Found: 422.1147; *Anal.* Calcd. for C₂₇H₁₈O₅: C, 76.77; H, 4.29. Found: C, 76.64; H, 4.14.

5-Theinyl-7,8-dihydro-1,4,9-trioxa-2,3-dioxanaphtho[b]oxepine[4,5-b]naphthalene (6g). Black-colored powder; yield 52%; Mp 154–156°C; IR (KBr) 1718 (C=O) 1611, 1447, 1363, 1186, 1071, 929, 761, 667 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + DMSO-d₆): δ 3.03 (t, 2H, CH₂), 4.76 (t, 2H, OCH₂), 6.57 (s, 1H, CH), 7.57 (m, 6H, Ar-H), 7.91 (d, 1H, Ar-H), 8.13 (d, 1H, Ar-H), 8.31 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₄H₁₄O₅S: 415.0640 (MH⁺), Found: 415.0631; *Anal.* Calcd. for C₂₄H₁₄O₅S: C, 69.56; H, 3.40. Found: C, 69.69; H, 3.44.

5-Furyl-7,8-dihydro-1,4,9-trioxa-2,3-dioxanaphtho[b]oxepine [4,5-b]naphthalene (6h). Dark brown-colored solid; yield 51%; Mp 108–110°C; IR (KBr): 1733 (C=O) 1616, 1459, 1327, 1197, 1092, 943, 769, 662 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + DMSO-d₆): δ 3.14 (t, 2H, CH₂), 4.78 (t, 2H, OCH₂), 6.54 (s, 1H, CH), 7.55 (m, 6H, Ar-H), 7.91 (d, 1H, Ar-H), 8.15 (d, 1H, Ar-H), 8.35 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₄H₁₄O₆: 398.0790 (M⁺), Found: 398.0779; *Anal.* Calcd. for C₂₄H₁₄O₆: C, 72.36; H, 3.54. Found: C, 72.49; H, 3.58.

General procedure for the synthesis of 2-(4-aryl)-2Hnaphtho[1,2-b]pyrano[2,3-d]oxepine-6(3H)ylidene)acetonitriles(9). November 2016 A Concise and an Efficient Base Induced Synthesis of Stair Shaped 5,6-Dihydronaphtho[1,2-b]oxepino 2077 [4,5-b]pyran, Dioxodinaphtho[1,2-b,d]oxepine and Naphtho[1,2-b]pyran[2,3-d]oxepine has been Reported

A mixiture of 6-aryl-2*H*-pyran-2-one-3-carbonitrile (**8**, 1 mmol), 3,4-dihydro-2*H*-naphtho[1,2-*b*]oxepin-5-one (**1**, 1 mmol) and powdered KOH (1.2 mmol) in DMSO (20 mL) was stirred at room temperature for 3 h, and the reaction mixture was poured onto crushed ice and neutralized with 5% aqueous HCl (if required) with stirring at room temperature. The resulting solution was filtered, washed with water and dried. The solid product obtained was crystallized with suitable solvent to yield **9**.

(Z)2-(4-Phenyl)-2*H*-naphtho[1,2-*b*]pyrano[2,3-*d*]oxepin-6(3*H*)ylidene)acetonitrile (9a). Scarlet-colored powder; yield 67%; Mp 280–282°C; IR (KBr): 2198 (CN), 1655, 1556, 1415, 1251, 1112, 1015, 764, 676 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆ + CDCl₃): δ 2.64 (t, 2H, CH₂), 4.42 (s, 1H, CH), 4.66 (dt, 2H, OCH₂), 6.37 (s, 1H, Ar-H), 7.48 (m, 9H, Ar-H), 8.12 (d, 1H, Ar-H), 8.21 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₅H₁₇NO₂: 363.1259 (M⁺), Found: 363.1251; *Anal.* Calcd. for C₂₅H₁₇NO₂: C, 82.63; H, 4.72; N, 3.85. Found: C, 82.51; H, 4.69; N, 3.81. (Z)2-(4-(4-Chlorophenyl)-2*H*-naphtho[1,2-*b*]pyrano[2,3-*d*]oxepin-

(Z)2-(4-(4-Chlorophenyl)-2*H*-naphtho[1,2-*b*]pyrano[2,3-*d*]oxepin-6(3*H*)-ylidene)acetonitrile (9b). Scarlet-colored powder; yield 87%; Mp 266–268°C; IR (KBr): 2194 (CN), 1655, 1543, 1340, 1250, 1102, 1015, 764, 676 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 3.31 (dt, 2H, CH₂), 5.11 (s, 1H, CH), 5.51 (dt, 2H, OCH₂), 6.48 (s, 1H, CH), 7.64 (m, 8H, Ar-H), 7.92 (d, 1H, Ar-H), 8.08 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₅H₁₆ClNO₂: 398.0948 (MH⁺) Found: 398.0929 (MH⁺); *Anal.* Calcd. for C₂₅H₁₆ClNO₂: C, 75.47; H, 4.05; N, 3.52. Found: C, 75.36; H, 4.01; N, 3.49.

(Z)2-(4-(4-Bromophenyl)-2H-naphtho[1,2-b]pyrano[2,3-d]oxepin-6(3H)-ylidene)acetonitrile (9c). Scarlet-colored powder; yield 85%; Mp 278–280°C; IR (KBr): 2195 (CN), 1653, 1536, 1343, 1102, 1012, 764, 676 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 3.30 (dt, 2H, CH₂), 5.11 (s, 1H, CH), 5.52 (dt, 2H, OCH₂), 6.48 (s, 1H, CH), 7.59 (m, 8H, Ar-H), 7.95 (d, 1H, Ar-H), 8.08 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₅H₁₆BrNO₂: 441.0364 (M⁺), Found: 441.0352; *Anal.* Calcd. for C₂₅H₁₆BrNO₂: C, 67.89; H, 3.65; N, 3.17. Found: C, 67.77; H, 3.52; N, 3.06.

(2)2-(4-Naphthyl)-2*H*-naphtho[1,2-*b*]pyrano[2,3-*d*]oxepin-6(3*H*)-ylidene)acetonitrile (9d). Brick red-colored powder; yield 75%; Mp 290–292°C; IR (KBr): 2190 (CN), 1655, 1343, 1102, 1018, 844, 764, 676 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 2.87 (t, 2H, CH₂), 4.76 (t, 2H, OCH₂), 5.11 (s, 1H, CH), 6.75 (s, 1H, CH), 7.71 (m, 7H, Ar-H), 7.91 (d, 2H, Ar-H), 8.13 (m, 3H, Ar-H), 8.28 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₉H₁₉NO₂: 413.1416 (M⁺), Found: 413.1410; *Anal.* Calcd. for C₂₉H₁₉NO₂: C, 84.24; H, 4.63; N, 3.39. Found: C, 84.09; H, 4.60; N, 3.36.

(Z)2-(4-Methylphenyl)-2*H*-naphtho[1,2-*b*]pyrano[2,3-*d*]oxepin-6(3*H*)-ylidene)acetonitrile (9e). Brick red-colored powder; yield 62%; Mp 248–250°C; IR (KBr): 2210 (CN), 1636, 1461, 1284, 1087, 886, 769, 703 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 1.23 (s, 3H, CH₃), 2.87 (t, 2H, CH₂), 4.76 (t, 2H, OCH₂), 5.11 (s, 1H, CH), 6.75 (s, 1H, CH), 7.66 (m, 6H, Ar-H), 7.95 (d, 1H, Ar-H), 8.14 (m, 2H, Ar-H), 8.24 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₆H₁₉NO₂: 377.1416 (M⁺), Found: 377.1408; *Anal.* Calcd. for C₂₆H₁₉NO₂: C, 82.74; H, 5.07; N, 3.71. Found: C, 82.80; H, 5.10; N, 3.74.

(Z)2-(4-(4-Methoxyphenyl)-2*H*-naphtho[1,2-*b*]pyrano[2,3-*d*] oxepin-6(3*H*)-ylidene)acetonitrile (9f). Dark brown-colored powder; yield 68%; Mp 216–218°C; IR (KBr): 2190 (CN), 1805, 1655, 1546, 1343, 1102, 1018, 764, 676 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 2.77 (t, 2H, CH₂), 4.33 (s, 3H, OCH₃), 4.77 (t, 2H, OCH₂), 5.21 (s, 1H, CH), 6.76 (s, 1H, CH), 7.68 (m, 6H, Ar-H), 7.89 (d, 1H, Ar-H), 8.13 (m, 2H, Ar-H), 8.28 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₆H₁₉NO₃: 393.1365 (M⁺),

Found: 393.1344; *Anal.* Calcd. for C₂₆H₁₉NO₃: C, 79.37; H, 4.87; N, 3.56. Found: C, 79.25; H, 4.84; N, 3.54.

(Z)2-(4-(Pyridin-4-yl)-2*H*-naphtho[1,2-*b*]pyrano[2,3-*d*]oxepin-6 (3*H*)-ylidene)acetonitrile (9g). Buff-colored powder; yield 56%; Mp 268–270°C; IR (KBr): 2201 (CN), 1657, 1411, 1112, 1023, 766, 708, 648 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 2.87 (t, 2H, CH₂), 4.76 (t, 2H, OCH₂), 5.11 (s, 1H, CH), 6.75 (s, 1H, CH), 7.68 (m, 6H, Ar-H), 7.91 (d, 1H, Ar-H), 8.12 (m, 2H, Ar-H), 8.40 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₄H₁₆N₂O₂: 364.1212 (M⁺), Found 364.1202; *Anal.* Calcd. for C₂₄H₁₆N₂O₂: C, 79.11; H, 4.43; N, 7.69. Found: C, 79.23; H, 4.47; N, 7.71

(Z)2-(4-(Furan-2-yl)-2*H*-naphtho[1,2-*b*]pyrano[2,3-*d*]oxepin-6(3*H*)-ylidene)acetonitrile (9h). Brown-colored powder; yield 54%; Mp 242–244°C; IR (KBr): 2204 (CN), 1660, 1475, 1421, 1253, 1026, 814, 747 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 3.18 (t, 2H, CH₂), 4.55 (s, 1H, CH), 4.78 (t, 2H, OCH₂), 6.88 (s, 1H, CH), 7.56 (m, 5H, Ar-H), 7.82 (d, 1H, Ar-H), 7.97 (d, 1H, Ar-H); 8.16 (d, 1H, Ar-H); 8.34 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₃H₁₅NO₃: 353.1052 (M⁺), Found 353.1044; *Anal.* Calcd. for C₂₃H₁₅NO₃: C, 78.17; H, 4.28; N, 3.96. Found: C, 78.05; H, 4.26; N, 3.92.

(Z)2-(4-(Thiophen-2-yl)-2H-naphtho[1,2-b]pyrano[2,3-d]oxepin-6(3H)-ylidene)acetonitrile (9i). Brown-colored powder; yield 52%; Mp 252–254°C; IR (KBr): 2190 (CN), 1633, 1450, 1114, 1021, 769, 680 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 3.16 (t, 2H, CH₂), 4.79 (t, 2H, OCH₂), 5.45 (s, 1H, CH), 6.88 (s, 1H, CH), 7.56 (m, 5H, Ar-H), 7.82 (d, 1H, Ar-H), 7.97 (d, 1H, Ar-H), 8.16 (d, 1H, Ar-H), 8.34 (d, 1H, Ar-H); HRMS (ESI) calcd for C₂₃H₁₅NO₂S: 369.0823 (M⁺), Found: 369.0814; *Anal.* Calcd. for C₂₃H₁₅NO₂S: C, 74.78; H, 4.09; N, 3.79. Found: C, 74.70; H, 4.06; N, 3.76.

Acknowledgments. HKM is thankful to DST, New Delhi, India, for DST Fast Track Young Scientist Fellowship. VJR is thankful to UGC, New Delhi, India, for Emeritus fellowship.

REFERENCES AND NOTES

[1] Potts, B. C. M.; Capon, R. J.; Faulkner, D. J.; J Org Chem 1992, 57, 2965.

[2] (a) Glacer, K. B.; Jacobs, R. S. Biochem Pharmacol 1986, 35, 449; (b) Bennett, C. F.; Mong, S.; Clarke, M. A.; Kruse, L. I.; Crooke, S. T. Biochem Pharmacol 1987, 36, 733; (c) Jacobson, P. B.; Marshall, L. A.; Sung, A.; Jacobs, R. S. Biochem Pharmacol 1990, 39, 1557.

[3] Verdan, M. H.; Barison, A.; Lemos de Sa, E.; Salvador, M. J.; Poliquesi, C. B.; Eberlin, M. N.; Stefanello, M. E. A. J Nat Prod 2010, 73, 1434.

[4] Goel, A.; Ram, V. J Tetrahedron 2009, 65, 7865.

[5] (a) Tandon, V. K.; Maurya, H. K.; Kumar, B.; Kumar, B.; Ram, V. J Synlett 2009, 2992; (b) Maurya, H. K.; Pratap, R.; Tandon, V. K; Mishra, P.; Kumar, B.; Ram, V. J Heterocycles 2012, 84, 555; (c) Maurya, H. K.; Tandon, V. K; Kumar, B.; Kumar, A.; Huch, V.; Ram, V. J Org Biomol Chem 2012, 12, 605; (d) Kuar, S.; Illa, H.; Junjappa, H. Tetrahedron 2007, 63, 10067.

[6] (a) Maurya, H. K.; Gautam, S. K.; Kumar, A.; Pratap, R.; Bajpai, V.; Tandon, V. K.; Kumar, B.; Ram, V. J Org Biomol Chem 2012, 10, 4977; (b) Maurya, H. K.; Gautam, S. K.; Pratap, R.; Tandon, V. K.; Kumar, A.; Kumar, B.; Saxena, S.; Tripathi, D.;Rajwanshi, M.; Das, M.; Ram, V. J. Eur J Med Chem 2014, 81, 367.

[7] (a) Paduranu, M. P.; Wilson, P. D. Org Lett 2003, 5, 4911; (b) Olivera, R.; SanMartin, R.; Churruca, F.; Dominguez, E. J Org Chem 2002, 67, 7215; (c) San Martin, R.; Olivera, R.; Churruca, F.; Tellitu, I.; Dominguez, E. Trends Heterocycl Chem 2003, 9, 259.

[8] Missir, R. A.; Limban, C.; Stecoza, C.; Morusciag, L.; Chirita, I. Formacia (Bucharest) 1998, 46, 17.

[9] (a) Jonas, J.; Forrest, T. P. J Org Chem 1970, 35, 836; (b) Kotha, S.; Mandal, K.; Tiwari, A.; Mobin, S. M. Chem Eur J 2006, 12, 8024; (c) Ramachary, D. B.; Narayana, V. V.; Ramkumar, K. Eur J Org Chem 2008, 3907.

[10] Tandon, V. K.; Chorr, R. B.; Goswamy, G. K. Ind J Chem
1998, 37B, 1027.
[11] (a) Maurya, H. K.; Vasudev, A.; Gupta, A. RSC Adv 2013, 3,

[11] (a) Matriya, H. K., Vasudev, A., Gupta, A. RSC Adv 2013, 5, 12955; (b) Gompper, R.; Töpfl, W. Chem Ber 1962, 95, 2881.

[12] Pratap, R.; Kumar, R.; Maulik, P. R.; Ram, V. J Tetrahedron Lett 2007, 48, 3311.

[13] (a) Becke, A. D. J Chem Phys 1993, 98, 5648; (b) Lee, C. T.; Yang, W. T.; Parr, R. G. Phys Rev B: Condens Matter Mater Phys 1998,

37, 1133. [14] Reed, A. E.; Weinstock, R. B.; Weinhold, F. J Chem Phys

[14] Reed, A. E., Weinstock, K. B., Weinstock, F. J Chem Filys 1985, 83, 735.

[15] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven

Jr. T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H. Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P. Komaromi, I.; Martin, R. L. Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, W. M.; Gonzalez, C.; Pople, J. A. Gaussian 03, Gaussian, Inc.: Wallingford CT, 2004.