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Divergent Pathways in the Intramolecular Diels-Alder Reaction of 2(1*H*)-Pyrazinones Substituted at the 3-Position with a Phenylalkyne Containing Side Chain.

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Abstract: 2(1*H*)-Pyrazinones bearing an X-(*o*-C_6H_4)-C≡C-R moiety (X=O or NH; R=H, Ph or TMS) at position 3 were subjected to intramolecular Diels-Alder reaction. For the ether compounds (X=O) cycloaddition-elimination occurred readily to produce either benzofuro[2,3-*c*]pyridin-1(2-*H*)-ones or benzofuro[2,3-*b*]pyridines. For the aniline derivatives (X=NH, R=H or TMS) thermolysis in acetic anhydride resulted in a similar product distribution of β-carbolinones and α-carbolines which, however, differed from that obtained previously in refluxing tetrahydronaphthalene. This result is explained by the cycloaddition proceeding from the aniline NH-acetylated precursor. However, the aniline derivatives with Ph as the acetylenic end group (X=NH, R=Ph) reacted *via* a divergent pathway to produce *N*-(2-oxopyrazin-3-yl)-2-Ph-substituted indoles.

Introduction

In a recent publication of our laboratory pyrazinones **1** bearing an -X-(*o*-C_6H_4)-C≡C-R moiety (X=NH, NAc) were subjected to intramolecular Diels-Alder reactions (scheme 1).[1] Cycloreversion of the intermediate adducts **2** produced α-carbolines **3** and β-carbolinones **4**, involving loss of R^1NCO and ClCN, respectively. Various reaction conditions were applied, *e.g.* thermolysis in refluxing tetrahydronaphthalene. The latter procedure led to selective formation of β-carbolinones **4** and proved to be successful even with severely hindered dienophilic side chains bearing Ph or TMS as the acetylenic end group. In contrast to the harsh conditions required for **1** (X=NH), spontaneous cycloaddition-elimination was observed for the analogous NAc precursors **1** (X=NAc). These were generated following *N*-acetylation of 3-(2-iodophenylamino)-2(1*H*)-pyrazinone *via* Pd-catalysed aromatic substitution with Ph- or TMS-acetylene. Acetylation of the anilino NH-group failed at the stage of the substituted pyrazinones **1** (X=NH; R=Ph or TMS).

Nevertheless thermolysis in acetic anhydride at 140°C was facilitated, providing carbolin(on)es **3** and **4** (R=CH_2OAc, CH_2OH) that were otherwise inaccessible. The enhanced cycloaddition effected by acetic anhydride therefore may be attributed to the intervention of the anilino NH-acetylated intermediate. In continuation of these studies, we further investigated the effect of acetic anhydride as a solvent for thermolysis of other -NH-(*o*-C_6H_4)-C≡C-R substituted pyrazinones (R=H, Ph, TMS). In addition, we also report on the intramolecular reaction of pyrazinones bearing an -O-(*o*-C_6H_4)-C≡C-R moiety which provides a convenient route to the benzofuro analogues of **3** and **4**.

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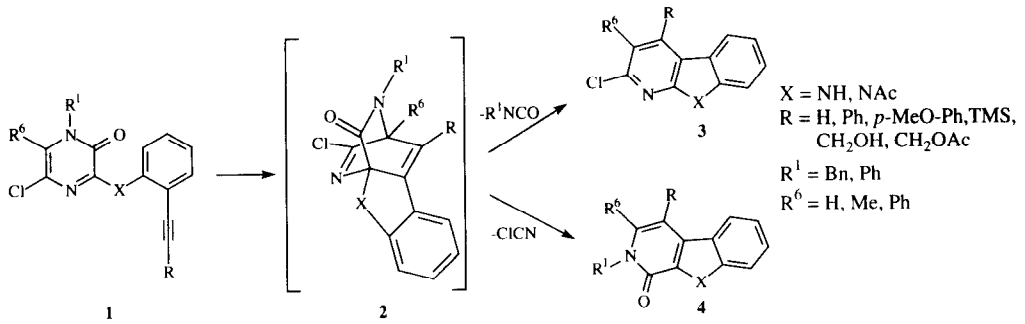
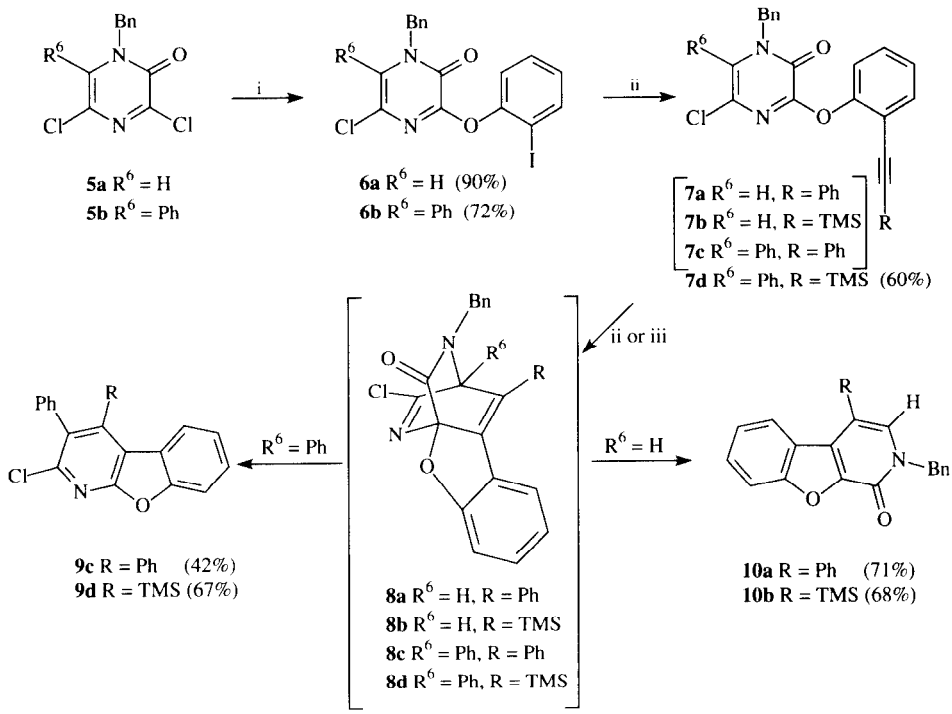


Scheme 1

Results and discussion

Benzofuro[2,3-*c*]pyridin-1(2-*H*)-ones[2-4] and benzofuro[2,3-*b*]pyridines[5-7] are scarcely mentioned in the literature. The former were prepared using methods similar to those for β-carbolinones, *i.e.* treatment of 2-carboxybenzofuran-3-acetic acid derivatives with acetic anhydride/pyridine followed by reaction with an amine (RNH_2)[4] or heating 2-carboxybenzofuran-3-acetic acid at 100°C in $POCl_3$/DMF.[2,3] In this way 3-methyl- or 2-methylbenzofuropyridinones were produced, respectively, with variable substituents in positions 6, 7 and 8. The 2-chloro and the unsubstituted benzofuro[2,3-*b*] pyridines were prepared using diazotization of (6-chloro)-3-amino-2-phenoxypyridine.[5] The 6-nitro and 6-chloro substituted analogues were obtained by treatment of *N*-*p*-nitrophenoxy- and *N*-*p*-chlorophenoxy-2-pyridinone with either $POCl_3$ or thionyl chloride; a [3,5]-shift was invoked to explain the *N,O*-bond cleavage and concomitant rearrangement.[6] Addition of 2-amino-3-thioformylbenzo[*b*]furan and mono- and disubstituted electron deficient alkynes gave 2,3-(COOEt)-disubstituted and 3-(COOEt or Ts)-monosubstituted benzofuro[2,3-b]pyridines.[7]

In our approach (scheme 2) we started from 3,5-dichloro-2(1*H*)-pyrazinones **5**. Substitution at the electrophilic 3-position of **5a-b** with sodium 2-iodophenolate in THF afforded the 3-(2-iodophenyloxy)-substituted pyrazinones **6a-b** in good yield. These were subjected to Pd-catalysed alkynylation with phenyl- or trimethylsilylacetylene at 40°C under the conditions mentioned in scheme 2. The resulting alkynylated intermediates **7a-d** underwent either spontaneous (**7a-c**) or thermally induced cycloaddition-elimination (**7d**), proceeding *via* cycloadducts of type **8**. In line with our previously reported findings for 6-substituted pyrazinones,[8] cycloreversion of **8a-b** (R^6=H) led to loss of ClCN producing benzo[2,3-*c*]pyridin-1(2*H*)-ones **10a-b**, whereas BnNCO was lost from the adducts **8c-d** (R^6=Ph) to give the benzofuro[2,3-*b*]pyridines **9c-d**. Probably due to the steric interaction between the voluminous 6-Ph and acetylenic TMS substituents, the TMS-alkynyl derivative **7d** was found to be less reactive than intermediates **7a-c**. Following isolation of **7d** (60%) and separate thermolysis in acetic anhydride for 2 h, benzofuro[2,3-*b*]pyridine **9d** was isolated in 67% yield. The mild conditions applied for the cycloaddition of the O-(*o*-C_6H_4)-alkynyl compounds **9a-c** are very similar to those reported previously for the analogous NAc compounds **1** (scheme 1, X=NAc). This similarity strongly suggests that both reactions proceed *via* a favourable 'inverse electron demand' transition state characterised by an electron deficient azadiene system and a low energy level of the LUMO's as compared to those for the NH-compounds **1** (X=NH).

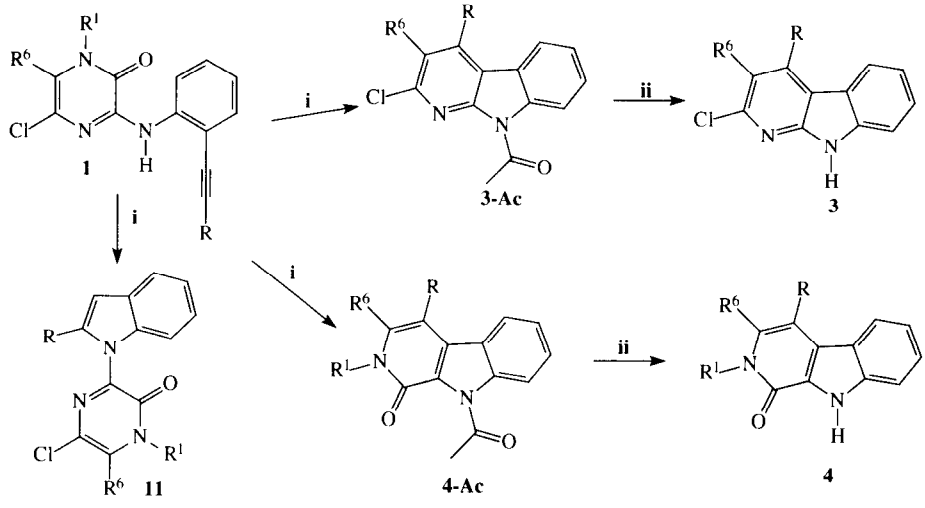


Scheme 2: Reagents and conditions: i) *o*-iodophenol, NaH,THF, r.t.; ii) R–C≡CH, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 40-70°C, 1-2 days; iii) Ac_2O, 140°C.

From these considerations it follows that *N*-acetylation of the anilino NH-group should enhance the rate of cycloaddition of compounds **1**. However, *N*-acetylated derivatives of **1** could not be isolated even when applying forcing conditions, *i.e.* acetic anhydride at 100°C or acetic anhydride-DMAP at 80°C. Nevertheless, since it was found before that thermolysis in acetic anhydride at 140°C was very effective for **1** (R=CH_2OH), this method was applied further to effect cycloaddition-elimination reactions of selected alkynyl compounds **1a-e** (R=TMS, H) and **1f-j** (R=Ph or *p*-MeO-Ph), prepared as reported in our previous publication.

The results of the thermolysis experiments (scheme 3) are collected in tables 1 (R=TMS, H) and 2 (R=Ph). For comparison purposes the tables also include some of our previous data[1] for the thermolysis of **1a-i** in boiling tetrahydronaphthalene (THN) (207°C) or bromobenzene (155°C) and for the reaction of the intermediates **1a-NAc** and **1h-NAc** generated *in situ* from the corresponding *N*-acetylated 3-(2-iodoanilino)-substituted pyrazinones *via* Pd-catalysed alkynylation at 40°C. From inspection of table 1 it appears that β-carbolinones **4** are the main products resulting from thermolysis of **1a,d-e** in both acetic anhydride and THN or bromobenzene. However, a deviating product distribution was observed for the reaction of **1b-c** (R^6=Ph) in acetic anhydride. Whereas in THN β-carbolinones **4b-c** were found as the main products, α-carbolines **3b-c** were formed exclusively in acetic anhydride. Hence, the product distribution resulting from the 6-Ph-substituted pyrazinones **1b-c** in Ac_2O is similar to that described before for the O-analogues **7c-d** which also

transform to the pyridine products (with and without acetic anhydride). In view of the widely different product distributions observed for the NH-compounds **1b-c** in THN and Ac_2O, one may conclude that the α-carbolines **3b-c** are formed *via* a more electron deficient NH-acetylated intermediate similar to the O-analogues **7c-d**.



Scheme 3: Reagents and conditions: i) Ac_2O, reflux, ii) K_2CO_3, H_2O, MeOH, r.t.

Table 1: Products from the thermolysis of alkynylpyrazinones **1a-e** (R=TMS, H)

Start	R^1	R^6	R	**3** or **3-Ac** yield (%)[a,b]	**4** or **4-Ac** yield (%)[a,b]	Conditions time (h)
1a	Bn	H	TMS	-	80[a]	Ac_2O (40)
1a	Bn	H	TMS	-	41[c]	PhBr (20)
1a	Bn	H	TMS	-	81[c]	THN (2)
1a-Nac	Bn	H	TMS	-	50[c]	Et_2NH (48)
1b	Bn	Ph	TMS	85[a]	-	Ac_2O (120)
1b	Bn	Ph	TMS	-	-	PhBr (96)
1b	Bn	Ph	TMS	-	69[d]	THN (48)
1c	Bn	Ph	H	80[a]	-	Ac_2O (72)
1c	Bn	Ph	H	20[c]	50[c]	THN (4)
1d	Bn	H	H	-	73[a]	Ac_2O (15)
1d	Bn	H	H	-	51[c]	PhBr (12)
1e	Bn	Me	H	6[b]	78[b]	Ac_2O (16)
1e	Bn	Me	H	-	52[c]	PhBr (12)

[a] yield of N-Ac product, [b] due to instability of the N-Ac derivatives, deacylation was performed (see experimental), [c] prepared and discussed in ref. 1 (products contain no N-Ac group), [d] yield of desilylated product

Table 2: Products from the thermolysis of alkynylpyrazinones **1f-j** (R=Ph and R=*p*-MeO-Ph)

Start	R^1	R^6	R	**3** or **3-Ac** yield (%)	**4** or **4-Ac** yield (%)	**11** yield (%)	Conditions Time (h)
1f	Ph	Me	Ph	24[a]	14[b]	50	Ac_2O (18)
1g	Bn	Me	Ph	-	-	85	Ac_2O (4)
1g	Bn	Me	Ph	-	83[c]	-	THN (18)
1h	Bn	H	Ph	-	25[b]	50	Ac_2O (12)
1h	Bn	H	Ph	-	90[c]	-	THN (4)
1h-Nac	Bn	H	Ph	-	60[c]	-	Et_2NH (48)
1l	Bn	Ph	Ph	-	-	90	Ac_2O (4)
1l	Bn	Ph	Ph	-	84[c]	-	THN (60)
1j	Bn	H	*p*-MeO-Ph	-	5[b]	55	Ac_2O (48)

[a] yield of N-Ac product, [b] yield of N-deacetylated product, [c] prepared and discussed in ref. 1 (products contain no N-Ac group)

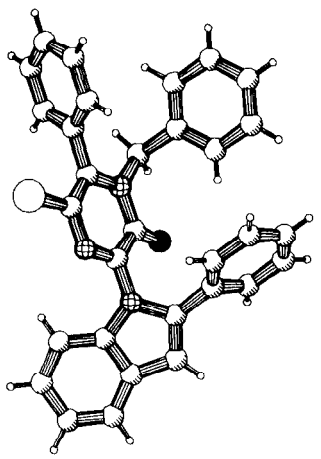


Figure 1: X-Ray Structure of compound **11i**

In opposition to the reaction of the alkynyl compounds **1a-e** (R=TMS and H), thermolysis of the phenylalkynyl compounds **1f-j** (R=Ph) in Ac_2O proceeded *via* a divergent reaction pathway to give indole derivatives **11f-j** as the major or the sole product. Furthermore, the indoles originating from **1g,i** (R^6=Me, Ph) with a larger substituent at the 6-position formed at a much faster rate than the corresponding β-carbolinones **4g,i** in THN (table 2). The indole structures were affirmed by spectroscopic data for **11f-j** (see experimental) and by X-ray analysis of compound **11i** (figure 1). All rings in **11i** are planar within experimental error. The indole and the pyrazinone rings make an angle of 49.45(9)° to each other.

Presumably, indole formation is facilitated by trace amounts of acetic acid present, which may assist in protonation of the acetylenic bond and NH-addition. However, when more acetic acid was added to the reaction mixture, other side products were formed, and the use of freshly distilled acetic anhydride was required for a clean reproduction of the indole forming reaction. To test our hypothesis that the reaction would proceed *via* a stabilised vinylic cation intermediate [Ph–$^+$C=CH–Ar], the *p*-methoxyphenyl substituted analogue of **1h** (**1j**, R^1 = Bn, R^6 = H, R = *p*-MeO-Ph) was prepared and subjected to thermolysis in freshly distilled acetic anhydride at 140° C. Under these conditions, the indole **11j** and the β-carbolinone **4j** were isolated in 55% and 5% yield, respectively. In contrast to our expectation the reaction rate was not increased relative to that of **1h**.

Conclusion:

When thermolysis of the pyrazinone precursors **1a-e** is carried out in acetic anhydride, the resulting product distribution of α-carbolines and β-carbolinones **3** and **4** appears to be similar to that found for the analogous benzofuropyridines **9** and benzofuropyridinones **10**, which are produced from the corresponding ether compounds **7**. This result, which contrasts with that for the reaction of **1a-e** in tetrahydronaphthalene or bromobenzene, probably is due to initial acetylation of the aniline NH-group. From the thermolysis of the phenylalkynyl compounds **1f-j** (R=Ph or *p*-MeO-Ph) in Ac_2O, indoles **11f-j** were formed as the major or the sole product *via* a divergent reaction pathway.

Experimental section

General methods: Melting points were taken using a Reichert-Jung Thermovar apparatus and an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 297 grating IR spectrophotometer and a Perkin-Elmer 1720 Fourier transform spectrometer. ^{1}H NMR spectra were recorded on a Bruker WM 250 or on a Bruker AMX 400 instrument. They were taken using $CDCl_3$ as solvent unless stated otherwise and the ^{1}H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane or the deuterated solvent as an internal reference. Mass spectra (electron impact) were run by using a Kratos MS50TC instrument and a Mach-3 data system. For the chromatography, analytical TLC plates (Alugram Sil G/UV_{254}) and 70-230 mesh silica gel 60 (E.M. Merck) were used. Microanalyses were performed by Janssen Pharmaceutica on a Carlo Erba elemental analyser type 1106.

The preparation and the analytical data for the 3,5-dichloro-2(1*H*)-pyrazinones **5a-b** and alkynylphenylamino-2(1*H*)-pyrazinones **1a-i** were reported previously as well as for compounds **3c**, **4a**, **4d-h**.[1]

1-Benzyl-5-chloro-3-{2-[(4-methoxyphenyl)ethynyl]anilino}-2(1*H*)-pyrazinone 1j
To a solution of 437 mg (1 mmol) of 1-benzyl-5-chloro-3-(2-iodophenylamino)-2(1*H*)-pyrazinone and 2 equiv. *p*-methoxyphenylacetylene (264mg, 2mmol) (prepared according to ref 9) in 10 ml diethylamine was added 13 mg (0.01 mmol) $PdCl_2(PPh_3)_2$ and 5 mg (0.03 mmol) CuI. After stirring for 4 h at 50°C the mixture was concentrated to give the crude compound **1j**. Column chromatography (silicagel) using 80% hexane/CH_2Cl_2 as eluent gave pure compound **1j**.
Yield: 362 mg, 82%; yellow crystals, m.p: 164°C; IR (KBr) cm^{-1}: 3297(NH), 2210(C≡C), 1651 (CO); ^{1}H NMR ($CDCl_3$) : 9.55 (s,1H, NH), 8.70 (d, J=8.3Hz, 1H, ArH), 7.67 (d, J=8.6Hz, 2H, ArH), 7.50 (d, J=7.6Hz, 1H, ArH), 7.36 (m, 6H, ArH), 7.04 (t, J=7.6 Hz, 1H, ArH), 6.92 (d, J=8.8Hz, 2H, ArH), 6.63 (s, 1H, H_6), 5.11 (s, 2H, CH_2Ph), 3.28 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): 159.9 (C-OMe), 150.9 (CO), 146.6 (C_5), 139.0 (Ar-C), 134.7 (Ar-C), 133.2, 131.1, 129.2, 129.1, 128.6, 128.4, 122.7, 118.0, 114.3 (Ar-CH), 125.9 (Ar-C), 114.2 (C_6), 113.2 (Ar-C), 97.6 (C≡CPh), 83.2 (C≡CPh), 55.3 (OCH_3), 52.1 (CH_2Ph); m/z (%): 441 ($M^{+\cdot}$, 100), 406 ($M^{+\cdot}$-Cl, 29), 91 ($C_7H_7^+$, 79); exact mass for $C_{26}H_{20}ClN_3O_2$: 441.1244; found: 441.1252.

Thermolysis of the pyrazinones **1**

The 2(1*H*)-pyrazinones **1** (1 mmol) were refluxed in acetic anhydride (25 ml) during 1-5 days under a nitrogen atmosphere to give compounds **11** and/or the acetylated derivatives **3Ac-4Ac**. After evaporation the crude mixture was purified using column chromatography (silicagel) with EtOAc/CH_2Cl_2 (**3Ac-4Ac**) or hexane/CH_2Cl_2 (**11**) as the eluent. Compounds **11** were recrystallized from diisopropyl ether.
Further identification of **3Ac-4Ac** was carried out by deacylation, *i.e.* treatment with a mixture of 5 ml of an aqueous saturated $NaHCO_3$ solution and 20 ml CH_3OH, to give compounds **3-4** described previously.

9-Acetyl-2-chloro-3-phenyl-4-trimethylsilyl-9*H*-pyrido[2,3-b]indole 3b-Ac
Yield: 333 mg, 85%; white crystals, m.p: 160-162°C; IR (KBr) cm^{-1}: 1703 (CO), 1600-1540-1455 (C=C); ^{1}H NMR : 8.82 (d, J=8.4Hz, 1H, H_{5or8}), 8.20 (d, J=8Hz, 1H, H_{5or8}), 7.57-7.27 (m, 7H, Ar-H), 3.16 (s, 3H, CH_3CON), 0.13 (s, 9H, $(CH_3)_3Si$); ^{13}C NMR : 171.2 (C(O)N), 148.5 (C_{9a}), 147.7 (C_2), 146.7 (C_4), 140.1 (C_{8a}), 138.8 to 123.0 (other Ar-C), 137.0 (C_3), 122.5 (C_{4b}), 117.3 (C_8), 28.3 (CH_3CON), 0.9 ($(CH_3)_3Si$); m/z (%): 392 (M^+, 24), 350 ($M^{+\cdot}$-CH_2CO, 100), 335 ($M^{+\cdot}$-CH_2CO-CH_3, 24), 73 ($(CH_3)_3Si^+$, 17), 43 (CH_3CO^+, 51); exact mass for $C_{22}H_{21}ClN_2OSi$: 392.1111; found: 392.1109.

2-Chloro-3-phenyl-4-trimethylsilyl-9*H*-pyrido[2,3-b]indole 3b
Yield: 276 mg, 93% ; white crystals, m.p.: 294°C; IR: 3176 (NH), 1515 (pyridine); ^{1}H NMR : 11.63 (s(br), 1H, NH), 8.17 (d, J=8Hz, 1H, H_{5or8}), 7.82 (d, J=8Hz, 1H, H_{5or8}), 7.5-7.26 (m, 7H, Ar-H), 0.19 (s, 9H, $(CH_3)_3Si$); ^{13}C NMR : 150.0 (C_{9a}), 147.9 (C_2), 146.6 (C_4), 140.8 (C_{8a}), 139.7 to 117 (other Ar-C), 121.0 (C_{4b}), 112.0 (C_8), 0.8 ($(CH_3)_3Si$); m/z (%): 350 ($M^{+\cdot}$, 93), 335 ($M^{+\cdot}$-CH_3, 74), 299 ($M^{+\cdot}$-CH_3-HCl, 100); exact mass

for $C_{20}H_{19}ClN_2Si$: 350.1006; found: 350.1005; Anal. Calcd for $C_{20}H_{19}ClN_2Si$: C, 68.45, H, 5.46, N, 7.98. Found: C, 68.40, H, 5.39, N, 7.96.

9-Acetyl-2-chloro-3-phenyl-9*H*-pyrido[2,3-b]indole 3c-Ac
Yield: 256 mg, 80%; white powder, m.p: 155°C; IR (KBr) cm^{-1}: 1710 (CO), 1600-1540-1450 (C=C); ^1H NMR : 8.8 (d, J=8.3Hz, 1H, H_{5or8}), 8.2 (d, J=8Hz, 1H, H_{5or8}), 7.6-7.2 (m, 8H, Ar-H), 3.1 (s, 3H, CH_3CON); ^{13}C NMR : 170.2 (C(O)N), 146.9 (C_{9a}), 146.4 (C_2), 140.2 (C_{8a}), 138-124.2 (other Ar-C), 136.9 (C_3), 121.9 (C_{4b}), 118 (C_8), 29 (CH_3CON); m/z (%): 320 (M^+, 22), 278 (M^+-CH_2CO, 100), 43 (CH_3CO^+, 49); exact mass for $C_{19}H_{13}ClN_2O$: 320.0716; found: 320.0713.

2-Chloro-3-methyl-9*H*-pyrido[2,3-*b*]indole 3e
Yield: 13 mg, 6%; white crystals ; IR (KBr) cm^{-1}: 3190 (NH), 1580 (pyridine); ^1H NMR (DMSO-d_6): 11.8 (s, 1H, NH), 8.48 (s, 1H), 8.1 (d, J = 7Hz, 1H), 7.47 (s (br), 2H), 7.2 (d, J=7Hz, 1H), 2.45 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6): 149.5 (C_{9a}), 146.4 (C_2), 139.1 (C_{8a}), 131.6 to 119.6 (other Ar-C), 114.6 (C_{4b}), 111.4 (C_8), 19.2 (CH_3); m/z (%): 216 (M^+, 100), 181 (M^+-Cl, 44); exact mass for $C_{12}H_9ClN_2$: 216.0454; found: 216.0451.

9-Acetyl-2-chloro-3-methyl-4-phenyl-9*H*-pyrido[2,3-*b*]indole 3f-Ac
Yield: 80 mg, 24%; white powder:IR (KBr) cm^{-1}: 1700 (CO), 1600-1540 (pyridine); ^1H NMR ($CDCl_3$): 8.7 (d, J=8.4Hz, 1H, Ar-H); 7.66-7.56 (m, 3H, Ar-H), 7.46-7.27 (m, 3H, Ar-H),7.06 (dt, J=8 and J=0.7Hz, 1H, Ar-H), 6.65 (dd, J=8 and J=0.7Hz, 1H, Ar-H), 3.15 (s, 3H, CH_3), 2.26 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): 171.0 (C(O)N), 147.9 (C_{9a}), 147.7 (C_2), 146.7 (C_4), 138.5 (C_{8a}), 136.9 to 119.6 (other Ar-C), 117.4 (C_8), 116.5 (C_{4b}), 27.9 (CH_3), 16.6 (CH_3); m/z (%): 334 (M^+, 39), 292 (M^+-CH_2CO, 100), 257 (M^+-CH_2CO-Cl, 36); exact mass for $C_{20}H_{15}ClN_2O$: 334.0872; found: 334.0875.

9-Acetyl-2-benzyl-4-trimethylsilyl-2,9-dihydro-1*H*-β-carbolin-1-one 4a-Ac
Yield: 310 mg, 80%; white powder, m.p.: 131-132°C; IR (KBr) cm^{-1}: 1713 (CO), 1650 (CO), ^1H NMR : 8.32 (d, J=8Hz, 1H, H_8), 8 (d, J=8Hz, 1H, H_5), 7.56-7.27 (m, 8H, Ar-H), 5.34 (s, 2H, CH_2), 2.8 (s, 3H, $COCH_3$), 0.48 (s, 9H, $(CH_3)_3Si$); ^{13}C NMR : 172.5 (C(O)N), 155.4 (CO), 140.2-136.4-134.3 ($C_{8a,9a,ipso}$),137.4 (C_3), 128.6-128.5-127.7-127.6-122.9-122.7 (ArCH, $C_{5,6,7}$), 126.1-123.9 ($C_{4a,4b}$), 113.9 (C_8), 109.4 (C_4), 51.9 (CH_2), 28.3 (CH_3), -0.4 (($CH_3)_3Si$); m/z (%): 388 (M^+, 11), 346 (M^+-CH_2CO, 100), 91 ($C_7H_7^+$, 63), 43 (CH_3CO^+, 59); exact mass for $C_{23}H_{24}N_2O_2Si$: 388.1607; found: 388.1610.

9-Acetyl-2-benzyl-2,9-dihydro-1*H*-β-carbolin-1-one 4d-Ac
Yield: 230 mg, 73%; white powder, m.p.: 181-182°C; IR (KBr) cm^{-1}: 1715 (CO), 1650 (CO); ^1H NMR : 8.3 (d, J=8.2Hz, 1H, H_8), 7.84 (d, J=7.4Hz, 1H, H_5), 7.59-7.27 (m, 8H, Ar-H), 6.87 (d, J=6.95Hz, 1H, H_4), 5.33 (s, 2H, CH_2Ph), 2.87 (s, 3H, $COCH_3$); ^{13}C NMR : 172.4 (C(O)N), 155.4 (CO), 140.1-136.5-131.9 ($C_{8a,9a,ipso}$), 132.6 (C_3), 129.3-128.7-127.7-127.5-123.3-120.4 (ArCH, $C_{5,6,7}$), 123.1-116.7 ($C_{4a,4b}$), 115.6 (C_8), 99.3 (C_4), 52.1 (CH_2), 28.3 (CH_3); m/z (%): 316 (M^+,10), 374 (M^+-CH_2CO,100), 91 ($C_7H_7^+$,95), 43 (CH_3CO^+,71); exact mass for $C_{20}H_{16}N_2O_2$: 316.1211; found: 316.1214.

2-Benzyl-4-(4-methoxyphenyl)-2,9-dihydro-1*H*-β-carbolin-1-one 4j
Yield: 19 mg, 5%; white crystals, m.p. 281°C; IR (KBr) cm^{-1}: 1650 (CO); 1H NMR ($CDCl_3$): 10.64 (s(br), 1H, NH), 7.50-7.44 (m, 4H, ArH), 7.39-7.29 (m, 6H, ArH), 7.04-6.99 (m, 4H, ArH), 5.44 (s, 2H, CH_2), 3.89 (s, 3H, CH_3); 13C NMR: 159.4 (C-OMe), 155.3(CO), 139.8-137.1-129.1-128.5 ($C_{8a,9a,ipso}$), 130.5-128.9-127.8-126.5-126.3-123.4-119.9-113.9 (ArCH, $C_{3,5,6,7}$) , 123.4-122.4 ($C_{4a,4b}$), 119.1 (C_4), 112.5(C_8), 55.4(CH_3), 51.6(CH_2); m/z (%): 380 (M^+, 100), 289 (M^+-C_7H_7, 68), 91 ($C_7H_7^+$, 20); exact mass for $C_{25}H_{20}N_2O_2$: 380.1525; found: 380.1515.

1-Phenyl-5-chloro-6-methyl-3-(2-phenyl-1*H*-indol-1-yl)-2(1*H*)-pyrazinone 11f
Yield: 205 mg, 50%; yellow powder, IR (KBr) cm^{-1}: 1665 (CO), 1600-1540 (indole); ^1H NMR : 7.64 (d, J=8Hz, 1H, $H_{7'}$); 7.6 (d, J=7.8Hz, 1H, $H_{4'}$), 7.43-7.18 (m, 10H, Ar-H), 6.80 (m, 2H, Ar-H), 6.7 (s, 1H, $H_{3'}$), 2.1 (s, 3H, CH_3); ^{13}C NMR : 152.5 (CO), 144.2 (C_3), 140.1-138 ($C_{2',7'a}$), 137.1 (C_6), 135.3-133.9-129.5 (Ar-C, $C_{3'a}$), 130.1-129.7-129.4-128.4-127.4-126.8- (Ar-CH), 123.7 (C_5), 123.1-121.8-120.6 ($C_{4',5',6'}$), 111.4

($C_{7'}$), 105.4 ($C_{3'}$), 18.2 (CH_3); m/z (%): 411 ($M^{+\cdot}$, 100), ($C_6H_5^+$, 10); exact mass for $C_{25}H_{18}ClN_3O$: 411.1138; found: 411.1147.

1-Benzyl-5-chloro-6-methyl-3-(2-phenyl-1*H*-indol-1-yl)-2(1*H*)-pyrazinone 11g

Yield: 361 mg, 85%; yellow crystals, m.p.: 167-168°C; IR (KBr) cm^{-1}: 1660 (CO), 1600-1540 (indole); ^1H NMR : 7.6 (d, J=8Hz, 1H, $H_{7'}$); 7.5 (d, J=8Hz, 1H, $H_{4'}$), 7.47-7.1 (m, 10H, Ar-H), 6.77 (s, 1H, $H_{3'}$), 6.74 (m, 2H, Ar-H), 4.9 (s (br), 2H, CH_2), 2.4 (s, 3H, CH_3); ^{13}C NMR : 152.9 (CO), 143.7 (C_3), 141.2-138.2 ($C_{2',7'a}$), 135.9 (C_6), 134.3-134.1-129.4 (Ar-C, $C_{3'a}$), 129.0-128.6-128.0-127.5-127.3-126.9 (Ar-CH), 123.7 (C_5), 123.1-121.8-120.7 ($C_{4',5',6'}$), 111.1 ($C_{7'}$) , 105.4 ($C_{3'}$), 49.1 (CH_2), 16.9 (CH_3); m/z (%): 425 ($M^{+\cdot}$, 100), 348 ($M^{+\cdot}$-C_6H_5, 26), 334 ($M^{+\cdot}$-C_7H_7, 18); exact mass for $C_{26}H_{20}ClN_3O$: 425.1294; found: 425.1298; Anal. Calcd for $C_{26}H_{20}ClN_3O$: C, 73.32, H, 4.73, N, 9.87. Found : C, 73.21, H, 4.52, N, 9.56.

1-Benzyl-5-chloro-3-(2-phenyl-1*H*-indol-1-yl)-2(1*H*)-pyrazinone 11h

Yield: 304 mg, 74%; yellow crystals, m.p.: 98-100°C; IR (KBr) cm^{-1}: 1660 (CO), 1600-1540 (indole); ^1H NMR : 7.6 (d, J=8Hz, 1H, $H_{7'}$); 7.5 (d, J=8Hz, 1H, $H_{4'}$), 7.4-7.15 (m, 10H, Ar-H), 7.14 (s, 1H, H_6), 6.96 (m, 2H, Ar-H), 6.76 (s, 1H, $H_{3'}$), 4.87 (s (br), 2H, CH_2); ^{13}C NMR : 151.8 (CO), 146.6 (C_3), 141.0-137.9 ($C_{2',7'a}$), 134.3-133.8-129.4 (Ar-C, $C_{3'a}$), 129.1-128.7-128.6-128.3-127.4-127.2 (Ar-CH), 125.8 (C_6), 124.1 (C_5), 123.3-122.1-120.7 ($C_{4',5',6'}$), 111.3 ($C_{7'}$), 105.9 ($C_{3'}$), 52.6 (CH_2); m/z (%): 411 ($M^{+\cdot}$, 100), 334 ($M^{+\cdot}$-C_6H_5, 16), 320 ($M^{+\cdot}$-C_7H_7, 11), 91 ($C_7H_7^+$, 54); exact mass for $C_{25}H_{18}ClN_3O$: 411.1138; found: 411.1142.

1-Benzyl-5-chloro-6-phenyl-3-(2-phenyl-1*H*-indol-1-yl)-2(1*H*)-pyrazinone 11i

Yield: 438 mg, 90%; yellow crystals, m.p.: 215-216°C; IR (KBr) cm^{-1}: 1660 (CO), 1600-1540 (indole); ^1H NMR : 7.7 (d, J=8Hz, 1H, $H_{7'}$); 7.6 (d, J=8Hz, 1H, $H_{4'}$), 7.5-7 (m, 15H, Ar-H), 6.7 (s, 1H, $H_{3'}$), 6.3 (m, 2H, Ar-H), 4.8 (s (br), 2H, CH_2); ^{13}C NMR : 152.6 (CO), 145.5 (C_3), 141.3-138.2 ($C_{2',7'a}$), 138.2 (C_6), 135.1-134.1-130.5-129.5 (Ar-C, $C_{3'a}$), 130.2-129.4-128.8-128.6-128.4-127.6-127.4-127.1 (Ar-H), 124.0 (C_5), 123.2-121.9-120.7 ($C_{4',5',6'}$), 111.3 ($C_{7'}$), 105.8 ($C_{3'}$), 50.2 (CH_2); m/z (%): 487 ($M^{+\cdot}$, 100), 410 ($M^{+\cdot}$-C_6H_5, 17), 396 ($M^{+\cdot}$-C_7H_7, 22); exact mass for $C_{31}H_{22}ClN_3O$: 487.1451; found: 487.1457; Anal. Calcd for $C_{31}H_{22}ClN_3O$: C, 76.30, H, 4.54, N, 8.61. Found : C, 76.13, H, 4.49, N, 8.64.

1-Benzyl-5-chloro-3-[2-(4-methoxyphenyl)-1*H*-indol-1-yl]-2(1*H*)-pyrazinone 11j

Yield: 243 mg, 55%; yellow crystals, m.p. :186°C; IR (KBr) cm^{-1}: 1678 (CO), 1584 (indole); ^1H NMR ($CDCl_3$): 7.67-7.51 (m, 2H, Ar-H), 7.39-7.15 (m, 8H, ArH), 7.03-6.94 (m, 2 H, Ar-H), 6.90-6.81 (m, 2H, Ar-H), 6.69 (s, 1H, $H_{3'}$), 4.92 (s(br), 2H, CH_2Ph), 3.83 (s, 3H, CH_3): ^{13}C NMR: 159.2 (C- OMe),151.8 (CO), 146.8 (C_3), 140.9-137.8 ($C_{2',7'a}$), 134.3-129.6-126.5 (Ar-C,$C_{3'a}$), 129.1-128.8-128.6-128.3 (Ar-CH), 125.8(C_6), 124.2 (C_5), 122.9-121.9-120.5($C_{4',5',6'}$),111.1 ($C_{7'}$), 105.0 ($C_{3'}$), 55.2 (CH_3), 52.7 (CH_2); m/z (%): 441 ($M^{+\cdot}$, 100), 350 ($M^{+\cdot}$-$C_7H_7^+$, 13), 91 ($C_7H_7^+$, 52); exact mass for $C_{26}H_{20}ClN_3O_2$: 441.1244; found : 442.1249.

Synthesis of 5-chloro-3-(2-iodophenoxy)-2(1*H*)-pyrazinones **6a-b**.

A mixture of 2.2 g (10 mmol) 2-iodophenol and 360 mg (15 mmol) NaH was stirred at room temperature in 150 ml of dry THF during 30 min under an atmosphere of nitrogen. After addition of 10 mmol 2(1*H*)-pyrazinone **5** the suspension was stirred at room temperature during 20 hours. The resulting yellow mixture was evaporated to a volume of 20ml, 50ml water was added and the water layer extracted with 3x50 ml CH_2Cl_2. The organic phases were combined and washed with water, dried with $MgSO_4$, filtered and concentrated under vacuum. The product was purified by column chromatography on silica gel using hexane/CH_2Cl_2 mixture as eluent.

1-Benzyl-5-chloro-3-(2-iodophenoxy)-2(1*H*)-pyrazinone 6a

Yield: 3.933 g, 90%; white crystals; m.p.: 114-115°C; IR (KBr) cm^{-1}: 1671 (CO); ^1H NMR : 7.84-6.94 (m,9H, Ar-H), 6.97 (s, 1H, H_6), 5.12 (s, 2H, CH_2); ^{13}C NMR : 153.5-152.6 (C_2,C_3), 139.6-121.6 (Ar-C), 90.0 (Ar-CI), 52.2 (CH_2Ph); m/z (%): 438 ($M^{+\cdot}$, 4), 311 ($M^{+\cdot}$-I, 34), 91 ($C_7H_7^+$, 100); exact mass for $C_{17}H_{12}ClIN_2O_2$: 437.9632; found: 437.9628.

1-Benzyl-5-chloro-6-phenyl-3-(2-iodophenoxy)-2(1*H*)-pyrazinone 6b
Yield: 3.693 g, 72%; white crystals; m.p.: 160°C; IR 1665 (CO); ^{1}H NMR : 7.9 (dd, J=7.9 and J=1.4 Hz, 1H, Ar-H), 7.45-6.8 (m, 13H, Ar-H), 5.15 (s, 2H, CH_2); ^{13}C NMR : 152.8-150.7 (C_2,C_3), 139.7-119.4 (Ar-C), 90.2 (Ar-C-I), 49.9 (CH_2Ph); m/z (%): 514($M^{+\cdot}$, 21), 387 ($M^{+\cdot}$-I, 66), 91 ($C_7H_7^+$, 100); exact mass for $C_{23}H_{16}ClIN_2O_2$: 513.9945; found: 513.9941.

Synthesis of pyrazinone **7d**, pyridines **9c-d** and pyridinones **10a-b**.

To a solution of 1 mmol **6a-b** and 1.5 equiv trimethylsilylacetylene (147 mg, 1.5 mmol)/phenylacetylene (153 mg, 1.5 mmol) in 15 ml triethylamine was added 14 mg (0.02 mmol) $PdCl_2(PPh_3)_2$ and 3 mg (0.02 mmol) CuI. The mixture was stirred for 1-2 days at 45-70 °C and the solvent evaporated to give the crude products. These were purified using column chromatography (Silicagel) with 40% hexane/CH_2Cl_2 as the eluent to give the pure compounds **7d** or **9c**, **10a-b**. The 2(1*H*)-pyrazinone **7d** was refluxed in acetic anhydride during 2h under a nitrogen atmosphere. After evaporation the crude compound **9d** was purified using column chromatography with silica gel and EtOAc/CH_2Cl_2 5/95 as eluent mixture.

1-Benzyl-5-chloro-6-phenyl-3-(2-trimethylsilylethynylphenoxy)-2(1*H*)-pyrazinone 7d
Yield: 290 mg, 60%; colourless oil; IR (KBr) cm^{-1}: 2150 (C≡C), 1660 (CO), 1570 (C=N); ^{1}H NMR : 7.54 (dd, J = 7.6 and J = 1.4 Hz, 1H, Ar-H); 7.45-6.87 (m, 13H, ArH); 5.13 (s, 2H, CH_2), 0.2 (s, 9H, CH_3); ^{13}C NMR : 153.7-150.6 (C_2,C_3), 135.5-117.3 (Ar-C), 100.4 and 100.2 (C≡C), 49.9 (CH_2Ph), -0.1 (CH_3); MS (m/z (%)) 484 ($M^{+\cdot}$, 71), 469 ($M^{+\cdot}$-CH_3, 10), 449 ($M^{+\cdot}$-Cl), 393 ($M^{+\cdot}$-C_7H_7, 19), 351 ($M^{+\cdot}$-C_8H_7NO, 27), 91 ($C_7H_7^+$, 100); exact mass for $C_{28}H_{25}ClN_2O_2Si$: 484.1373; found: 484.1371.

2-Chloro-3,4-diphenyl-benzofuro[2,3-b]pyridine 9c
Yield: 149 mg, 42%; yellow powder; m.p.: 206°C; IR (KBr) cm^{-1} : 1565 and 1454 (C=C Ph); ^{1}H NMR : 7.63 (d, J = 8.3 Hz, 1H, ArH), 7.49 (dt, J = 8.3 and J = 1.2 Hz, 1H, ArH); 7.43 - 7.1 (m, 11H, ArH), 7.0 (d, J = 7.9 Hz, 1H, ArH); ^{13}C NMR : 162-155 (C-O), 147.5 (CCl), 136.1-135.8-131.6 (Ar-C), 130.8-128.8-128.3-127.8-127.5 (Ar-CH), 123.4-122.3 ($C_{6,7}$), 122.1 (Ar-C), 112.1 (C_8); MS (m/z (%)): 355 (M^+, 100), 336 ($M^{+\cdot}$-Cl, 30); exact mass for $C_{23}H_{14}ClNO$: 355.0763; found: 355.0763.

2-Chloro-3-diphenyl-4-trimethylsilyl-benzofuro[2,3-b]pyridine 9d
Yield: 235 mg, 67%; white powder, m.p.: 171°C; IR (KBr) cm^{-1}:1555, 1531 and 1455 (C=C); ^{1}H NMR : 8.05 (d, J = 8Hz, 1H, Ar-H), 7.69 (d, J = 8Hz, 1H, Ar-H), 7.54 (t, J= 7.4 Hz, 1H, Ar-H), 7.5-7.28 (m, 6H, Ar-H), 0.14 (s, 9H, CH_3); ^{13}C NMR : 159.9-154.8 (C-O), 149 (C-Cl), 147.3-138.7-136.9 (Ar-C), 130.6-128.1-127.9-127.8-124.9-122.8-120.4-112.1 (Ar-CH), 112.6-119.8 (Ar-C), -0.1 (CH_3); MS (m/z,(%)): 351 ($M^{+\cdot}$, 74), 336 ($M^{+\cdot}$-15, 100); exact mass for $C_{20}H_{18}ClNOSi$: 351.0846 ; found: 351.0847.

2-Benzyl-4-phenyl-benzofuro[2,3-c]pyridin-1(2*H*)-one 10a
Yield: 249 mg, 71%; white crystals ;m.p.: 183°C; IR (KBr) cm^{-1}: 1664 (s,CO); ^{1}H NMR : 7.8-7.23 (m, 14H, Ar-H), 7.15 (s, 1H, 3-H), 5.37 (s, 2H, CH_2Ph); ^{13}C NMR : 157.0 (C_{8a}), 152.4 (CO), 145.7 (C_{9a}), 140.6 (C_3), 136.9-124.0 (other Ar-C), 131.5 (C_{4a}), 122.6 (C_{4b}), 120.7 (C_8), 111.3 (C_4), 53.3 (CH_2); MS (m/z (%)): 347 ($M^{+\cdot}$, 97), 332 ($M^{+\cdot}$-CH_3, 67), 91 ($C_7H_7^+$, 100); MS (m/z (%)): 351 (M^+, 76), 274 ($M^{+\cdot}$-C_6H_5, 22), 91 ($C_7H_7^+$, 100); exact mass for $C_{24}H_{17}NO_2$: 351.1259; found: 351.1265.

2-Benzyl-4-trimethylsilyl-benzofuro[2,3-c]pyridin-1(2*H*)-one 10b
Yield: 235 mg, 68%; white crystals; m.p.: 120-121°C; IR (KBr) cm^{-1}: 1668 (s, CO); ^{1}H NMR : 7.7-7.25 (m, 9H, Ar-H), 7.19 (s, 1H, H_3), 5.33 (s, 2H, CH_2), 0.41 (s, 9H, CH_3); ^{13}C NMR : 157 (C_{8a}), 154.4 (CO), 144.3 (C-9a), 136.6 (C_3), 136.5 to 123.3 (other Ar-C), 131.3 (C_{4a}), 123.9 (C_{4b}), 113.1 (C_8), 109.7 (C_4), 51.5 (CH_2), -0.65 (CH_3); MS (m/z (%)): 347 ($M^{+\cdot}$, 97), 332 ($M^{+\cdot}$-CH_3, 67), 91 ($C_7H_7^+$, 100); exact mass for $C_{21}H_{21}NO_2$: 347.1341 ; found: 347.1343.

X-ray Structural Analysis of **11i**:[10]

Crystal data: $C_{31}H_{22}ClN_3O$, M=487.97. Triclinic, a=10.096(2), b=10.504(2), c=13.772(3)Å, α=111.84(1), β=111.01(1), γ=90.14(1)°, V=1249.9(5)Å^3 (by least-squares refinement on diffractometer angles for 39 automatically centered reflections, λ=0.71073Å), space group P-1, Z=2, d_{calc}=1.297 gcm^{-3}, F(000)=508. Crystal dimensions 0.40 x 0.35 x 0.25 mm, μ(Mo-Kα)=0.182 mm^{-1}.

Data Collection and Processing: Siemens P4-PC diffractometer, graphite monochromatized Mo-Kα radiation, T=289K, ω-scan, Δω=0.6°, $2.0 \leq \omega \leq 60.0°$ min^{-1}, $3.4 \leq 2\theta \leq 49.4°$, 4973 collected reflections ($(\sin\theta/\lambda)_{max}$=0.588), 4183 independent reflections (R_{int}=0.0324). Three checks measured every 100 reflections showed no significant decrease in intensity.

Structure Analysis and Refinement: Structure solved by direct methods and refined by full-matrix least-squares on F^2, with all non-hydrogen atoms anisotropic, and riding hydrogen atoms (C-H distance free to refine) with isotropic temperature factors fixed at 1.2 times U(eq) of their parent atom. Final R indices: R_1=0.0382 for 3333 reflections with $I > 2\sigma(I)$ and R_1=0.0518, wR_2=0.1084 for all data. The program package SHELXTL was used for all calculations.[11]

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