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Synthesis of New Bridgehead Heterocycles: Pyrimido[3′,2′:3,4]-1,2,4-triazino[5,6-*b*]-indoles

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ABSTRACT: *A new bridgehead nitrogen heterocycle viz. 11-carboethoxy-9-oxo-pyrimido[3′2′:3,4]-1,2,4-triazino[5,6-b]indole* **3** *has been synthesized from 3-azido-5H-1,2,4-triazino[5,6-b]indole* **2** *by its reaction with diethyl fumerate. The intermediate* **2** *was obtained by treating 3-hydrazino-5H-1,2,4-triazino[5,6-b]indole with $NaNO_2$ in presence of polyphosphoric acid. A plausible mechanism for the formation of* **3** *has been formulated and discussed.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:272–276, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20199

INTRODUCTION

The importance of heterocycles in biological systems has stimulated interest in designing and synthesizing new heterocyclic compounds. In the past much attention has been paid to the synthesis of condensed heterocyclic systems [1], as they possess enhanced bioactivities as compared to the individual heterocyclic moiety of which they are made of. Among the various biologically active fused systems, the one that contains a ring junction nitrogen [2,3] is the most important, as it is a part of various naturally occurring alkaloids [4]. The fusion of triazine and indole moieties has aroused considerable interest in the past as many triazino indoles are found to exhibit potent biological activities [5,6]. Moreover, some of these have been used as a carrier for diverse functional groups, suitable for the development of several chemotherapeutic agents [7,8]. The 3-hydrazino derivatives of triazino indole have also shown good analgesic and antiviral activities [9,10] and their 5-substituted analogues are effective in hypertension [11].

Similarly, fused pyrimidines viz. pyrimido-astriazine are of current interest, since it is also present in various naturally occurring antibiotics [12,13]. An interesting spectrum of biological activities associated with this system coupled with triazino indole has attracted us to design and develop the synthesis of a new bridgehead nitrogen heterocyclic system, viz. pyrimido-triazino-indole containing three biologically active nuclei. Surprisingly, the literature is silent on the synthetic as well as on the biological aspect of this system as of date.

Furthermore, introduction of fluorine in heterocyclic systems is well known to bring tremendous changes in their biological activities. Many pharmaceutical researchers are therefore introducing fluorine or trifluoromethyl group in place of hydrogen at critical site in the old/new molecules to modify their bioactivities [14]. We, therefore, also envisaged to synthesize some of the fluorinated analogues of the newly developed bridgehead nitrogen heterocycle and the details are presented here.

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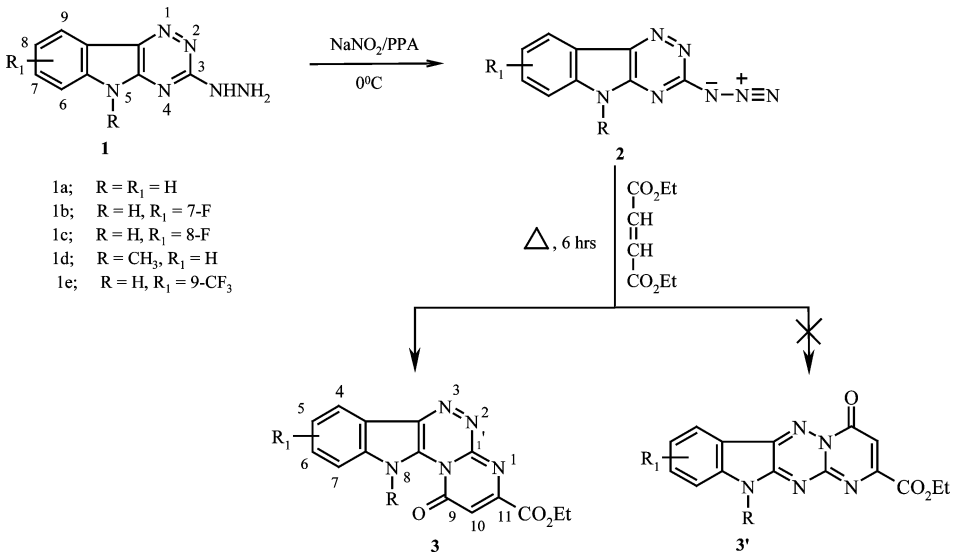
RESULTS AND DISCUSSION

In our comprehensive plan for developing new brigehead nitrogen heterocycles, a series of novel 11-carboethoxy-9-oxo-pyrimido[3′2′:3,4]-1,2,4-triazino [5,6-*b*]indoles **3a–e** have been synthesized starting from their corresponding 3-hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indoles **1a–e**. The synthetic strategy makes use of 3-azido-5*H*-1,2,4-triazino[5,6-*b*]indole **2** as the intermediate which was obtained by diazotization of 3-hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indole **1** in polyphosphoric acid (PPA). Compound **1** was synthesized by the reaction of indole-2,3-dione with thiosemicarbazide in weakly alkaline medium to obtain first 3-thioxo-5*H*-1,2,4-triazino[5,6-*b*]indole which with hydrazine hydrate yielded the desired compound [15]. Compound **2** on heating with diethyl fumerate (DEF) finally resulted in the formation of a pyrimidine ring (Scheme 1) to give compound identified as **3**.

The reaction of 3-hydrazino-5*H*-1,2,4-triazino[5, 6-*b*]indole **1a** with nitrous acid (sodium nitrite, PPA) at low temperature resulted in the formation of a yellow product. The literature survey has revealed that there was some controversy in the past about the structure of this product. Joshi and Chand [15] reported the formation of tetrazolo-triazino-indole whereas Latif and Shaker [16] identified the product as 3-azido-5*H*-1,2,4-triazino[5,6-*b*]indole obtained under similar condition. We have characterized this yellow product as 3-azido-5*H*-1,2,4-triazino[5,6-*b*]indole **2a** on the basis of detailed spectral studies. IR spectrum of diazotized product **2a** showed absorption bands at 3310 (>NH) and 2145 cm^{-1} (azide group). Appearance of this band indicates existence of product in the azido form ($-N^{-}-N^{+}\equiv N$) in solid state at room temperature. The ^{1}H NMR of **2a** showed multiplet at δ 7.52 indicating the presence of aromatic protons and a broad band at δ 9.18 (>NH). Chemical evidence in support of structure **2a** has come from its reaction with DEF, which resulted in the formation of pyrimido-triazino-indoles **3**. This clearly supported the formation of azido form and not the tetrazole form as earlier reported by Latif and Shaker [16].

Azide **2a** was then heated with DEF at 180°C for 6 h resulted in the formation of a brown colored compound labeled as **3a**. The IR spectrum of **3a** exhibited strong absorptions at 3100 (>NH), 1725 (ester carbonyl), 1640 (α, β unsaturated >C=O), and 1600 (C=C) cm^{-1}. The disappearance of absorptions band corresponding to azido group and appearance of carbonyl absorption indicated the formation of product. The ^{1}H NMR spectra displayed characteristic peaks at δ 1.51 (t, 3H, $J = 7.4$ Hz, $COOCH_2\mathbf{CH_3}$), 4.40 (q, 2H, $J = 7.4$ Hz, $COO\mathbf{CH_2}CH_3$), 7.22 (s, H-10) and a broad signal at δ 11.78 (>NH). Aromatic protons appeared as multiplet at δ 7.55. In ^{13}C NMR spectra signals were observed at δ 14.2 ($COOCH_2\mathbf{CH_3}$), 60.7 ($COO\mathbf{CH_2}CH_3$), 164.6 ($\mathbf{C}OOCH_2CH_3$), 172.6 (C-9), 146.2 (C-10), 152.6 (C-11), and 160.5 (C-1a). The mass spectrum of **3a** showed molecular ion peak at *m/z* 309 (12%) corresponding to the expected molecular weight.

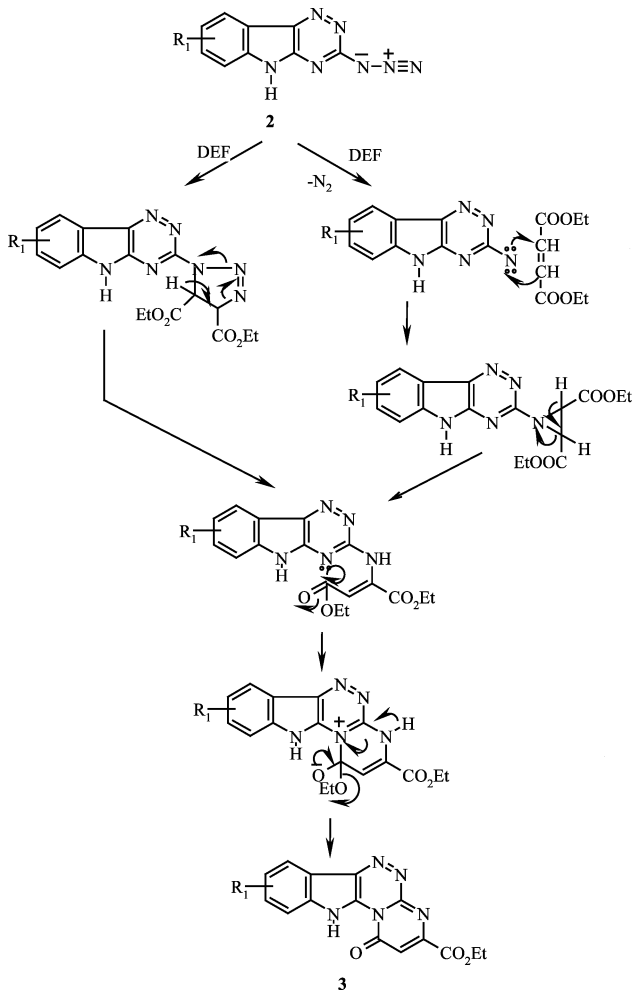
Cyclization of **2** with DEF can take place in two ways, involving N-4 or N-2, resulting in the formation of either angular product **3** or linear product **3′**. However, the IR and NMR data of the resulting compound are indicative of its angular structure. In IR spectra, shift in the absorption bands corresponding to >NH



SCHEME 1

and >C=O appearing toward lower wavenumber is an indication of intramolecular hydrogen-bonding which is possible only in the angular structure. In the ^{1}H NMR, the NH has been shifted substantially downfield (δ 9.18 in **2a** to δ 11.78 in **3a**) supporting the presence of chelated NH. Further support to the angular structure has also come from its stability. Literature reports favor the formation of a more benzenoid structure [17] in similar cases earlier. Thus, in the present case, formation of angular product involving cyclization at N-4 should be preferred as in this structure 10π electron system, i.e., aromatic characters of indole ring is preserved and is stabilized by high resonance energy.

The plausible mechanism for this type of reaction may be either the 1,3-dipolar addition with the intermediate formation of triazole, followed by loss of nitrogen or via addition of nitrene intermediate to the dienophile giving aziridine, which undergoes ring opening followed by prototropic shift and then cyclocondensation. The N-4 being more nucleophilic than N-2 will attack at electron deficient carbonyl carbon of DEF, which undergoes prototropic changes followed by loss of ethanol to give **3** (Scheme 2).



SCHEME 2

EXPERIMENTAL

The melting points were taken in open glass capillaries and were uncorrected. IR spectra were recorded on Perkin-Elmer IR™ spectrophotometer Model BX-II in KBr pellets while ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on Bruker spectrometer at 300 and 75.47 MHz in DMSO-d_6. All chemical shifts are reported in δ downfield from tetramethylsilane. Mass spectra were recorded on Jeol JMS-DX 303 instrument by using Electron Ionization at 70 eV and only major peaks are quoted. 1-Methyl, 5-fluoro, 6-fluoro, and 4-trifluoromethyl indole-2,3-diones and their corresponding 3-hydrazino-5*H*-1,2,4-triazino-[5,6-*b*]indoles were prepared by literature methods [15].

Synthesis of 3-Azido-5H-1,2,4-triazino[5,6-b]-indoles **2a–e**

These were prepared according to the following procedure. To a cooled solution of 3-hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indoles **1a–e** (10 mmol) in PPA (15 mL), sodium nitrite solution (5 N, 12 mL) was added dropwise and contents stirred for 30 min at 0°C. The solid that separated was recrystallized from dimethylformamide as yellow crystals to give the desired compound.

3-Azido-5H-1,2,4-triazino[5,6-b]indole **2a**. Yellow solid, mp >300°C, yield 71%; IR (KBr): 3310 (>NH), 2145 (—N$^-$—N$^+$≡N), 1612, 1586, 1523 cm^{-1}; ^{1}H NMR ((DMSO-d_6): 7.52 (m, 4H, Ar-H), 9.18 (br s, 1H, NH).

3-Azido-7-fluoro-5H-1,2,4-triazino[5,6-b]indole **2b**. Yellow solid, mp >300°C, yield 65%; IR (KBr): 3323 (>NH), 2146 (—N$^-$—N$^+$≡N), 1615 (C=N), 1584, 1522 cm^{-1}; ^{1}H NMR (DMSO-d_6): 7.41 (m, 3H, Ar-H), 9.20 (br s, 1H, NH).

3-Azido-8-fluoro-5H-1,2,4-triazino[5,6-b]indole **2c**. Yellow solid, mp >300°C, yield 68%; IR (KBr): 3305 (>NH), 2144 (—N$^-$—N$^+$≡N), 1621, 1582 cm^{-1}; ^{1}H NMR (DMSO-d_6): 7.35 (m, 3H, Ar-H), 9.13 (br s, 1H, NH).

3-Azido-5-methyl-5H-1,2,4-triazino[5,6-b]indole **2d**. Yellow solid, mp >300°C, yield 48%; IR (KBr):

2151 (—N^-—N^+≡N), 1623 (C=N), 1562, 1543 cm^{-1}; ^{1}H NMR (DMSO-d_6): 3.24 (s, 3H, —NCH_3), 7.44 (m, 4H, Ar-H).

3-Azido-9-trifluoromethyl-5H-1,2,4-triazino[5,6-b]indole **2e**. Yellow solid, mp >300°C, yield 40%; IR (KBr): 3251 (>NH), 2147 (—N^-—N^+≡N), 1613 (C=N), 1570, 1534 cm^{-1}; ^{1}H NMR (DMSO-d_6): 7.51 (m, 3H, Ar-H), 9.39 (br s, 1H, NH).

Synthesis of 11-Carboethoxy-9-oxo-pyrimido[3′,2′:3,4]-1,2,4-triazino[5,6-b]indoles **3a–e**

A mixture of 3-azido-5*H*-1,2,4-triazino[5,6-*b*]indoles **2a–e** (10 mmol) and diethylfumerate (10 mmol) was heated on an oil bath at 180°C for about 6 h. After cooling to room temperature, the reaction mixture was triturated with cyclohexane and kept overnight. The brown colored solid thus obtained was purified by column chromatography using silica gel as an adsorbent and labeled as **3a–e**.

11-Carboethoxy-9-oxo-pyrimido[3′,2′:3,4]-1,2,4-triazino[5,6-b]indole **3a**. Recrystallized from methanol/chloroform as yellowish brown solid, mp >300°C, yield 72%. IR (KBr): 3100 (>NH), 1725 (ester carbonyl), 1640 (α, β-unsaturated carbonyl), 1600 (C=C), 1585, 1520 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.51 (t, 3H, —$COOCH_2$**CH_3**), 4.40 (q, 2H, —COO**CH_2**CH_3), 7.22 (s, 1H, H-10), 7.55 (m, 4H, Ar-H), 11.78 (>NH). ^{13}C NMR (DMSO-d_6): δ 14.2 ($COOCH_2$**CH_3**), 60.7 (COO**CH_2**CH_3), 111.7, 115.4, 116.6, 122.3, 125.5, 135.3, 141.6, 146.2 (C-10), 152.6 (C-11), 153.1, 160.5 (C-1a), 164.6 (**C**OOC_2H_5), 172.6 (C-9); EIMS *m/z*(%): 309 (M^+, 12), 281 (15), 264 (21), 236 (18), 183 (28), 155 (46), 128 (46), 103 (58), 76 (27), 44 (100). Anal. Calcd for $C_{15}H_{11}N_5O_3$ (309.28): C, 58.25; H, 3.58; N, 22.64%. Found: C, 58.39; H, 3.49; N, 22.72%.

11-Carboethoxy-6-fluoro-9-oxo-pyrimido-[3′,2′:3,4]-1,2,4-triazino[5,6-b]indole **3b**. Recrystallized from methanol/chloroform as bright yellow solid, mp >300°C, yield 70%. IR (KBr): 3151 (>NH), 1725 (ester carbonyl), 1642 (α, β-unsaturated carbonyl), 1605 (C=C), 1579, 1528 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.33 (t, 3H, —$COOCH_2$**CH_3**), 4.45 (q, 2H, —COO**CH_2**CH_3), 7.17 (s, 1H, H-10), 7.62 (m, 3H, Ar-H), 11.89 (>NH); ^{13}C NMR (DMSO-d_6): δ 14.5 ($COOCH_2$**CH_3**), 61.2 (COO**CH_2**CH_3), 118.8, 116.28, 123.4, 134.8, 140.25, 145.04 (C-10), 148.4, 150.3, 151.2 (C-11), 159.6 (C-1a), 162.5 (**C**OOC_2H_5), 170.4 (C-9); EIMS *m/z* (%): 327 (M^+, 11), 299 (19), 282 (28), 254 (22), 201 (46), 173 (33), 94 (25), 62 (92). Anal. Calcd for $C_{15}H_{10}FN_5O_3$ (327.27): C, 55.05; H, 3.08; N, 21.40%. Found: C, 55.17; H, 3.15; N, 21.46%.

11-Carboethoxy-5-fluoro-9-oxo-pyrimido-[3′,2′:3,4]-1,2,4-triazino[5,6-b]indole **3c**. Recrystallized from methanol/chloroform as yellowish solid, mp >300°C, yield 68%. IR (KBr): 3150 (>NH), 1722 (ester carbonyl), 1635 (α, β-unsaturated carbonyl), 1610 (C=C), 1575, 1535 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.41 (t, 3H, $J = 6.8$ Hz, —$COOCH_2$**CH_3**), 4.42 (q, 2H, —COO**CH_2**CH_3), 7.15 (s, 1H, H-10), 7.40–7.59 (m, 3H, Ar-H), 12.11 (>NH); ^{13}C NMR (DMSO-d_6): δ 13.3 (—$COOCH_2$**CH_3**), 60.4 (COO**CH_2**CH_3), 114.1, 118.1, 118.2, 122.2, 133.2, 141.2, 144.1 (C-10), 148.1, 150.2 (C-11), 152.6, 158.4 (C-1a), 160.4 (**C**OOC_2H_5), 169.3 (C-9); EIMS *m/z*(%): 327 (M^+, 13), 299 (14), 282 (28), 254 (22), 201 (46), 173 (33), 94 (20), 62 (100). Anal. Calcd for $C_{15}H_{10}FN_5O_3$ (327.27): C, 55.05; H, 3.08; N, 21.40%. Found: C, 55.12; H, 3.12; N, 21.48%.

11-Carboethoxy-8-methyl-9-oxo-pyrimido-[3′,2′:3,4]-1,2,4-triazino[5,6-b]indole **3d**. Recrystallized from methanol/chloroform as yellowish orange solid, mp >300°C, yield 65%. IR (KBr): 1710 (ester carbonyl), 1675 (α, β-unsaturated carbonyl), 1620 (C=C), 1581, 1533 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.32 (t, 3H, $J = 7.3$ Hz, —$COOCH_2$**CH_3**), 3.42 (s, 3H, >N—CH_3), 4.25 (q, 2H, —COO**CH_2**CH_3), 7.05 (s, 1H, H-10), 7.41 (m, 3H, Ar-H); ^{13}C NMR (DMSO-d_6): δ 14.2 (—$COOCH_2$**CH_3**), 36.4 (N—CH_3), 62.5 (COO**CH_2**CH_3), 112.2, 115.8, 118.0, 124.2, 124.5, 135.2, 139.6, 144.2 (C-10), 150.0, 152.3 (C-11), 160.1 (C-1a), 163.2 (**C**OOC_2H_5), 166.3 (C-9); EIMS *m/z*(%): 323 (M^+, 15), 308 (15), 280 (19), 263 (12), 235 (32), 207 (6), 182 (45), 154 (22), 102 (30), 43 (60). Anal. Calcd for $C_{16}H_{13}N_5O_3$ (323.31): C, 59.44; H, 4.05; N, 21.66%. Found: C, 59.31; H, 4.11; N, 21.78%.

11-Carboethoxy-4-trifluoromethyl-9-oxo-pyrimido-[3′,2′:3,4]-1,2,4-triazino[5,6-b]indole **3e**. Recrystallized from methanol/chloroform as yellowish solid, mp >300°C, yield 62%. IR (KBr): 3100 (>NH), 1724 (ester carbonyl), 1639 (α, β-unsaturated carbonyl), 1616 (C=C), 1583, 1528 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.35 (t, 3H, $J = 6.8$ Hz, —$COOCH_2$**CH_3**), 4.21 (q, 2H, —COO**CH_2**CH_3), 6.99 (s, 1H, H-10), 7.48 (m, 3H, Ar-H), 11.98 (>NH); ^{13}C NMR (DMSO-d_6): δ 12.5 (—$COOCH_2$**CH_3**), 58.2 (COO**CH_2**CH_3), 114.2, 115.1 (CF_3), 120.0, 126.3, 134.6, 138.4, 144.0 (C-10), 152.4 (C-11), 157.4 (C-1a), 162.3 (**C**OOC_2H_5), 172.4 (C-9); EIMS *m/z*(%): 377 (M^+, 13), 349 (18), 332 (14), 304 (24), 251 (35), 223 (28), 170 (42), 44 (54). Anal. Calcd for $C_{16}H_{10}F_3N_5O_3$ (377.28): C, 50.94; H, 2.67; N, 18.56%. Found: C, 50.86; H, 2.72; N, 18.64%.

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