Heteroatom Chemistry
Volume 18, Number 3, 2007

Synthesis and Interconversion of Isomeric Pyrrolotriazolopyrimidines

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Received 6 November 2005; revised 13 March 2006

ABSTRACT: *4-Hydrazino-7H-pyrrolo[2,3-d]pyrimidines* **4** *were cyclocondensed with formic acid or triethyl orthoformate to give 7H-pyrrolo[3,2-e][1,2,4] triazolo[1,5-c]pyrimidines* **6** *and 7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidines* **7**,*respectively. The [4,3-c] isomers* **7** *were rearranged into thermodynamically more stable [1,5-c] isomers* **6**. *The identical compounds* **6** *were prepared using another route by reacting 3-amino-4-imino-7H-pyrrolo[2,3-d]pyrimidines* **3** *with formic acid or triethyl orthoformate. The reaction of 2-amino-3-cyanopyrroles* **1** *with triethyl orthoformate gave N-ethoxymethylene-2-amino-3-cyanopyrroles* **2**. *Further reaction with an equivalent of hydrazine hydrate provided 3-amino-4-imino-7H-pyrrolo[2,3-d]pyrimidines* **3**, *whereas treatment with excess of hydrazine hydrate,* **3** *rearranged to 4-hydrazino-7H-pyrrolo[2,3-d]pyrimidines* **4**. *Compounds* **4** *were also obtained by the treatment of N-ethoxymethylene-2-amino-3-cyanopyrroles* **2** *in excess of hydrazine hydrate.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:265–273, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20295

INTRODUCTION

In the past years, the literature is enriched with progressive finding about the synthesis and pharmacological actions of fused triazolopyrimidines and their related compounds. Triazolopyrimidines are extensively reviewed as adenosine receptor antagonists [1]. They are also associated with potent biological activity, such as antitumor [2], antihypertensive [3], anti-inflammatory [4], antiasthmatic [5], anxiolytic [6], and antifungal [7]. A number of reports have been published for the synthesis of fused triazolopyrimidines by cyclocondensation of 4-hydrazinopyrimidines with various one-carbon donor moieties [8–15]. In many instances, formic acid was used as a cyclizing agent, in which the possibility of the formation of isomeric triazole was overlooked [15–18]. However, the possibility of isomeric rearrangement was taken into consideration in the reaction of 4-hydrazinothienopyrimidines, 4-hydrazinopyrazolopyrimidines, and 4-hydrazinoquinazolines with one-carbon donor moieties yielding respective isomeric triazolothienopyrimidines [19,20], triazolopyrazolopyrimidines [21], and triazoloquinazolines [22], respectively. So far, there has not been any report on isomeric conversion in the pyrrolotriazolopyrimidine system. Few works have been found in which a triazole ring was annellated onto existing pyrrolo[2,3-*d*]pyrimidines [23–25]. Therefore, in continuation of our interest in fused triheterocyclic pyrimidines [26–29], it was interesting to report the synthesis of 7*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines and 7*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines by the annellation of the triazole ring onto the existing pyrrolo[2,3-*d*]pyrimidine ring systems. Furthermore, the conversion of *N*-ethoxymethylene-2-amino-3-cyanopyrroles and 3-amino-4-imino-7*H*-pyrrolo[2,3-*d*]pyrimidines to

Dedicated to the memory of Dr. Chaitanya G. Dave.

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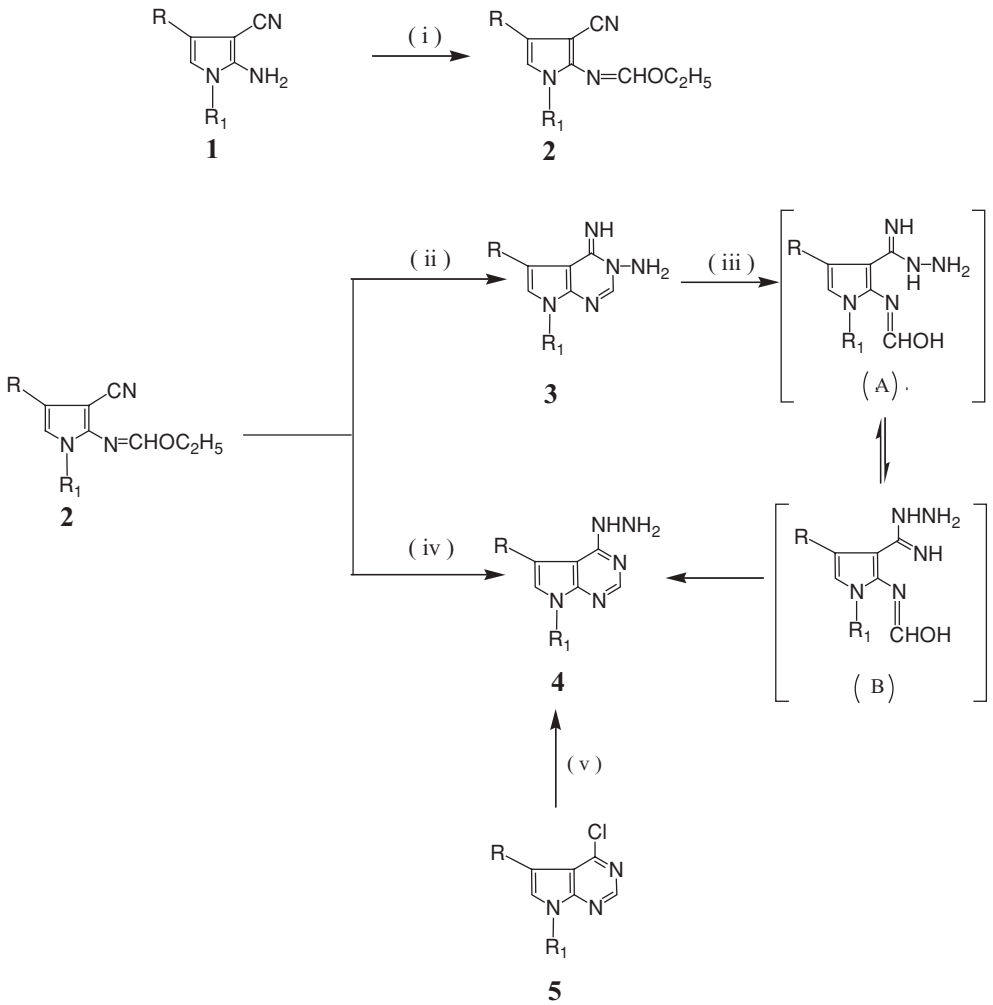
4-hydrazino-7*H*-pyrrolo[2,3-*d*]pyrimidines and an isomeric rearrangement of pyrrolotriazolopyrimidines to the more stable form have also been studied.

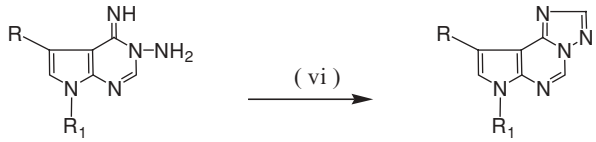
RESULTS AND DISCUSSION

1,4-Disubstituted-2-amino-3-cyanopyrroles **1** [30] were reacted in boiling triethyl orthoformate to give 1,4-disubstituted-*N*-ethoxymethylene-2-amino-3-cyanopyrroles **2**. The reaction of **2** with an equivalent of hydrazine hydrate afforded 3-amino-4-imino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines **3** rather than the expected 4-hydrazino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines **4**; these results are in accordance with Hosmane et al. [31]. Products **4** were obtained by the Dimroth rearrangement of **2** (method A) and **3** (method B) upon prolonged heating in excess of hydrazine hydrate in aqueous ethanol [32]. Structure **4** was confirmed by unambiguous synthesis between 4-chloro-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines **5** (method C) and hydrazine hydrate [30] (Scheme 1).



1,**2**,**3**,**4**,**5**	R	R_1
a	C_6H_5	4-F-C_6H_4
b	C_6H_5	3-Cl-4-F-C_6H_3
c	4-OCH_3-C_6H_4	4-F-C_6H_4
d	4-OCH_3-C_6H_4	3-Cl-4-F-C_6H_3
e	4-Cl-C_6H_4	4-F-C_6H_4
f	4-Cl-C_6H_4	3-Cl-4-F-C_6H_3

SCHEME 1 Reagent and conditions (i) $CH(OC_2H_5)_3$, reflux 3–4 h.; (ii) equivalent $NH_2NH_2 \cdot H_2O$, EtOH, 40–50 min.; (iii) $NH_2NH_2 \cdot H_2O$ in excess, EtOH, 60–65°C, 12–13 h.; (iv) $NH_2NH_2 \cdot H_2O$ in excess, EtOH, reflux, 13–14 h.; (v) $NH_2NH_2 \cdot H_2O$, reflux, 3–4 h.



3 **6**

3, 6	R	R_1
a	C_6H_5	4-F-C_6H_4
b	C_6H_5	3-Cl-4-F-C_6H_3
c	4-OCH_3-C_6H_4	4-F-C_6H_4
d	4-OCH_3-C_6H_4	3-Cl-4-F-C_6H_3
e	4-Cl-C_6H_4	4-F-C_6H_4
f	4-Cl-C_6H_4	3-Cl-4-F-C_6H_3

SCHEME 2 Reagent and conditions (vi) $CH(OC_2H_5)_3$ or HCOOH, Reflux, 5–6 h.

The cyclocondensation of 3-amino-4-imino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines **3** with one-carbon donor moiety, such as triethyl orthoformate or formic acid, under reflux conditions yielded 7,9-disubstituted-7*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **6** (method D) (Scheme 2).

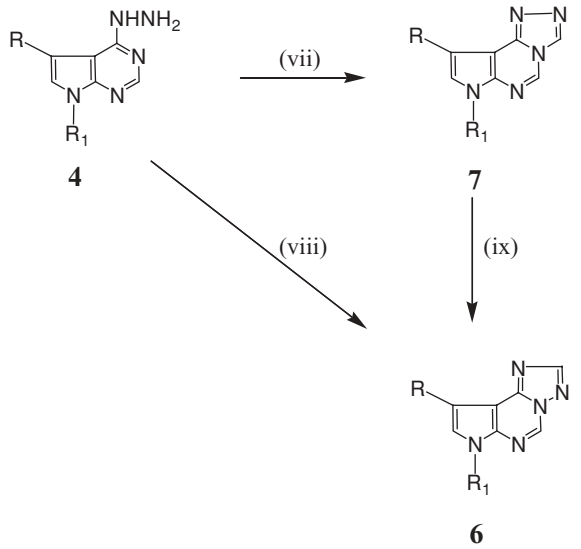
The identical pyrrolotriazolopyrimidines **6** were synthesized by another route (method E) in which 4-hydrazino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines **4** were condensed with formic acid under boiling condition. The attempted reaction was believed to initiate with the formation of **7** that was rearranged to more stable isomers **6** in the presence of acidic reagent under thermal conditions. The reaction between **4** and triethyl orthoformate at 70°C provided 7,9-disubstituted-7*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **7**. The [4,3-*c*] isomers **7** on heating with formic acid were isomerized to thermodynamically more stable unsymmetrical [1,5-*c*] isomers **6** via the Dimroth rearrangement (method F) [19,20] (Scheme 3).

The UV (methylene chloride) spectra of 1,4-disubstituted-*N*-ethoxymethylene-2-amino-3-cyanopyrroles **2** show two prominent λ_{max} near 297 and 249 nm. The IR (potassium bromide) spectra of 1,4-disubstituted-*N*-ethoxymethylene-2-amino-3-cyanopyrroles **2** exhibit a sharp absorption near 2210 cm^{-1} due to a cyano group. ^1H NMR ($CDCl_3$) spectra of **2** display a triplet at δ 1.20–1.46 and a quartet at δ 4.20–4.35 integrating for three and two protons, respectively, because of ethyl protons of ethoxymethylene group. A multiplet responsible for aromatic protons appeared near δ 7.10–7.86, the proton resonance of the pyrrole ring is observed as a singlet at δ 6.85–6.91, and an aliphatic –CH proton of ethoxymethylene functionality appears in the downfield region at δ 8.45–8.85 as a singlet.

The UV (methylene chloride) spectra of 3-amino-4-imino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines **3** show two λ_{max} near 293 and 246 nm, respectively. The IR (potassium bromide) spectra of 3-amino-4-imino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines **3** exhibited stretching vibrations in the region of 3440–3140 cm^{-1} together with a bending vibration at 1648–1632 cm^{-1} because of imino and amino functionalities. A broad singlet at δ 5.41–5.48 and a multiplet at δ 7.20–8.10 were assigned to amino and aromatic protons, respectively, while δ 8.34–8.59 was attributed to an imino proton in the ^1H NMR (DMSO-d_6) spectra of **3**.

The UV (methylne chloride) spectra of 7,9-disubstituted-7*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **6** displayed two λ_{max} at 247 and 257–293 nm. The IR (potassium bromide) spectra of **6** and **7** exhibited absorption bands in the region of 1628–1496 cm^{-1} for aromatic C=C, C=N stretching vibrations, whereas the resonance due to aromatic protons as a multiplet was obtained at δ 7.0–8.43 in the ^1H NMR (DMSO-d_6) spectra of **6** and **7**. The more deshilded triazole proton in the [1,5-*c*] isomers **6** present at position 2 appears as a singlet at δ 8.9–9.22, whereas the proton at position 3 in the [4,3-*c*] isomer **7** was found to appear at little downfield in the region of δ 9.39–9.49 in the form of a singlet [19–22].

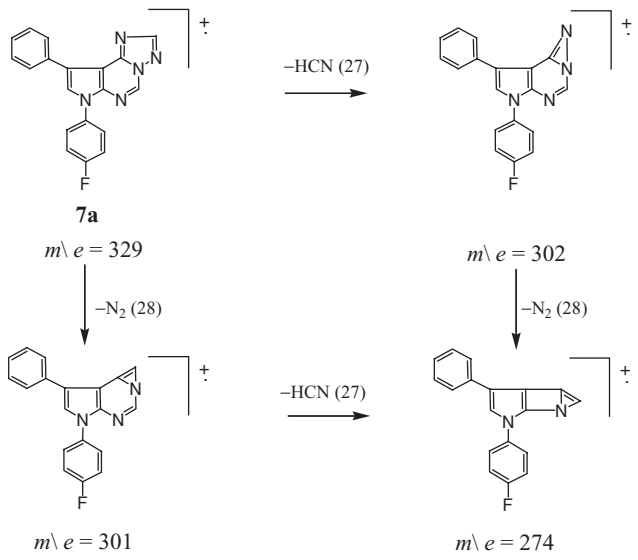
The mass fragmentation pattern of **7a** is depicted in Scheme 4, which is in agreement with the pattern of fused triazolopyrimidine [19,20] giving a molecular ion peak at 329. The fragments 301, 302, and 274 were obtained because of subsequent elimination of



4,6,7	R	R_1
a	C_6H_5	4-F-C_6H_4
b	C_6H_5	3-Cl-4-F-C_6H_3
c	4-OCH_3-C_6H_4	4-F-C_6H_4
d	4-OCH_3-C_6H_4	3-Cl-4-F-C_6H_3
e	4-Cl-C_6H_4	4-F-C_6H_4
f	4-Cl-C_6H_4	3-Cl-4-F-C_6H_3

SCHEME 3 Reagent and conditions (vii) $CH(OC_2H_5)_3$, 70°C, 1–1.5 h.; (viii) HCOOH, Reflux, 6–8 h.; (ix) HCOOH, reflux, 3–4 h.

nitrogen and hydrogen cyanide or hydrogen cyanide and nitrogen molecules.



SCHEME 4 Mass fragmentation pattern of **7a**.

EXPERIMENTAL

Melting points were determined by electrothermal method in an open capillary tube and are uncorrected. The UV (methylene chloride) spectra were taken on Backman Du-64 spectrophotometer. The IR spectra were recorded in cm^{-1} for KBr pellets on Buck-500 spectrophotometer. The ^1H NMR spectra were recorded on Varian 300 MHz spectrophotometer in deuteriochloroform or deuteriodimethyl sulfoxide using TMS as an internal standard, and the chemical shifts are expressed in δ ppm. MS spectra were recorded on LKB 9000 mass spectrophotometer. The purity of the compounds was routinely checked by TLC using silica gel G, and spots were exposed in iodine vapor.

General Procedure for the Synthesis of 1,4-Disubstituted-N-ethoxymethylene-2-amino-3-cyanopyrroles **2a–f**

1,4-disubstituted-2-amino-3-cyanopyrrole (**1**, 0.01 mol) was refluxed with triethyl orthoformate (10 mL) for 3.0–4.0 h. After completion of the reaction, excess of triethyl orthoformate was recovered in

vacuo. The solid thus obtained was treated with cold water, filtered, dried, and crystallized from ethanol to give **2a–f**.

*1-(4-Fluorophenyl)-N-ethoxymethylene-2-amino-3-cyano-4-phenylpyrrole (**2a**).* Yield, 68%; mp 109–110°C; IR (KBr): $\nu = 2210$ (CN), 1616, 1504 cm^{-1} (C=C, C=N ring); ^1H NMR ($CDCl_3$): $\delta = 1.34$ (t, $J = 6.72$ Hz 3H, $OCH_2\underline{CH_3}$), 4.27 (q, $J = 7.02$ Hz 2H, $O\underline{CH_2}CH_3$), 6.85 (s, 1H, H at C_5), 7.18–7.68 (m, 9H, Ar-H), 8.53 (s, 1H, $N{=}C\underline{H}OC_2H_5$); Anal. calcd for $C_{20}H_{16}FN_3O$ (333.36): C, 72.06; H, 4.84; N, 12.61; found: C, 72.26; H, 4.98; N, 12.67.

*1-(3-Chloro-4-fluorophenyl)-N-ethoxymethylene-2-amino-3-cyano-4-phenylpyrrole (**2b**).* Yield, 70%, mp 127–128°C; IR (KBr): $\nu = 2220$ (CN), 1612, 1504 cm^{-1} (C=C, C=N ring); ^1H NMR ($CDCl_3$): $\delta = 1.28$ (t, $J = 6.78$ Hz 3H, $OCH_2\underline{CH_3}$), 4.27 (q, $J = 6.9$ Hz 2H, $O\underline{CH_2}CH_3$), 6.87 (s, 1H, H at C_5), 7.21–7.76 (m, 8H, Ar-H), 8.45 (s, 1H, $N{=}C\underline{H}OC_2H_5$); Anal. calcd for $C_{20}H_{15}ClFN_3O$ (367.80): C, 65.31; H, 4.11; N, 11.42; found: C, 65.38; H, 4.32; N 11.27.

*1-(4-Fluorophenyl)-N-ethoxymethylene-2-amino-3-cyano-4-(4-methoxyphenyl)pyrrole (**2c**).* Yield, 63%, mp 156–158°C; IR (KBr): $\nu = 2210$ (CN), 1624, 1500 cm^{-1} (C=C, C=N ring); ^1H NMR ($CDCl_3$): $\delta = 1.34$ (t, $J = 6.84$ Hz 3H, $OCH_2\underline{CH_3}$), 3.90 (s, 3H, OCH_3), 4.27 (q, $J = 6.78$ Hz 2H, $O\underline{CH_2}CH_3$), 6.89 (s, 1H, H at C_5), 7.22–7.74 (m, 8H, Ar-H), 8.48 (s, 1H, $N{=}C\underline{H}OC_2H_5$); Anal. calcd for $C_{21}H_{18}FN_3O_2$ (363.38): C, 69.41; H, 4.99; N 11.56; found: C, 69.63; H, 5.10; N, 11.39.

*1-(3-Chlorophenyl-4-fluorophenyl)-N-ethoxymethylene-2-amino-3-cyano-4-(4-methoxyphenyl)-pyrrole (**2d**).* Yield, 75%, mp 165–167°C; IR (KBr): $\nu = 2210$ (CN), 1620, 1508 cm^{-1} (C=C, C=N ring); ^1H NMR ($CDCl_3$): $\delta = 1.3$ (t, $J = 6.84$ Hz 3H, $OCH_2\underline{CH_3}$), 3.92 (s, 3H, OCH_3), 4.27 (q, $J = 7.14$ Hz 2H, $O\underline{CH_2}CH_3$), 6.88 (s, 1H, H at C_5), 7.12–7.68 (m, 7H, Ar-H), 8.52 (s, 1H, $N{=}C\underline{H}OC_2H_5$); Anal. calcd for $C_{21}H_{17}ClFN_3O_2$ (397.83): C, 63.40; H, 4.31; N, 10.56; found: C, 63.62; H, 4.11; N, 10.48.

*1-(4-Fluorophenyl)-N-ethoxymethylene-2-amino-3-cyano-4-(4-chlorophenyl)pyrrole (**2e**).* Yield, 80%, mp 193–195°C; IR (KBr): $\nu = 2220$ (CN), 1608, 1512 cm^{-1} (C=C, C=N ring); ^1H NMR ($CDCl_3$): $\delta = 1.32$ (t, $J = 6.78$ Hz 3H, $OCH_2\underline{CH_3}$), 4.27 (q, $J = 7$ Hz 2H, $O\underline{CH_2}CH_3$), 6.85 (s, 1H, H at C_5), 7.24–7.82 (m, 8H, Ar-H), 8.48 (s, 1H, $N{=}C\underline{H}OC_2H_5$); Anal. calcd for $C_{20}H_{15}ClFN_3O$ (367.80): C, 65.31; H, 4.11; N, 11.42; found: C, 65.26; H, 4.08; N, 11.69.

*1-(3-Chloro-4-fluorophenyl)-N-ethoxymethylene-2-amino-3-cyano-4-(4-chlorophenyl)pyrrole (**2f**).* Yield, 85%, mp 181–183°C; IR (KBr): $\nu = 2210$ (CN), 1620, 1508 cm^{-1} (C=C, C=N ring); ^1H NMR ($CDCl_3$): $\delta = 1.28$ (t, $J = 6.82$ Hz 3H, $OCH_2\underline{CH_3}$), 4.27 (q, $J = 6.98$ Hz 2H, $O\underline{CH_2}CH_3$), 6.89 (s, 1H, H at C_5), 7.22–7.73 (m, 7H, Ar-H), 8.56 (s, 1H, $N{=}C\underline{H}OC_2H_5$); Anal. calcd for $C_{20}H_{14}Cl_2FN_3O$ (402.25): C, 59.72; H, 3.51; N, 10.45; found: C, 59.58; H, 3.44; N, 10.70.

General Procedure for the Synthesis of 3-Amino-4-imino-5,7-disubstituted-7H-pyrrolo[2,3-d]pyrimidines **3a–f**

1,4-Disubstituted-*N*-ethoxymethylene-2-amino-3-cyanopyrrole (**2**, 0.01 mol) was treated with hydrazine hydrate (99%, 0.01 mol) in absolute methanol (25 mL) under gentle reflux condition for 40–50 min. The mixture was allowed to cool; precipitates thus formed were filtered, dried, and crystallized from benzene.

3-Amino-4-imino-5-phenyl-7-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine **3a**. Yield, 58%, mp 119–120°C; IR (KBr): $\nu = 3380$, 3270, 3170 (NH), 1620, 1508 cm^{-1} (C=C, C=N ring); ^1H NMR (DMSO-d_6): $\delta = 5.45$ (br s, 2H, NH_2, exchangeable), 7.20–7.89 (m, 11H, Ar-H), 8.32 (br s, 1H, NH, exchangeable); MS: $m/z = 319$ (M^+). Anal. calcd for $C_{18}H_{14}FN_5$ (319.34): C, 67.70; H, 4.42; N, 21.93; found: C, 67.58; H, 4.62; N, 21.70.

3-Amino-4-imino-5-phenyl-7-(3-chloro-4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine **3b**. Yield, 70%, mp 158–160°C; IR (KBr): $\nu = 3400$, 3280, 3190 (NH), 1620, 1508 cm^{-1} (C=C, C=N ring); ^1H NMR (DMSO-d_6): $\delta = 5.43$ (br s, 2H, NH_2, exchangeable), 7.18–7.82 (m, 10H, Ar-H), 8.39 (br s, 1H, NH, exchangeable); MS: $m/z = 353$ (M^+). Anal. calcd for $C_{18}H_{13}ClFN_5$ (353.78): C, 61.11; H, 3.70; N, 19.80; found: C, 60.95; H, 3.68; N, 19.75.

3-Amino-4-imino-5-(4-methoxyphenyl)-7-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine **3c**. Yield, 58%, mp 167–169°C; IR (KBr): $\nu = 3370$, 3300, 3170 (NH), 1608, 1512 cm^{-1} (C=C, C=N ring); ^1H NMR (DMSO-d_6): $\delta = 3.91$ (s, 3H, OCH_3), 5.47 (br s, 2H, NH_2, exchangeable), 7.15–7.77 (m, 10H, Ar-H), 8.34 (br s, 1H, NH, exchangeable); MS: $m/z = 349$ (M^+). Anal. calcd for $C_{19}H_{16}FN_5O$ (349.36): C, 65.32; H, 4.62; N, 20.05; found: C, 65.49; H, 4.47; N, 20.17.

3-Amino-4-imino-5-(4-methoxyphenyl)-7-(3-chloro-4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine **3d**. Yield, 77%, mp 192–194°C; IR (KBr): $\nu = 3360$, 3290,

3150 (NH), 1612, 1500 cm^{-1} (C=C, C=N ring); ^1H NMR (DMSO-d_6): $\delta = 3.93$ (s, 3H, OCH_3), 5.42 (br s, 2H, NH_2, exchangeable), 7.23–7.78 (m, 9H, Ar-H), 8.41 (br s, 1H, NH, exchangeable); MS: $m/z = 383$ (M^+). Anal. calcd for $C_{19}H_{15}ClFN_5O$ (383.81): C, 59.46; H, 3.94; N, 18.25; found: C, 59.51; H, 4.21; N, 18.18.

3-Amino-4-imino-5-(4-chlorophenyl)-7-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine **3e**. Yield, 80%, mp 200–202°C; IR (KBr): $\nu = 3390$, 3270, 3160 (NH), 1620, 1508 cm^{-1} (C=C, C=N ring); ^1H NMR (DMSO-d_6): $\delta = 5.46$ (br s, 2H, NH_2, exchangeable), 7.20–7.89 (m, 10H, Ar-H), 8.30 (br s, 1H, NH, exchangeable); MS: $m/z = 353$ (M^+). Anal. calcd for $C_{18}H_{13}ClFN_5$ (353.78): C, 61.11; H, 3.70; N, 19.80; found: C, 61.01; H, 3.56; N, 19.71.

3-Amino-4-imino-5-(4-chlorophenyl)-7-(3-chloro-4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine **3f**. Yield, 85%, mp 233–235°C; IR (KBr): $\nu = 3360$, 3270, 3150 (NH), 1624, 1512 cm^{-1} (C=C, C=N ring); ^1H NMR (DMSO-d_6): $\delta = 5.42$ (br s, 2H, NH_2, exchangeable) 7.22–7.76 (m, 9H, Ar-H), 8.44 (br s, 1H, NH, exchangeable); MS: $m/z = 388$ (M^+). Anal. calcd for $C_{18}H_{12}Cl_2FN_5$ (388.23): C, 55.69; H, 3.12; N, 18.04; found: C, 55.80; H, 3.16; N, 17.88.

General Procedure for the Preparation of 4-Hydrazino-5,7-disubstituted-7H-pyrrolo[2,3-d]pyrimidines **4a–f**

Method A: Reaction of **2** *with Excess of Hydrazine Hydrate.* To a stirring solution of 1,4-disubstituted-*N*-ethoxymethylene-2-amino-3-cyanopyrrole (**2**, 1.0 g) in absolute ethanol (25 mL), hydrazine hydrate (99%, 5 mL) was added. The solution was stirred at 60–65°C for 12–13 h. The precipitated solid was filtered in vacuo, dried, and crystallized to obtain **4a–f**. The physical and analytical data are represented in Table 1.

Method B: Reaction of **3** *with Excess of Hydrazine Hydrate.* A mixture of 3-amino-4-imino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidine (**3**, 1.0 g), absolute ethanol (25 mL), and hydrazine hydrate (99%, 5 mL) was refluxed for 12–14 h. The precipitated solid was filtered, dried, and crystallized to obtain **4a–f** (Table 1). The spectral data of these compounds were identical with those of **4** obtained by method A or C [30].

Method C. 4-Chloro-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidine [30] (**5**, 0.01 mol) was reacted with hydrazine hydrate (99%, 15 mL) in boiling ethanol (30 mL) for 3–4 h. The cooled reaction mixture was then added onto crushed ice and neutralized with aqueous acetic acid (pH 7); the solid thus obtained was filtered, washed with water, and crystallized to get **4a–f** (Table 1).

General Procedure for the Synthesis of 7,9-Disubstituted-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]-pyrimidines **6a–f**

Method D. 3-Amino-4-imino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidine (**3**, 0.01 mol) was heated with boiling formic acid (15 mL) for 5–6 h.

TABLE 1 Physical and Analytical Data of 4-Hydrazino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines **4a–f**

Compound No.	Yield[a] (%) Method			mp (°C)\Solvent for Crystallization[c]	Molecular Formula (Molecular Wt.)	Analysis Calcd.\(Found)		
	A	*B*	*C*[b]			*C*	*H*	*N*
4a	65	55	69	198–200	$C_{18}H_{14}FN_5$	67.70	4.42	21.93
				G	(319.34)	67.64	4.33	21.74
4b	68	63	78	240–242	$C_{18}H_{13}ClFN_5$	61.11	3.70	19.80
				H	(353.78)	60.97	3.85	19.96
4c	58	55	63	172–173	$C_{19}H_{16}FN_5O$	65.32	4.62	20.05
				H	(349.36)	65.09	4.48	19.85
4d	66	60	72	202–204	$C_{19}H_{15}ClFN_5O$	59.46	3.94	18.25
				H	(383.80)	59.58	4.12	18.40
4e	70	64	79	210–212	$C_{18}H_{13}ClFN_5$	61.11	3.70	19.80
				G	(353.78)	61.33	3.82	19.99
4f	68	62	77	243–245	$C_{18}H_{12}ClFN_5$	55.69	3.12	18.04
				H	(388.23)	55.82	2.96	17.86

[a]Overall yield for methods A and B from **2** and for method C from **5**.
[b]Method reported in [30].
[c]G = chloroform; H = *N*,*N*-dimethyl formamide.

TABLE 2 Physical and Analytical Data of 7,9-Disubstituted-7*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **6a–f**

Compound No.	Yield[a] (%) Method			mp (°C)\Solvent for Crystallization[b]	Molecular Formula (Molecular Wt.)	Analysis Calcd\(Found)		
	D	E	F			C	H	N
6a	65	55	68	207–209	$C_{19}H_{12}FN_5$	69.29	3.67	21.27
				J	(329.33)	69.34	3.52	21.39
6b	68	60	66	249–250	$C_{19}H_{11}ClFN_5$	62.73	3.05	19.25
				H	(363.78)	62.92	2.87	19.44
6c	63	61	69	197–199	$C_{20}H_{14}FN_5O$	66.85	3.93	19.49
				H	(359.36)	67.09	4.05	19.57
6d	60	58	64	219–221	$C_{20}H_{13}ClFN_5O$	61.00	3.33	17.78
				H	(393.80)	61.22	3.57	17.66
6e	68	65	70	230–232	$C_{19}H_{11}ClFN_5$	62.73	3.05	19.25
				J	(363.78)	61.61	3.10	19.48
6f	66	63	70	259–261	$C_{19}H_{10}Cl_2FN_5$	57.31	2.53	17.59
				H	(398.22)	57.41	2.48	17.67

[a]Overall yields for method D from **3**, for method E from **4**, and for method F overall yields from **7**.
[b]J = dioxane; H = *N*,*N*-dimethyl formamide.

The mixture was then cooled, poured onto crushed ice, and neutralized with sodium hydroxide solution (1N). The solid obtained was filtered, washed with water, dried, and crystallized in order to get **6a–f**. The physical and analytical data for **6a–h** are given in Table 2.

Method E. A mixture of 4-hydrazino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidine (**4**, 0.01 mol) and formic acid (20 mL) was refluxed for 6–8 h. The resulting mixture was cooled, poured onto crushed ice, and neutralized with sodium hydroxide solution (1N). The obtained solid was filtered, washed with water, dried, and crystallized to get the title compounds (Table 2).

7-(4-Fluorophenyl)-9-phenyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine **6a**. IR (KBr): ν = 3090, 2860 (CH), 1624, 1512 cm^{-1} (C=C, C=N ring); ^{1}H NMR (DMSO-d_6): δ = 7.22–8.22 (m, 11H, Ar-H), 9.05 (s, 1H, H at C_2); MS: m/z = 329 (M^+).

7-(3-Chloro-4-fluorophenyl)-9-phenyl-7H-pyrrolo-[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine **6b**. IR (KBr): ν = 3060, 2840 (CH), 1612, 1508 cm^{-1} (C=C, C=N ring); ^{1}H NMR (DMSO-d_6): δ = 7.10–8.20 (m, 10H, Ar-H), 9.12 (s, 1H, H at C_2); MS: m/z = 363 (M^+).

7-(4-Fluorophenyl)-9-(4-methoxyphenyl)-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine **6c**. IR (KBr): ν = 3070, 2880 (CH), 1616, 1508 cm^{-1} (C=C, C=N ring); ^{1}H NMR (DMSO-d_6): δ = 3.89 (s, 3H, OCH_3), 7.0–8.29 (m, 10H, Ar-H), 9.12 (s, 1H, H at C_2); MS: m/z = 359 (M^+).

7-(3-Chloro-4-fluorophenyl)-9-(4-methoxyphenyl)-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine **6d**. IR (KBr): ν = 3070, 2880 (CH), 1616, 1508 cm^{-1} (C=C, C=N ring); ^{1}H NMR (DMSO-d_6): δ = 3.89 (s, 3H,OCH_3), 7.0–8.29 (m, 9H, Ar-H), 9.12 (s, 1H, H at C_2); MS: m/z = 393 (M^+).

7-(4-Fluorophenyl)-9-(4-chlorophenyl)-7H-pyrrolo-[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine **6e**. IR (KBr): ν = 3080, 2860 (CH), 1624, 1512 cm^{-1} (C=C, C=N ring); ^{1}H NMR (DMSO-d_6): δ = 7.18–8.26 (m, 10H, Ar-H), 9.18 (s, 1H, H at C_2); MS: m/z = 363 (M^+).

7-(3-Chlorophenyl-4-fluorophenyl)-9-(4-chlorophenyl)-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine **6f**. IR (KBr): ν = 3090, 2880 (CH), 1620, 1512 cm^{-1} (C=C, C=N ring); ^{1}H NMR (DMSO-d_6): δ = 7.18–8.26 (m, 9H, Ar-H), 9.20 (s, 1H, H at C_2); MS: m/z = 398 (M^+).

General Procedure for the Synthesis of 7,9-Disubstituted-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidines **7a–f**

A mixture of 4-hydrazino-5,7-disubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidine (**4**, 0.01 mol) and triethyl orthoformate (20 mL) was stirred at 70°C for 1–1.5 h. The excess of reagent was distilled under pressure, and to the cold reaction mixture *n*-hexane (10 mL) was added. Thus obtained solid was filtered, dried, and crystallized from a mixture of *N*,*N*-dimethylformamide: ethanol (4:6 v/v) to get the title compounds **7a–f**.

7-(4-Fluorophenyl)-9-phenyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine **7a**. Yield, 62%, mp 216–218°C; IR (KBr): $\nu = 3090$, 2950 (CH), 1620, 1512 cm^{-1} (C=C, C=N ring); ^1H NMR (DMSO-d_6): $\delta = 7.22–8.22$ (m, 11H, Ar-H), 9.46 (s, 1H, H at C_2); Anal. calcd for $C_{19}H_{12}FN_5$ (329.33): C, 67.29; H, 3.67; N, 21.27; found: C, 67.45; H, 3.56; N, 21.08.

7-(3-Chloro-4-fluorophenyl)-9-phenyl-7H-pyrrolo-[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine **7b**. Yield, 67%, mp 258–260°C; IR (KBr): $\nu = 3070$, 2870 (CH), 1612, 1504 cm^{-1} (C=C, C=N ring); ^1H NMR (DMSO-d_6): $\delta = 7.00–8.16$ (m, 10H, Ar-H), 9.45 (s, 1H, H at C_2); Anal. calcd or $C_{19}H_{11}ClFN_5$ (363.78): C, 62.73; H, 3.05; N, 19.25; found: C, 62.56; H, 3.19; N, 19.38.

7-(4-Fluorophenyl)-9-(4-methoxyphenyl)-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine **7c**. Yield, 50%, mp 203–205°C; IR (KBr): $\nu = 3090$, 2930 (CH), 1620, 1504 cm^{-1} (C=C, C=N ring); ^1H NMR (DMSO-d_6): $\delta = 3.90$ (s, 3H, OCH_3), 7.12–8.26 (m, 10H, Ar-H), 9.43 (s, 1H, H at C_2); Anal. calcd for $C_{20}H_{14}FN_5O$ (359.36): C, 66.85; H, 3.93; N, 19.49; found: C, 66.74; H, 4.12; N, 19.17.

7-(3-Chloro-4-fluorophenyl)-9-(4-methoxyphenyl)-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine **7d**. Yield, 65%, mp 256–258°C; IR (KBr): $\nu = 3070$, 2880 (CH), 1608, 1500 cm^{-1} (C=C, C=N ring); ^1H NMR (DMSO-d_6): $\delta = 3.89$ (s, 3H, OCH_3), 7.11–8.26 (m, 9H, Ar-H), 9.45 (s, 1H, H at C_2); Anal. calcd for $C_{20}H_{13}ClFN_5O$ (393.80): C, 61.00; H, 3.33; N, 17.78; found: C, 59.80; H, 3.16; N, 17.88.

7-(4-Fluorophenyl)-9-(4-chlorophenyl)-7H-pyrrolo-[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine **7e**. Yield, 60%, mp 250–252°C; IR (KBr): $\nu = 3060$, 2940 (CH), 1620, 1512 cm^{-1} (C=C, C=N ring); ^1H NMR (DMSO-d_6): $\delta = 7.14–8.08$ (m, 10H, Ar-H), 9.43 (s, 1H, H at C_2); Anal. calcd for $C_{19}H_{11}ClFN_5$ (363.78): C, 62.73; H, 3.05; N, 19.25; found: C, 62.80; H, 3.16; N, 19.30.

7-(3-Chlorophenyl-4-fluorophenyl)-9-(4-chlorophenyl)-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine **7f**. Yield, 68%, mp 290–292°C; IR (KBr): $\nu = 3090$, 2880 (CH), 1612, 1516 cm^{-1} (C=C, C=N ring); ^1H NMR (DMSO-d_6): $\delta = 7.20–8.24$ (m, 9H, Ar-H), 9.45 (s, 1H, H at C_2); Anal. calcd for $C_{19}H_{10}Cl_2FN_5$ (398.22): C, 57.31; H, 2.53; N, 17.59; found: C, 57.14; H, 2.47; N, 17.81.

General Procedure for Conversion of **7a–f** *to* **6a–f**

Method F. 7,9-Disubstituted-7*H*-pyrrolo[3,2-*e*]-[1,2,4]triazolo[4,3-*c*]pyrimidine (**7**, 1.0 g) and formic acid (10 mL) was heated under reflux condition for 3–4 h. The reaction mixture was allowed to cool, poured onto crushed ice, and the obtained solid was filtered, washed with water, dried, and crystallized to get **6a–f**. The IR and ^1H NMR data were superimposed on those of **6** obtained from either method D or E as described above.

ACKNOWLEDGMENTS

We thank the Regional Sophisticated Instrumentation Center, Central Drug Research Institute, Lucknow and Chandigarh, India for ^1H NMR and mass spectral analysis and to the Director, Loyola Center for R&D, St. Xavier's College, Ahmedabad, India for providing the facility to carry out this work.

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