**Abstract** : Liquid–liquid phase-transfer conditions were employed in an improved synthesis of 7,9-substituted 7H-pyrrolo[3,2-e]tetrazolo[1,5-c]pyrimidines and 5,7-substituted 4-amino-7H-pyrrolo[2,3-d]pyrimidines. The latter were obtained either by reductive ring cleavage of the former, or by one-pot synthesis from 5,7-substituted 4-chloro-7H-pyrrolo[2,3-d]pyrimidines.

**Key words**: pyrrolotetrazolopyrimidines, reductive ring cleavage, phase-transfer catalyst, Aliquat 336, 18-crown-6

The investigation of fused tetrazolopyrimidines as a potent antagonist has shown that they have a wide range of biological activities such as anticancer, antibacterial, anti-ulcer, anti-inflammatory, antihypertensive, antimalarial and antibacterial. Moreover, fused tetrazolopyrimidines are capable of undergoing reductive ring cleavage to form fused aminopyrimidines, which are known for their valuable pharmacological properties and as intermediates in the construction of a variety of triheterocycles. Phase-transfer catalysis (PTC) has been established as a widespread synthetic technique. Reactions using phase-transfer catalysis can be readily scaled up and have been used particularly for clean and efficient processes involving high yields, operational simplicity, mild conditions, low cost, safety, and environmental profit. A literature survey reveals that phase-transfer conditions have been least exploited for the synthesis and reduction of fused tetrazoles. These observations and pharmacological interest have led us to improve the synthesis of 7,9-substituted 7H-pyrrolo[3,2-e]tetrazolo[1,5-c]pyrimidines 2 and their transformation to 5,7-substituted 4-amino-7H-pyrrolo[2,3-d]pyrimidines 3 via reductive ring cleavage under phase-transfer conditions. An efficient one-pot synthesis of 3 was also achieved for the first time to form 5,7-substituted 4-chloro-7H-pyrrolo[2,3-d]pyrimidines 1 via in situ generation of pyrrolotetrazolopyrimidines 2.

The chloro substituent present at C4 in the pyrrolo[2,3-d]pyrimidine ring system was found to be highly reactive towards nucleophilic substitution reactions with sodium azide and hydrazine hydrate. Our earlier publication exploited both reactions to synthesize pyrrolotetrazolopyrimidines 2. In one of the methods, 5,7-substituted 4-chloro-7H-pyrrolo[2,3-d]pyrimidines 1 were reacted with sodium azide in the presence of ammonium chloride; the in situ generation of ammonium azide facilitated the reaction in dimethyl sulfoxide at 90 °C. Recovery of dimethyl sulfoxide from the reaction mixture is the main problem associated with such reactions and the use of other solvents was unsuccessful in generating the products in quantitative yield. With a view to this problem, the synthesis was improved by using liquid–liquid phase-transfer conditions with toluene and water as solvents and Aliquat 336 (methyltrioctylammonium chloride) as the catalyst (Scheme 1). This improved synthetic protocol enhanced the reaction rates and the products were obtained in good yields.

**Scheme 1**

<table>
<thead>
<tr>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Yield (%)</th>
<th>Mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>Ph</td>
<td>4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>72</td>
</tr>
<tr>
<td>2b</td>
<td>Ph</td>
<td>3-Cl-4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>68</td>
</tr>
<tr>
<td>2c</td>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>65</td>
</tr>
<tr>
<td>2d</td>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3-Cl-4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>58</td>
</tr>
<tr>
<td>2e</td>
<td>4-CIC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>70</td>
</tr>
<tr>
<td>2f</td>
<td>4-CIC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3-Cl-4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>69</td>
</tr>
<tr>
<td>2g</td>
<td>4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4-CIC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>60</td>
</tr>
<tr>
<td>2h</td>
<td>4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>69</td>
</tr>
<tr>
<td>2i</td>
<td>4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3-Cl-4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>75</td>
</tr>
</tbody>
</table>
Azides and tetrazoles can be viewed as latent amino functionalities. While azides undergo chemoselective reduction using a novel system,\textsuperscript{7} lithium aluminum hydride,\textsuperscript{8} catalytic hydrogenation,\textsuperscript{9a–d} or various other reagents\textsuperscript{10} to yield amines, tetrazoles are highly resistant to reduction.\textsuperscript{11} Dave et al.\textsuperscript{6} successfully reduced pyrrolotetrazolopyrimidines 2 with zinc dust and acetic acid. With respect to the literature methods, the phase-transfer catalysis technique has the novelty of using sodium borohydride as an efficient reducing agent for tetrazoles. It affords pure products in high yields and offers the advantages of permitting a one-pot conversion of 4-chloropyrrolo[2,3-d]pyrimidines 1a–i into 4-aminopyrrolo[2,3-d]pyrimidines 3a–i with very simple operating conditions. Thus, in a modified procedure, two synthetic strategies based on phase-transfer catalysis were adopted for the reductive ring cleavage of pyrrolotetrazolopyrimidines 2 keeping sodium borohydride as the reducing agent. Under liquid–liquid phase-transfer conditions (Method I), Aliquat 336 was used as the catalyst and toluene and water were preferred as solvents whereas under solid–liquid phase-transfer conditions (Method II), 18-crown-6 was used as the catalyst along with powdered potassium hydroxide and acetonitrile as the solvent. The obtained compounds 3a–i are identical with those synthesized by condensation of 2-amino-3-cyanopyroles 4a–i and formamide\textsuperscript{12} (Scheme 2).

One-pot synthesis of 5,7-substituted 4-amino-7H-pyrrolo[2,3-d]pyrimidines 3a–i was achieved efficiently using liquid–liquid phase-transfer catalysis conditions using toluene and water as solvents and Aliquat 336 as the catalyst (Method III); however, a higher mol\% of catalyst was required. Firstly, 1 was reacted with sodium azide to form 2; on completion of the reaction, an equivalent quantity of powdered sodium borohydride was added portionwise to the same reaction mixture to give 3 (Scheme 3).

### Table 2 Synthesis of 5,7-Substituted 4-Amino-7H-pyrrolo[2,3-d]pyrimidines 3a–i

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Yield(^a) (%)</th>
<th>Method I</th>
<th>Method II</th>
<th>Method III</th>
<th>Found</th>
<th>Lit.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>4-FC(_6)H(_4)</td>
<td>54</td>
<td>56</td>
<td>50</td>
<td>183–185</td>
<td>183–185 \textsuperscript{12b}</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>3-Cl-4-FC(_6)H(_5)</td>
<td>66</td>
<td>67</td>
<td>62</td>
<td>238–240</td>
<td>238–240 \textsuperscript{12b}</td>
<td></td>
</tr>
<tr>
<td>4-MeOC(_6)H(_4)</td>
<td>4-FC(_6)H(_4)</td>
<td>58</td>
<td>58</td>
<td>54</td>
<td>153–154</td>
<td>154–156 \textsuperscript{12b}</td>
<td></td>
</tr>
<tr>
<td>4-MeOC(_6)H(_4)</td>
<td>3-Cl-4-FC(_6)H(_3)</td>
<td>75</td>
<td>76</td>
<td>71</td>
<td>220–222</td>
<td>222–223 \textsuperscript{12b}</td>
<td></td>
</tr>
<tr>
<td>4-ClC(_6)H(_4)</td>
<td>4-FC(_6)H(_4)</td>
<td>80</td>
<td>82</td>
<td>75</td>
<td>276–278</td>
<td>276–278 \textsuperscript{12b}</td>
<td></td>
</tr>
<tr>
<td>4-ClC(_6)H(_4)</td>
<td>3-Cl-4-FC(_6)H(_3)</td>
<td>69</td>
<td>69</td>
<td>65</td>
<td>308–310</td>
<td>309–310 \textsuperscript{12b}</td>
<td></td>
</tr>
<tr>
<td>4-FC(_6)H(_4)</td>
<td>4-ClC(_6)H(_4)</td>
<td>58</td>
<td>58</td>
<td>52</td>
<td>275–277</td>
<td>276–278 \textsuperscript{12b}</td>
<td></td>
</tr>
<tr>
<td>4-FC(_6)H(_4)</td>
<td>4-FC(_6)H(_4)</td>
<td>61</td>
<td>65</td>
<td>54</td>
<td>163–165</td>
<td>165–166 \textsuperscript{12b}</td>
<td></td>
</tr>
<tr>
<td>4-FC(_6)H(_4)</td>
<td>3-Cl-4-FC(_6)H(_3)</td>
<td>67</td>
<td>70</td>
<td>63</td>
<td>241–243</td>
<td>243–245 \textsuperscript{12b}</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Overall yields for Method I and Method II from compound 2 and for Method III from compound 1.
In summary, we have described a convenient and practical synthesis of pyrrolothetrazolo[1,5-c]pyrimidines and their reductive ring cleavage using various phase-transfer conditions. We have also described, for the first time, a one-pot synthesis of 4-amino-7H-pyrrolo[2,3-d]pyrimidines from 4-chloro-7H-pyrrolo[2,3-d]pyrimidines using liquid–liquid phase-transfer catalysis without the need to work up every step. The operational simplicity of this synthetic route will be helpful to elaborate the chemistry and bioactivity of fused tetrazoles and aminopyrimidines.

Melting points were determined by electrothermal method in open capillary tube and are uncorrected. The IR spectra were recorded KBr pellets on a Buck-500 spectrophotometer. The 1H NMR spectra were recorded on a Bruker 300 MHz spectrometer in CDCl₃ or DMSO-d₆, using TMS as internal standard. MS spectra were recorded on a JEOL SX-102 mass spectrometer under electron-impact (EI) ionization. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar Vario EL III microanalyzer. The purity of the compounds was routinely checked by TLC using silica gel G and spots were exposed to iodine vapor.

Compounds 1a–i were obtained according to procedures published in the literature. All the other starting materials were obtained from commercial suppliers and were used without further purification.

7.9-Substituted 7H-Pyrrolo[3,2-e]tetrazolo[1,5-c]pyrimidines 2a–i: General Procedure
To a well-stirred soln of 5,7-substituted 4-chloro-7H-pyrrolo[2,3-d]pyrimidine 1 (5 mmol) and Aliquat 336 (0.202 g, 0.5 mmol) in toluene (25 mL) was added NaCN (0.390 g, 6 mmol) in H₂O (5 mL). The mixture was stirred under reflux for 1–1.5 h. The progress of the reaction was monitored by TLC. On completion, the two phases were separated. The aqueous phase was extracted with toluene (15 mL) and the combined organic layers were washed with H₂O (10 × 2 mL) and dried (anhyd Na₂SO₄). The solvent was recovered in vacuo and the oily residue obtained after distillation was treated with chilled MeOH. The solid thus obtained was filtered off, dried, and crystallized (DMF–EtOH, 6:4) (Table 1).

7-(4-Fluorophenyl)-9-phenyl-7H-pyrrolo[3,2-e]tetrazolo[1,5-c]pyrimidine (2a)³
IR (KBr): 1604, 1516 cm⁻¹ (C=C, C=N ring).
1H NMR (CDCl₃): 1.2–7.8 (m, 8 H, ArH), 7.2–8.9 (m, 9 H, ArH), 8.42 (s, 1 H, H5).
MS: m/z = 352 (M⁺).
Found: C, 65.66; H, 3.27; N, 25.19.

7-(3-Chloro-4-fluorophenyl)-9-phenyl-7H-pyrrolo[3,2-e]tetrazolo[1,5-c]pyrimidine (2b)³
IR (KBr): 1604, 1492 cm⁻¹ (C=C, C=N ring).
1H NMR (DMSO-d₆): 1.2–7.8 (m, 9 H, ArH), 8.43 (s, 1 H, H5).
MS: m/z = 364 (M⁺).
Found: C, 59.54; H, 2.50; N, 22.86.

7-(4-Fluorophenyl)-9-(4-methoxyphenyl)-7H-pyrrolo[3,2-e]tetrazolo[1,5-c]pyrimidine (2c)³
IR (KBr): 1600, 1504 cm⁻¹ (C=C, C=N ring).
1H NMR (DMSO-d₆): 1.2–7.9 (m, 3 H, OCH₃), 7.3–8.1 (m, 9 H, ArH), 8.41 (s, 1 H, H5).
MS: m/z = 360 (M⁺).

7-(3-Chloro-4-fluorophenyl)-9-(4-methoxyphenyl)-7H-pyrrolo[3,2-e]tetrazolo[1,5-c]pyrimidine (2d)³
IR (KBr): 1608, 1504 cm⁻¹ (C=C, C=N ring).
1H NMR (DMSO-d₆): 1.2–7.9 (m, 3 H, OCH₃), 7.3–8.1 (m, 9 H, ArH), 8.41 (s, 1 H, H5).
MS: m/z = 364 (M⁺).

7-(3-Chloro-4-fluorophenyl)-9-(4-fluorophenyl)-7H-pyrrolo[3,2-e]tetrazolo[1,5-c]pyrimidine (2e)³
IR (KBr): 1612, 1496 cm⁻¹ (C=C, C=N ring).
1H NMR (DMSO-d₆): 1.2–7.8 (m, 9 H, ArH), 8.41 (s, 1 H, H5).
MS: m/z = 394 (M⁺).

7-(4-Chlorophenyl)-9-(4-fluorophenyl)-7H-pyrrolo[3,2-e]tetrazolo[1,5-c]pyrimidine (2f)³
IR (KBr): 1604, 1504 cm⁻¹ (C=C, C=N ring).
1H NMR (DMSO-d₆): 1.2–7.2–8.2 (m, 8 H, ArH), 8.40 (s, 1 H, H5).
MS: m/z = 399 (M⁺).

7-(4-Chlorophenyl)-9-(4-fluorophenyl)-7H-pyrrolo[3,2-e]tetrazolo[1,5-c]pyrimidine (2g)³
IR (KBr): 1604, 1496 cm⁻¹ (C=C, C=N ring).
1H NMR (CDCl₃): 1.2–7.2–8.1 (m, 9 H, ArH), 8.44 (s, 1 H, H5).
MS: m/z = 364 (M⁺).

7-(4-Chlorophenyl)-9-(4-fluorophenyl)-7H-pyrrolo[3,2-e]tetrazolo[1,5-c]pyrimidine (2h)³
IR (KBr): 1608, 1496 cm⁻¹ (C=C, C=N ring).
1H NMR (CDCl₃): 1.2–7.16–8.24 (m, 8 H, ArH), 8.41 (s, 1 H, H5).
MS: m/z = 364 (M⁺).

7-(4-Chlorophenyl)-9-(4-fluorophenyl)-7H-pyrrolo[3,2-e]tetrazolo[1,5-c]pyrimidine (2i)³
IR (KBr): 1608, 1504 cm⁻¹ (C=C, C=N ring).
1H NMR (CDCl₃): 1.2–7.16–8.24 (m, 8 H, ArH), 8.42 (s, 1 H, H5).
MS: m/z = 348 (M⁺).

7-(3-Chloro-4-fluorophenyl)-9-(4-fluorophenyl)-7H-pyrrolo[3,2-e]tetrazolo[1,5-c]pyrimidine (2j)³
IR (KBr): 1608, 1504 cm⁻¹ (C=C, C=N ring).
1H NMR (CDCl₃): 1.2–7.16–8.24 (m, 8 H, ArH), 8.42 (s, 1 H, H5).
MS: m/z = 382 (M⁺).

5.7-Substituted 4-Amino-7H-pyrrolo[2,3-d]pyrimidines 3a–i: General Procedures
Method 1: Liquid–Liquid Phase-Transfer Catalysis Conditions
A mixture of 7,9-substituted 7H-pyrrolo[2,3-d]pyrimidine 1 (2 mmol) and Aliquat 336 (0.202 g, 0.5 mmol), toluene (15 mL), and H₂O (5 mL) was stirred on in a flat-bottom flask at 60 °C. Powdered NaBH₄ (0.302 g, 8 mmol) was added to this mixture portionwise cautiously over a period of 30 min. The mixture was then
refluxed for 1 h. On completion (TLC) the aqueous phase was separated. The aqueous phase was taken with toluene (15 mL) and the combined organic layers were washed with H2O (10 × 2 mL) and dried (anhyd Na2SO4). The solvent was recovered in vacuo, the residue was treated with n-hexane and the solid thus formed was filtered off, washed with cold MeOH, dried, and crystallized (EtOH–CHCl3, 8:2) (Table 2).

Method II: Solid–Liquid Phase-Transfer Catalysis Conditions

A mixture of 7,9-substituted 7H-pyrrolo[2,3-d]pyrimidine 2 (2 mmol), MeCN (25 mL), 18-crown-6 (0.132 g, 0.5 mmol), powdered KOH (0.841 g, 15 mmol) and powdered NaBH4 (0.302 g, 8 mmol) was heated at 80 °C for 2–2.5 h, the supernatant reddish liquid was decanted from the solid residue and filter off. The solvent was recovered in vacuo and the resulting oily residue was treated with CHCl3, 8:2) (Table 2).

Solvent was recovered in vacuo and the resulting oily residue was washed with MeOH, dried, and crystallized (Table 2).

Method III: One-Pot Reaction

To the well-stirred soln of 5,7-substituted 4-chloro-7H-pyrrolo[2,3-d]pyrimidine 3a–i (5 mmol) and Aliquat 336 (0.323 g, 0.8 mmol) in toluene (25 mL) was added NaN3 (0.390 g, 6 mmol) in H2O (5 mL). The mixture was stirred under reflux for 1–1.5 h. The progress of the reaction was monitored with TLC, after the formation of pyrrolo[2,3,d]pyrimidine 2a–i powdered NaBH4 (0.302 g, 8 mmol) was added to the mixture in order to get the corresponding 4-amino-2,3-dipyrimidine 3a–i. The workup was effected according to Method I (Table 1).

4-Amino-7-(3-chloro-4-fluorophenyl)-5-phenyl-7H-pyrrolo[2,3-d]pyrimidine (3h)12b

IR (KBr): 3480, 3300 (NH), 1580, 1485 cm–1 (C=C, C=N ring). 1H NMR (CDCl3): = 5.30 (s, 2 H, NH2), 7.20–8.36 (m, 10 H, ArH).

Acknowledgment

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References


