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An efficient synthesis of (*E*)-(2-arylpyrazino[1,2-*a*]pyrimidine-4-ylidene)acetonitriles and cyanomethyl appended pyrimidines☆

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Abstract—A series of (*E*)-(2-arylpyrazino[1,2-*a*]pyrimidine-4-ylidene)acetonitriles **5a**–**j** and aryl/heteroaryl tethered pyrimidin-4-yl acetonitriles **6a**–**e** has been synthesized in excellent yields through base catalyzed ring transformation of suitably functionalized 2*H*-pyran-2-ones **3** using 2-aminopyrazine **4a** and arylamidinium salts **4b**, separately.

An extensive literature survey revealed that the chemistry of pyrazino[1,2-*a*]pyrimidine ring system **I**, first reported by Eble and co-workers[1] in 1968, is poorly developed. The chemistry of pyrazino[2,3-*d*]pyrimidines **II** has been widely explored while that of pyrazino-[1,2-*c*]pyrimidines **III** are still underdeveloped (see Fig. 1).

The therapeutic importance of pyrazino[1,2-*a*]pyrimidine ring system **I** in the treatment of migraine,[2] ulcers,[3] depression[1,4] and anorexia[5] has made it an indispensable class of compounds. These compounds also exhibit NF-kB549 inhibitory activity.[6]

Previously, these compounds have been synthesized[4–7] by heating a mixture of diethyl ethoxymethylenemalonate or diethyl phenylmalonate with 2-aminopyrazine **4a**. The other method[8] commonly used for the construction of pyrazino[1,2-*a*]pyrimidines is through the condensation of methyl 2-benzoylamino-3-dimethylaminopropanoate with 2-aminopyrazine. This method was further improved[9] by using methyl (*Z*)-[(benzyloxycarbonyl)amino]-3-dimethylaminopentanoate as a reagent for the condensation reaction with **4a**. Hexahydropyrazino[1,2-*a*]pyrimidine derivatives have also been synthesized[10] in six steps from 4-chlorophenylalanine, allyl chloroformate, 2,2-(diethoxymethyl)isopropylamine, 3-amino-2-benzyloxycarbonylaminopropionic acid and 2,4-dichlorophenylsulfonyl chloride followed by the cyclization of the intermediate formed. Some of the reduced compounds are very useful in the treatment of metabolic disorders[10] such as obesity and diabetes. These diverse pharmacological activities and the lack of efficient synthetic methodologies encourage us to develop a concise synthetic route to these compounds.

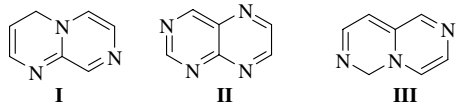

Figure 1. Pyrazino[1,2-*a*]pyrimidine **I**, pyrazino[2,3-*d*]pyrimidines **II** and pyrazino[1,2-*c*]pyrimidines **III**.

Pyrimidine rings are an integral part of various natural products.[11] They serve as building blocks for numerous pharmaceuticals and occupy a unique place in heterocyclic and medicinal chemistry. This class of compounds also has coordinating ability similar to pyridyl ligands in supramolecular metallo-gridlike architecture[12] and in novel inorganic–organic hybrid molecular wires.[13] In addition, they are pharmacologically active and display anticonvulsant,[14] anti-inflammatory,[15] antibacterial[16] and antimycotic[17] activities.

The pyrimidine ring, being electron deficient, resists electrophilic substitution and facilitates nucleophilic addition and substitution reactions.[18] A common approach for the construction of pyrimidine rings is through condensation of the 1,3-dicarbonyl compounds with

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amidines.[19] However, 2,4,6-triaryl pyrimidines are constructed stepwise.[19] The use of formamide or an ortho-ester in combination with ammonia[20] as a potential surrogate NCN reagent has been reported in the synthesis of pyrimidines. Tris(formylamino)methanes,[21] 2-amino-2-formylmalonaldehyde[22] and 3-methyl-5-nitro-3*H*-pyrimidin-4-one[23] have also been used as 1,3-dicarbonyl equivalents in pyrimidine synthesis. A simple cyclocondensation of amidine salts with chalcones also yields pyrimidines.[24]

Herein, we report an innovative and efficient synthesis of pyrazino[1,2-*a*]pyrimidines **5** and (2,6-diaryl-pyrimidin-4-yl)acetonitriles **6** via base catalyzed ring transformations of suitably functionalized 2*H*-pyran-2-ones using 2-aminopyrazine and arylamidinium salts as nucleophiles, respectively. To the best of our knowledge this is the first report on the synthesis of these classes of compounds through a ring transformation reaction of 6-aryl-4-amino-2*H*-pyran-2-one-3-carbonitriles **3** with 2-aminopyrazine and arylamidinium salts.

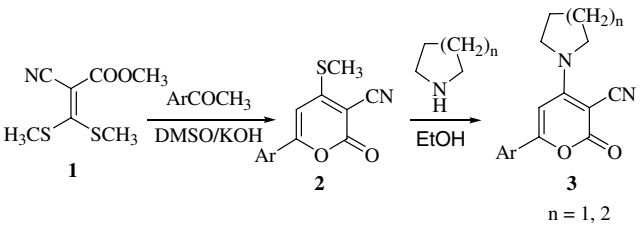
The 6-aryl-4-amino-2*H*-pyran-2-one-3-carbonitriles **3** have been conveniently prepared in two steps. The first step is the formation of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles **2** from the reaction of an aryl methyl ketone with methyl 2-cyano-3,3-dimethylthioacrylate **1** as described earlier.[25] Amination[26] of **2** with a *sec*-amine in refluxing ethanol gave 6-aryl-4-amino-2*H*-pyran-2-one-3-carbonitriles **3** which were used as the synthons for ring transformation reactions (Scheme 1).

Thus, a mixture of 6-aryl-4-amino-2*H*-pyran-2-one-3-carbonitrile **3** and 2-aminopyrazine **4a** was stirred in DMF at room temperature for 1 h followed by the addition of powdered KOH. The stirring was continued for an additional 1 h and thereafter the mixture was poured onto crushed ice with vigorous stirring and neutralized with 10% aqueous HCl. The resulting precipitate was filtered, washed with water and purified by column chromatography.

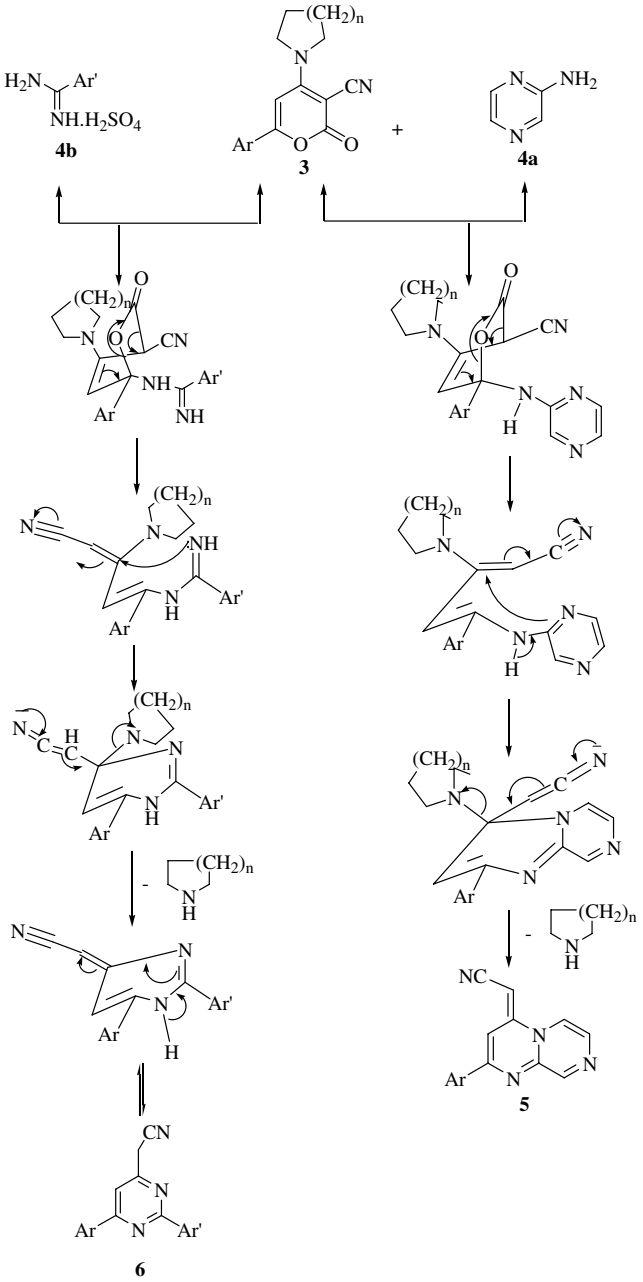
It is evident from the topography of 2*H*-pyran-2-ones **3**, that the C-2, C-4 and C-6 positions are electrophilic in nature. However, the C-6 position is highly susceptible to nucleophilic attack due to an extended conjugation and the presence of an electron-withdrawing substituent at position 3 of the pyran ring. The reaction of **3** with **4a** may be possibly initiated by the attack of the amino group at C-6 of the pyran ring with ring opening followed by decarboxylation and recyclization involving the ring nitrogen of pyrazine and C-4 of the pyran ring with elimination of the secondary amine. The reaction of **3** with the arylamidinium salts possibly commenced with the attack of the nucleophile at C-6 with ring closure involving the C-4 position of the pyran ring and concomitant loss of carbon dioxide and the amine to yield **6** (see Scheme 2).

All the compounds synthesized are listed in Tables 1 and 2 and were characterized by spectroscopic techniques.[27]

The configuration of the geometrical isomers of **5** was ascertained on the basis of NOE experiments. Irradia-



Scheme 1. Synthesis of 6-aryl-4-amino-2*H*-pyran-2-one-3-carbonitriles **3**.



Scheme 2. A plausible mechanism for the formation of (2-arylpyrazino[1,2-*a*]pyrimidine-4-ylidene) acetonitriles **5** and (2,6-diaryl-pyrimidin-4-yl)acetonitriles **6**.

Table 1. Reaction times and yields of the synthesized (*E*)-(2-aryl-pyrazino[1,2-*a*]pyrimidine-4-ylidene)acetonitriles **5**

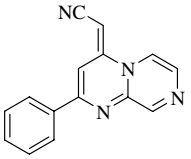
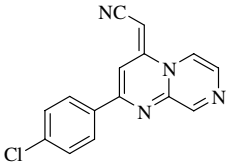
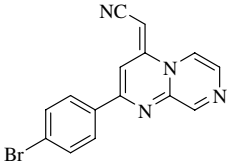
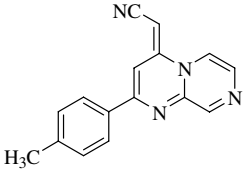
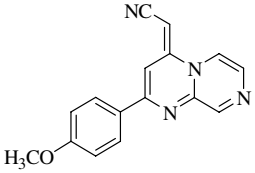
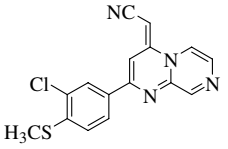
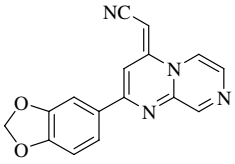
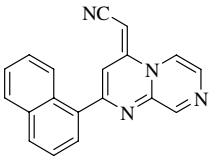
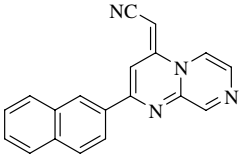
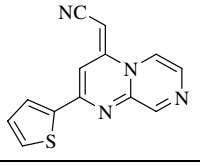
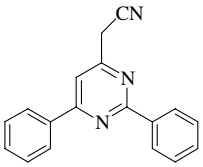
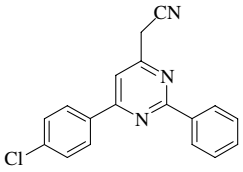
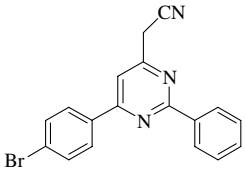
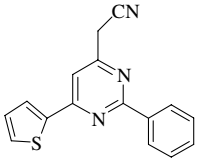
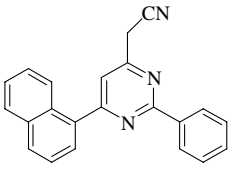
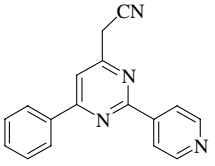
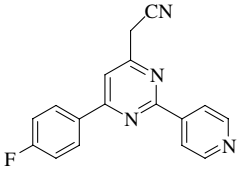
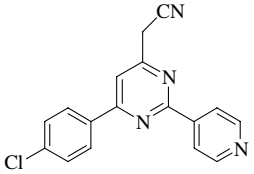
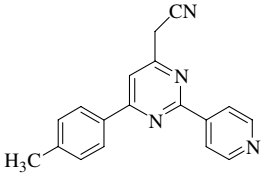
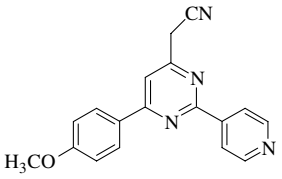
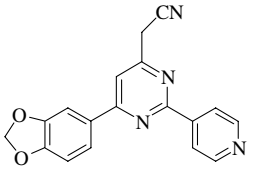
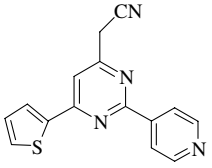
Compound	Structure	Time (h)	Yield (%)
5a		1.5	88
5b		2.0	89
5c		2.0	84
5d		2.5	83
5e		2.0	78
5f		2.0	85
5g		1.5	79
5h		2.5	84
5i		2.5	86
5j		2.0	83

Table 2. Reaction times and yields of the various (2,6-diaryl-pyrimidin-4-yl)acetonitriles **6**

Compound	Structure	Time (h)	Yield (%)
6a		1.5	85
6b		2.0	79
6c		2.0	84
6d		2.5	83
6e		2.0	78
6f		2.0	85
6g		1.5	79
6h		2.5	81
6i		2.5	76

(*continued on next page*)

Table 2 (*continued*)

Compound	Structure	Time (h)	Yield (%)
6j		2.0	83
6k		2.0	85
6l		1.5	85

tion of the vinylic proton of **5a** at δ 4.33 and the C-5 proton at δ 7.34 enhanced the signal intensity mutually whilst leaving the signal intensity of the C-3 proton at δ 7.40 unaffected, thereby confirming the (*E*)-configuration.

In summary, our methodology opens a new avenue for the stereoselective synthesis of (*E*)-(2-arylpyrazino[1,2-*a*]-pyrimidine-4-ylidene)acetonitriles **5** and cyanomethyl appended pyrimidines **6** in high yields under mild reaction conditions.

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References and notes

1. Trepanier, D. L.; Rampy, L. W.; Shriver, K. L.; Eble, J. N.; Shea, P. J. *J. Med. Chem.* **1968**, *11*, 1045.
2. Andres, C. J.; Scola, P. M.; Grant-Young, K. A. U. S. Patent 222158, 2005; *Chem. Abstr.* **2005**, *143*, 360126g.
3. Matsutani, S.; Mizushima, Y. EP 329126, 1989; *Chem. Abstr.* **1990**, *112*, 98557r.
4. Trepanier, D. L. (Dow Chemical Co.) U. S. Patent 3558,618, January 1971; *Chem. Abstr.* **1971**, *74*, 141870y.
5. Flohr, S.; Stengelin, S.; Gossel, M.; Klabunde, T.; Stahl, P.; Safar, P.; Spoonamore, J.; Smrcina, M.; Klein, J. T.; Merriman, G. H.; Whiteley, B. K.; Lanter, C.; Bordeau, K. J.; Yang, Z., Ger. Offen. DE 10,305,885, 26 August 2004; *Chem. Abstr.* **2004**, *141*, 225526f.
6. Kim, J.-W.; Cho, J.-H.; Han, T.; Lee, J.; Oh, C.-H. *Bull. Korean Chem. Soc.* **2006**, *27*, 484.
7. Denin, F.; Blondeau, D.; Sliwa, H. *J. Heterocycl. Chem.* **1990**, *27*, 1639.
8. Stanovnik, B.; van de Bovenkamp, H.; Svete, J.; Havala, A.; Simonič, I.; Tišler, M. *J. Heterocycl. Chem.* **1990**, *27*, 359.
9. Toplak, R.; Svete, J.; Grdadolnik, S. G.; Stanovnik, B. *Collect. Czech. Chem. Commun.* **1999**, *64*, 177.
10. Lennig, P.; Stengelin, S.; Klabunde, T.; Gossel, M.; Safar, P.; Smrcina, M.; Spoonamore, J.; Merriman, G.; Klein, J. T.; Whiteley, B.; Lanter C.; Bordeau, K.; Yang, Z. PCT Int. Appl. 2006, WO 2006, 24390; *Chem. Abstr.* **2006**, *144*, 274545g.
11. (a) Brown, D. J. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Ed.; The Pyrimidines; Wiley-Interscience: New York, 1970; Vol. 16, (b) Lister, J. H. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Fused Pyrimidines, Part II, The Purines; Wiley-Interscience: New York, 1971; Vol. 24, (c) Hoffmann, M. G. In *Houben-Weyl, Methoden der Organischen Chemie*; Schaumann, E., Ed.; G. Thieme: Stuttgart, 1996; Vol. E9, (d) Hurst, D. T. In *An Introduction to the Chemistry and Biochemistry of Pyrimidines, Purines and Pteridines*; Wiley: Chichester, 1980; (e) Bojarski, J. T.; Mokrosz, J. L.; Barton, H. J.; Paluchowska, M. H. *Adv. Heterocycl. Chem.* **1985**, *38*, 229; (f) Brown, D. J.. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, New York, Toronto, Sydney, Paris, Frankfurt, 1984; Vol. 3, Chapter 2.13.
12. (a) Lehn, J.-M. *Supramolecular Chemistry-Concepts and Perspectives*; VCH: Weinheim, 1995, Chapter 9; (b) Hanan, G. S.; Volkmer, D.; Schubert, U. S.; Lehn, J.-M.; Baum, G.; Fenske, D. *Angew. Chem., Int. Ed.* **1997**, *36*, 1842; (c) Semenov, A.; Spatz, J. P.; Möller, M.; Lehn, J.-M.; Sell, B.; Schubert, D.; Weidl, C. H.; Schubert, U. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 2547.
13. (a) Harriman, A.; Ziessel, R. *Coord. Chem. Rev.* **1998**, *171*, 31; (b) Harriman, A.; Ziessel, R. *Chem. Commun.* **1996**, 1707.
14. (a) Eddington, N. D.; Cox, D. S.; Roberts, R. R.; Butcher, R. J.; Edafiogho, I. O.; Stables, J. P.; Cooke, N.; Goodwin, A. M.; Smith, C. A.; Scott, K. R. . *Eur. J. Med. Chem.* **2002**, *37*, 635; (b) Eddington, N. D.; Cox, D. S.; Roberts, R. R.; Stables, J. P.; Powell, C. B.; Scott, K. R. *Curr. Med. Chem.* **2000**, *7*, 417; (c) Scott, K. R.; Rankin, G. O.; Stables, J. P.; Alexander, M. S.; Edafiogho, I. O.; Farrar, V. A.; Kolen, K. R.; Moore, J. A.; Sims, L. D.; Tonnut, A. D. *J. Med. Chem.* **1995**, *38*, 4033; (d) Edafiogho, I. O.; Alexander, M. S.; Moore, J. A.; Farrar, V. A.; Scott, K. R. *Curr. Med. Chem.* **1994**, *1*, 159.
15. Dannhardt, G.; Bauer, A.; Nowe, U. *Arch. Pharm.* **1997**, *330*, 74.
16. Ahluwalia, V. K.; Kaila, N.; Bala, S. *Indian J. Chem., Sect. B* **1987**, *26B*, 700.
17. Keutzberger, A.; Gillessen, J. *Arch. Pharm.* **1985**, *318*, 370.
18. (a) Eicher, T.; Hauptmann, S. *Chemie der Heterocyclen*; Georg Thieme: Stuttgart, New York, 1994; pp 398; (b) Gilchrist, T. L. In *Heterocyclenchemie*; Neunhoeffer, H., Ed.; Wiley-VCH: New York, 1995; p 270.
19. For an efficient repetitive synthesis of (oligo)pyrimidines based upon vinamidinium salt amidine condensations, see: Gompper, R.; Mair, H.-J.; Polborn, K. *Synthesis* **1997**, 696.
20. Bredereck, H.; Gompper, R.; Morlock, G. *Chem. Ber.* **1957**, *90*, 942.
21. Bredereck, H.; Gompper, R.; Schuh, H. G.; Theilig, G. *Angew. Chem.* **1959**, *71*, 753.
22. Iuhas, P. C.; Georgescu, E.; Georgescu, F.; Draghici, C.; Caproiu, T. M. *Rev. Roum. Chim.* **2001**, *46*, 55.
23. Matsunaga, T.; Tohda, Y.; Ariga, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 27.

24. (a) Dodson, R. M.; Seyler, J. K. *J. Org. Chem.* **1951**, *16*, 461; (b) Al-Hajjar, F. H.; Sabri, S. S. *J. Heterocycl. Chem.* **1982**, *19*, 1087; (c) Simon, D.; Lafont, O.; Farnoux, C. C.; Miocque, M. *J. Heterocycl. Chem.* **1985**, *22*, 1551; (d) Boykin, D. W.; Kumar, A.; Bajic, M.; Xiao, G.; Wilson, W. D.; Bender, B. C.; McCurdy, D. R.; Hall, J. E.; Tidwell, R. R. *Eur. J. Med. Chem.* **1997**, *32*, 965.
25. (a) Ram, V. J.; Verma, M.; Hussaini, F. A.; Shoeb, A. *Liebigs Ann. Chem.* **1991**, 1229; (b) Ram, V. J.; Verma, M.; Hussaini, F. A.; Shoeb, A. *J. Chem. Res. (S)* **1991**, 98.
26. Ram, V. J.; Nath, M.; Srivastava, P.; Sarkhel, S.; Maulik, P. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3719.
27. *General procedure for the synthesis of (2-arylpyrazino-[1,2-a]pyrimidine-4-ylidene)acetonitriles* (**5a**–**j**): A mixture of 6-phenyl-4-(piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitrile (**3a**, 280 mg, 1 mmol) and 2-aminopyrazine (**4**, 1.2 mmol) was stirred for 1 h in DMF (5.0 mL) followed by the addition of powdered KOH (84 mg, 1.5 mmol). Consumption of the starting material was monitored by TLC. After completion of the reaction, excess DMF was removed under reduced pressure and the residue was poured onto crushed ice with vigorous stirring. Neutralization with 10% aqueous HCl (5.0 mL) led to a precipitate which was filtered, washed with water, dried and purified through neutral alumina column chromatography using 10% hexane in chloroform as eluent. Compound **5a**: Yield 88%; mp 220–222 °C; column chromatography, 10/90 hexane/$CHCl_3$ v/v, R_f 0.38 ($CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.33 (s, 1H, CH), 7.34 (d, $J = 4.95$ Hz, 1H, ArH), 7.40 (s, 1H, ArH), 7.48–7.50 (m, 3H, ArH), 7.85 (d, $J = 5.07$ Hz, 1H, ArH), 8.02–8.06 (m, 2H, ArH), 8.86 (d, $J = 0.93$ Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 57.66, 105.06, 115.75, 125.59, 127.65, 129.38, 129.61, 134.10, 148.10, 154.06; IR (KBr) 2180 cm^{-1} (CN); mass (ESI-MS) *m/z* 247 [M^++1]; EI-HRMS: (M^+) calcd for $C_{15}H_{10}N_4$ 246.09055, found 246.09017. Compound **5b**: Yield 89%; mp 216–218 °C; column chromatography, 10/90 hexane/$CHCl_3$ v/v, R_f 0.32 ($CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.37 (s, 1H, CH), 7.34 (d, $J = 5.37$ Hz, 1H, ArH), 7.37 (s, 1H, ArH), 7.47 (d, $J = 8.85$ Hz, 2H, ArH), 7.87 (d, $J = 5.40$ Hz, 1H, ArH), 8.00 (d, $J = 8.46$ Hz, 2H, ArH), 8.62 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 58.24, 104.86, 115.70, 117.89, 126.86, 127.86, 129.49, 132.53, 135.84, 141.62, 148.78, 150.25, 153.93; IR (KBr) 2197 cm^{-1} (CN); mass (ESI-MS) *m/z* 281 [M^++1]; EI-HRMS: (M^+) calcd for $C_{15}H_9ClN_4$ 280.05157, found 280.05112.

Representative procedure for the synthesis of (6-phenyl-2-pyridin-4-ylpyrimidin-4-yl)acetonitrile (**6f**): An equimolar mixture of 6-phenyl-4-(piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitrile (280 mg, 1 mmol) and arylamidinium salt **4b** (1.2 mmol) in the presence of powdered KOH (84 mg, 1.5 mmol) in DMF (5.0 mL) was stirred for 2 h. Consumption of the starting material was monitored by TLC. After completion of the reaction, excess DMF was removed under reduced pressure and the residue was poured onto crushed ice with vigorous stirring. Neutralization with 10% HCl (5.0 mL) gave a precipitate which was filtered, washed with water, dried and purified by silica gel column chromatography using 10% hexane in chloroform as the eluent. Yield 85%; mp 155–157 °C; column chromatography, 30/70 hexane/$CHCl_3$ v/v, R_f 0.27 ($CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.05 (s, 2H, CH_2), 7.56–7.58 (m, 3H, ArH), 7.82 (s, 1H, ArH), 8.21–8.25 (m, 2H, ArH), 8.40 (d, $J = 6.06$ Hz, 2H, ArH), 8.81 (d, $J = 5.49$ Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.45, 112.47, 114.39, 120.82, 126.10, 127.86, 130.62, 134.45, 142.95, 149.23, 159.03, 161.63 and 164.54; IR (KBr, cm^{-1}) 2935, 2367, 2341, 2251, 1591, 1381, 1354, 1286, 1196, 1126, 1066, 994, 924, 845, 765; mass (ESI-MS) *m/z* 273.4 [M^++1]; EI-HRMS: (M^+) calcd for $C_{17}H_{12}N_4$ 272.10619, found 272.10665.