Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 947–951
Tetrahedron Letters

Multi-component reactions between 2-aminopyrimidine, aldehydes and isonitriles: the use of a nonpolar solvent suppresses formation of multiple products

Vladislav Z. Parchinsky, Olga Shuvalova, Olga Ushakova, Dmitry V. Kravchenko and Mikhail Krasavin*

Chemical Diversity Research Institute, 2a Rabochaya St., Khimki, Moscow Reg., 114401, Russia

Received 20 October 2005; revised 17 November 2005; accepted 29 November 2005
Available online 20 December 2005

Abstract—A reliable and convenient protocol for MCRs between 2-aminopyrimidine, aldehydes and isonitriles is described. Toluene was chosen as the reaction solvent based on mechanistic reasoning. The product mixtures were found to contain a single imidazo[1,2-*a*]pyrimidine product in each case, which were isolated and purified by precipitation and crystallization. Chromatographic recovery from filtrates raised the total yields to 49–66%. The procedure provides a practical alternative to hitherto reported methods in which formation of multiple products was observed.

Multi-component reactions (MCRs) have become a significant part of today's arsenal of methods in combinatorial chemistry due to their valued features such as atom economy, straightforward reaction design, and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical event.[1] Typically, purification of products resulting from MCRs is also simple since all the organic reagents employed are consumed and are incorporated into the target compound.

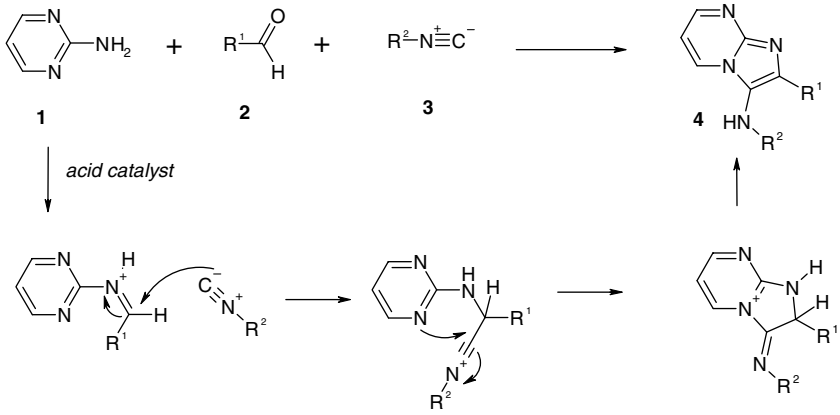
In 1998, Blackburn,[2] Bienaymé,[3] and Groebke[4] reported an elegant variant of the Ugi MCR involving 2-aminoazines (in particular, 2-aminopyrimidine, **1**)—the reagents played a dual role by (i) forming a Schiff base with the aldehyde, and (ii) providing a nucleophilic ring nitrogen to intercept the intermediate formed after insertion of the isonitrile. In the case of **1**, the products were imidazo[1,2-*a*]pyrimidines (**4**, Scheme 1). The reactions were performed at room temperature by combining all three reagents in methanolic solution with a catalyst ($Sc(OTf)_3$,[2] perchloric acid,[3] or glacial acetic acid[4]). After consumption of the starting materials, the products were isolated by chromatography. The moderate yields observed in some cases were attributed to incomplete conversions.

However, after Bradley[5] carefully examined these low-yielding reactions, it became evident that they follow a more complicated course leading to the formation of almost equal amounts of isomeric imidazo[1,2-*a*]pyrimidine products **5**. These products are thought to arise from formation of alternative iminium intermediate **I-2** involving the ring nitrogen of **1** (pathway B, Scheme 2), as opposed to the anticipated exclusive formation of the protonated imine **I-1** (pathway A, Scheme 2). Additionally, nucleophilic solvents (like methanol) were found to promote interaction of **I-1** with the second molecule of 2-aminopyrimidine as well as the solvent itself to give products like **6**, albeit in low yields (5%).[5]

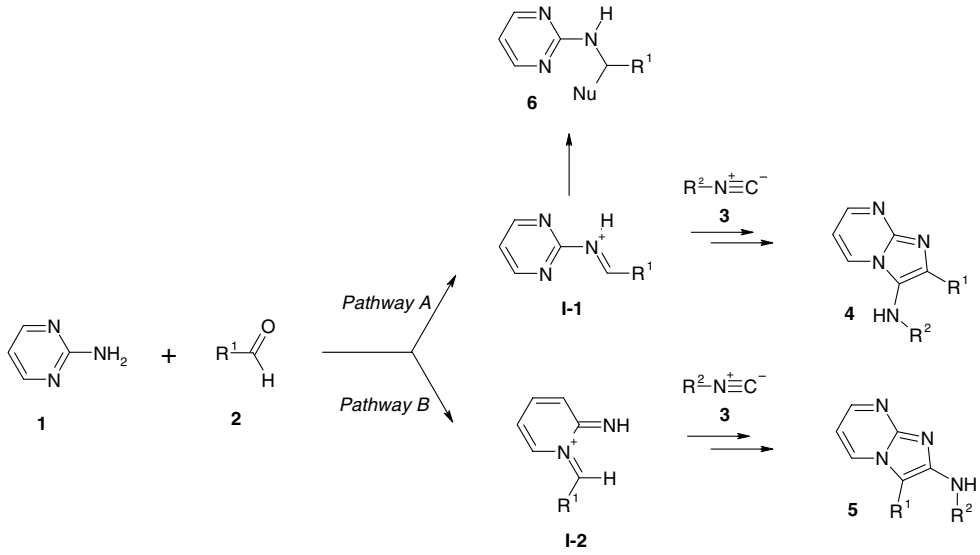
Being aware of these complications and faced with the challenge of producing combinatorial arrays of medicinally important[6] 3-alkylamino-2-substituted imidazo-[1,2-*a*]pyrimidines **4** for biological screening, we sought to develop a synthetic protocol that would disfavor the formation of the unwanted adduct **I-2** and thus allow exclusive formation and straightforward purification of the target compounds.

Keywords: Imidazo[1,2-*a*]pyrimidine; Ugi reaction; Combinatorial chemistry; Toluene; Ammonium chloride.
* Corresponding author. Tel.: +7 095 995 4942; fax: +7 095 926 9780; e-mail: myk@chemdiv.com

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.11.152



Scheme 1. Imidazo[1,2-*a*]pyrimidine synthesis using MCR.

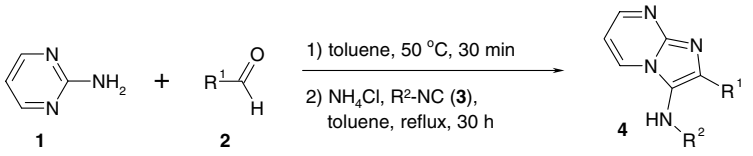


Scheme 2. Mechanistic considerations justifying possible formation of multiple products in the multicomponent reaction under investigation.

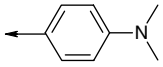
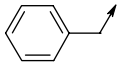
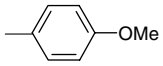
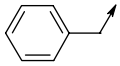
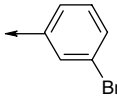
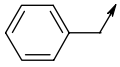
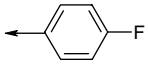
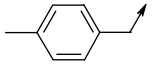
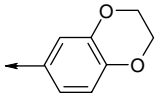
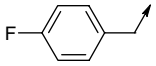
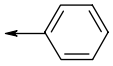
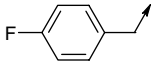
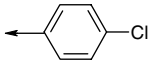
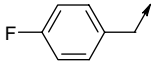
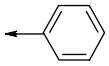
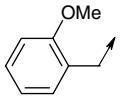
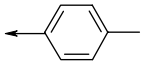
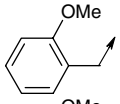
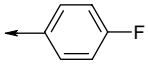
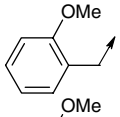
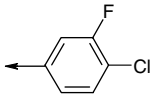
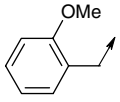
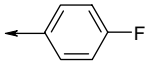
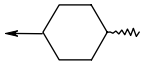
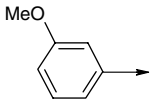
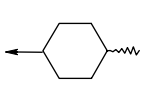
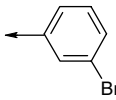
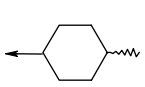
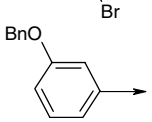
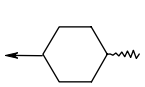
We reasoned that while formation of the charged **I-2** is plausible in a polar protic solvent like methanol, in a nonpolar solvent the stability of **I-1** (probably in its non-protonated form) would be far greater than that of **I-2**. Additionally, a non-nucleophilic aprotic solvent is also unlikely to give rise to adducts like **6**. Since the publication of the first report[7] on an Ugi reaction promoted by ammonium chloride in toluene, there have been a number of examples[8,9] in the literature of the successful use of this set of conditions. Therefore, we tested its applicability to the MCR-based synthesis of **4**.

In all cases studied (Table 1), an imine intermediate (a non-protonated form of **I-1**, Scheme 2) was pre-formed by heating equimolar amounts 2-aminopyrimidine **1** and an aldehyde **2** at 50 °C for 30 min[10] prior to the addition of 2 equiv of solid ammonium chloride and 1 equiv of isonitrile **3**. After the reaction mixture was brought to reflux, the progress of the reaction was monitored by the disappearance of **1** according to TLC analysis. All reactions went to completion within 30 h to provide dark-brown solutions containing an ammonium chloride precipitate. These mixtures were washed with hot water, without cooling to room temperature, and diluted with hexane to provide thick precipitates, which were filtered off and their identity as imidazo[1,2-*a*]pyrimidines **4** was confirmed by LCMS analysis (in some cases, the precipitated products were at least 90% pure) and, subsequently, by the X-ray structure of a representative product (**4j**, Fig. 1). Further crystallization from ether provided analytically pure material. The yields after crystallization were moderate to good (Table 1). The filtrates were analyzed by LCMS and, to our delight, were also found to contain mostly the same imidazo[1,2-*a*]-pyrimidines **4**, which were recovered by column chromatography thereby raising the total yield of **4** by 6–23% (Table 1). Notably, neither isomeric products **5** nor adducts like **6** were detected in these processes. While the yields in these reactions are still modest, the method described offers a very practical alternative to the hitherto reported protocols[2–4] in which formation of multiple products is possible[5] and is likely to complicate product purification. Furthermore, this method was

Table 1. 3-Alkylamino-2-substituted imidazo[1,2-*a*]pyrimidines **4** prepared in this study



1 **2** **4**

Compound	R^1	R^2	Yield (%) after trituration or crystallization	Yield (%) after recovery from filtrate
4a			52	60
4b			45	64
4c			43	66
4d			43	49
4e			47	62
4f			49	61
4g			47	66
4h			48	65
4i			45	65
4j			51	61
4k			45	58
4l			28	52
4m			37	52
4n			24	55
4o			25	60

found applicable for 2-aminopyridine and 2-aminopyrazine: a similar MCR of these 2-aminoazines with *p*-methoxybenzaldehyde and benzylisonitrile (the reagents used for preparation of **4b**) provided good yields of

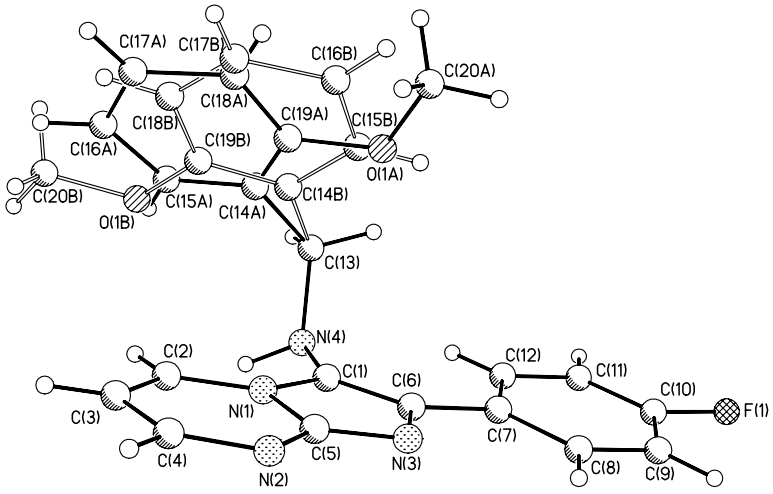
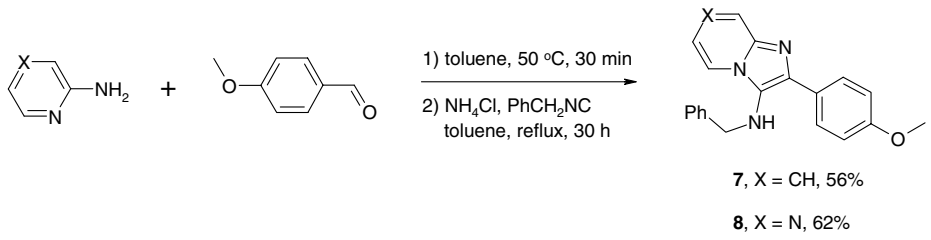


Figure 1. X-ray structure of the compound **4j**.



Scheme 3. Other 2-aminoazines employed in the MCR under investigation.

imidazo[1,2-*a*]pyridine **7** and imidazo[1,2-*a*]pyrazine **8**, respectively[11] (Scheme 3).

In conclusion, we have demonstrated that judicious choice of a nonpolar reaction medium for multi-component reactions between 2-aminopyrimidine, aldehydes and isonitriles results in the formation of the target imidazo[1,2-*a*]pyrimidines **4** as sole products. This new protocol can be extended to other 2-aminoazines and is suitable for the convenient production of combinatorial compound libraries.

General procedure for MCR of 2-aminopyrimidine, aldehydes and isonitriles: A solution of 2-aminopyrimidine (**1**, 1 mmol) and an aldehyde (**2**, 1 mmol) in toluene (15 mL) was heated at 50 °C for 30 min. Solid ammonium chloride (2 mmol) and an isonitrile (**3**, 1 mmol) were added and the reaction mixture was brought to reflux. After 30 h, the resulting dark brown solution, while still hot, was washed with water (50 °C, 25–50 mL), cooled down to rt, and diluted with hexane (50 mL). The resulting precipitate was collected by filtration, washed with hexane (2 × 25 mL), air dried and recrystallized from ether to provide imidazo[1,2-*a*]pyrimidines **4**. The filtrate and crystallization liquor were combined, concentrated in vacuo, and subjected to column chromatography on silica gel using 2.5–10% methanol in dichloromethane as the eluent to provide an additional quantity of **4** with analytical data[11] identical to those of the material obtained by crystallization.

References and notes

1. Doemling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.
2. Blackburn, C. *Tetrahedron Lett.* **1998**, *39*, 5469–5472.
3. Bienaymé, H.; Bouzid, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2234–2237.
4. Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661–663.
5. Mandair, G. S.; Light, M.; Russell, A.; Hursthouse, M.; Bradley, M. *Tetrahedron Lett.* **2002**, *43*, 4267–4269.
6. (a) Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170–1176; (b) Rival, Y.; Taudou, A.; Ecalle, R. *Farmaco* **1993**, *48*, 857–869; (c) Tully, R. W.; Gardner, C. R.; Gillespie, R. J.; Westwood, R. *J. Med. Chem.* **1991**, *34*, 2060–2067; (d) Barlin, G. B.; Davies, L. P.; Ireland, S. J.; Ngu, M. M. L.; Zhang, J. *Aust. J. Chem.* **1992**, *45*, 877–888.
7. Cristau, P.; Vors, J.-P.; Zhu, J. *Org. Lett.* **2001**, *3*, 4079–4082.
8. Janvier, P.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 2560–2567.
9. Fayol, A.; Zhu, J. *Org. Lett.* **2004**, *6*, 115–118.
10. Omitting the imine formation step resulted in significant reduction the yields of **4.** Longer reaction times prior to

addition of ammonium chloride and isonitrile **3** did not improve the yields. The unstable imine intermediate could not be detected by TLC due to hydrolysis on silica gel.

11. Analytical data for selected compounds: **4a**—yellowish solid, mp = 134–138 °C; δ_H (300 MHz, DMSO-d_6) 8.46 (unresolved dd, $J = 6.8$ Hz, 1H), 8.34 (m, 1H), 8.06 (d, $J = 8.6$ Hz, 2H), 7.20–7.30 (m, 5H), 6.87 (dd, $J = 4.1$, 6.8 Hz, 1H), 6.82 (d, $J = 8.6$ Hz, 2H), 5.32 (t, $J = 5.9$ Hz, 1H), 4.08 (d, $J = 5.9$ Hz, 2H), 2.96 (s, 6H); δ_C (75 MHz, DMSO-d_6) 149.7, 148.2, 143.3, 139.8, 136.2, 130.6, 128.2, 127.8, 127.0, 123.1, 121.5, 112.0, 107.5, 51.1, 40.0; LCMS m/z 344 (M+1); HRMS m/z (EI) found: 343.4348; $C_{21}H_{21}N_5$ requires 343.4350. **4b**—pale solid, mp = 146–148 °C (decomp.); δ_H (300 MHz, DMSO-d_6) 8.57 (dd, $J = 1.9$, 6.8 Hz, 1H), 8.43 (dd, $J = 4.1$, 1.9 Hz, 1H), 8.10 (d, $J = 8.9$ Hz, 2H), 7.18–7.26 (m, 5H), 7.04 (d, $J = 8.9$ Hz, 2H), 6.97 (dd, $J = 4.1$, 6.8 Hz, 1H), 5.47 (unresolved t, 1H), 4.08 (d, $J = 4.5$ Hz, 2H), 3.82 (s, 3H); δ_C (75 MHz, DMSO-d_6) 158.9, 149.5, 143.0, 139.6, 134.3, 131.3, 128.3, 128.2, 127.1, 125.6, 124.0, 113.9, 108.3, 95.4, 55.1, 51.0; LCMS m/z 331 (M+1); HRMS m/z (EI) found: 330.3923; $C_{20}H_{18}N_4O$ requires 330.3927. **4j**—yellowish solid, mp = 156–158 °C; δ_H (300 MHz, DMSO-d_6) 8.49 (dd, $J = 1.9$, 6.8 Hz, 1H), 8.42 (dd, $J = 1.9$, 4.0 Hz, 1H), 8.20 (dd, $J = 5.6$, 8.7 Hz, 2H), 7.26 (t, $J = 8.9$ Hz, 2H), 7.19 (d, $J = 7.6$ Hz, 2H), 6.94 (dd, $J = 4.0$, 6.6 Hz, 1H), 6.88 (d, $J = 8.1$Hz, 1H), 6.80 (t, $J = 7.4$ Hz, 1H), 5.23 (t, $J = 6.0$ Hz, 1H), 4.08 (d, $J = 6.0$ Hz, 2H), 3.65 (s, 3H); δ_C (75 MHz, DMSO-d_6) 161.4 (d, $J_{C-F} = 243.3$ Hz), 157.1, 149.2, 143.5, 134.4, 131.2, 130.5 (d, $J_{C-F} = 2.9$ Hz), 128.7, 128.6 (d, $J_{C-F} = 7.4$ Hz), 127.1, 124.9, 120.0, 115.1 (d, $J_{C-F} = 21.1$ Hz), 110.5, 107.7, 55.1, 46.1; LCMS m/z 349 (M+1); HRMS m/z (EI) found: 348.3829; $C_{20}H_{17}FN_4O$ requires 348.3831.**7**—beige solid; mp = 126–128 °C; δ_H (300 MHz, DMSO-d_6) 8.70 (m, 1H), 8.06 (m, 2H), 7.86 (m, 2H), 7.10–7.37 (m, 9H), 6.22 (br s, 1H), 4.13 (s, 2H), 3.83 (s, 3H); δ_C (75 MHz, DMSO-d_6) 159.5, 139.2, 138.4, 137.0, 133.8, 130.6, 128.8, 128.2, 127.7, 127.1, 125.0, 123.5, 116.8, 114.0, 55.2, 49.5, 39.5; LCMS m/z 330 (M+1); HRMS m/z (EI) found: 329.4055; $C_{21}H_{19}N_3O$ requires 329.4051. **8**—yellow solid; mp = 133–136 °C (decomp.); δ_H (300 MHz, DMSO-d_6) 9.04 (s, 1H), 8.63 (d, $J = 4.5$ Hz, 1H), 7.95 (d, $J = 7.9$ Hz, 2H), 7.83 (d, $J = 4.5$ Hz, 1H), 7.16 (s, 5H), 7.03 (d, $J = 7.9$ Hz, 2H), 6.76 (br s, 1H), 4.21 (s, 2H), 3.80 (s, 3H); δ_C (75 MHz, DMSO-d_6) 160.0, 138.9, 136.1, 132.2, 128.7, 128.2, 127.2, 126.3, 125.1, 119.2, 116.1, 114.4, 111.6, 55.3, 50.4, 39.5; LCMS m/z 331 (M+1); HRMS m/z (EI) found: 330.3931; $C_{20}H_{18}N_4O$ requires 330.3927.