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Exploring Catalyst and Solvent Effects in the Multicomponent Synthesis of Pyridine-3,5-dicarbonitriles

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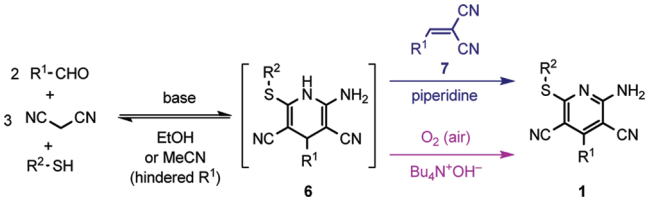

The effects of an ionic base, tetrabutylammonium hydroxide (TBAH), and an amine base, piperidine, on the direct synthesis of pyridine-3,5-dicarbonitriles using a multicomponent reaction (MCR) from aldehydes, malononitrile, and thiols were systematically investigated. The amine base showed better results when the MCR was performed in ethanol, whereas employing the ionic base in acetonitrile resulted in similar yields but in a much shorter reaction time. A modified protocol to overcome the difficulty in the direct synthesis of pyridine-3,5-dicarbonitriles via the MCR from sterically hindered aldehydes using either base was realized by changing the reaction solvent from ethanol to acetonitrile. Mechanistically, the two catalysts were found to each promote different pathways in the final oxidation step of the penultimate product, 1,4-dihydropyridine **6**. A reaction intermediate, Knoevenagel adduct **7**, plays the major role in the amine base-catalyzed system, while in the presence of an ionic base, aerobic oxygen acts as the primary oxidant.

Introduction

The pyridine-3,5-dicarbonitrile scaffold **1** represents a class of medicinally significant compounds. Dependent upon substitutions around the core pyridine ring, this class of compounds has demonstrated a diverse range of biological activities: **2** is an interesting antiprion agent;[2,3] related 6-amino structures of type **3** are active antitumor agents against several human cancer cell lines;[4] **4** (LUF5831) is the first confirmed non-nucleoside agonist of the human adenosine A_1 receptor;[5] and compound **5** was identified as a potent inhibitor of HIV-1 integrase[6] (Figure 1).

Though multistep routes to **1** exist, one-pot synthesis through an established MCR[7] (route i, Scheme 1) self-evidently represents the most efficient approach to the medicinal chemist. Regrettably, this reaction proceeds only in low to moderate yield necessitating development of an improved method. In our previous investigation,[8] we successfully improved the reaction yield by generating an extra equivalent of Knoevenagel adduct **7** in situ (route ii, Scheme 1), since it acts as the major oxidant in the final oxidation of 1,4-dihydropyridine **6** to pyridine product **1**, according to the earlier study.[8]

We previously confirmed[8] the presence of all intermediates involved in the formation of penultimate 1,4-dihydropyridine products **6** (Scheme 2). However, it is the final step—oxidation of these compounds to pyridines **1**—that remains

(1) For recent reviews on the use of privileged structures in drug discovery, see: (a) Costantino, L.; Barlocco, D. *Curr. Med. Chem.* **2006**, *13*, 65–85. (b) DeSimone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. A. *Comb. Chem. High Throughput Screening* **2004**, *7*, 473–494.

(2) May, B. C. H.; Zorn, J. A.; Witkop, J.; Sherrill, J.; Wallace, A. C.; Legname, G.; Prusiner, S. B.; Cohen, F. E. *J. Med. Chem.* **2007**, *50*, 65–75.

(3) Guo, K.; Mutter, R.; Heal, W.; Reddy, T. K. R.; Cope, H.; Pratt, S.; Thompson, M. J.; Chen, B. *Eur. J. Med. Chem.* **2008**, *43*, 93–106.

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(7) (a) Kambe, S.; Saito, K.; Sakurai, A.; Midorikawa, H. *Synthesis* **1981**, *7*, 531–533. (b) Elghandour, A. H. H.; Ibrahim, M. K. A.; Ali, F. M. M.; Elshikh, S. M. M. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1997**, *36*, 79–82.

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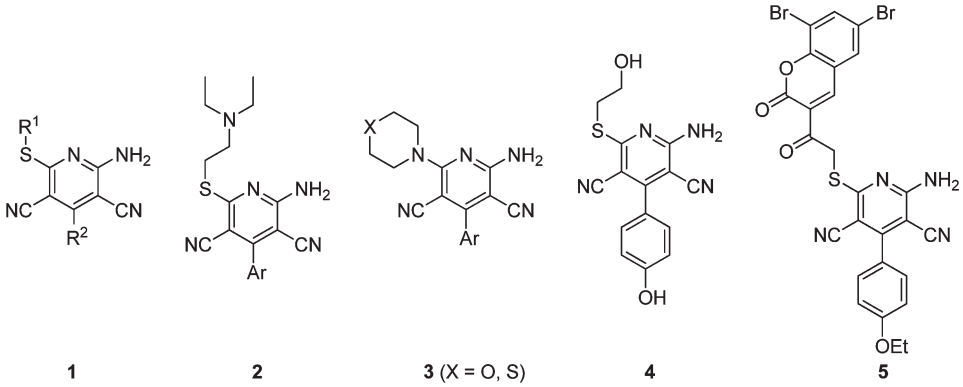
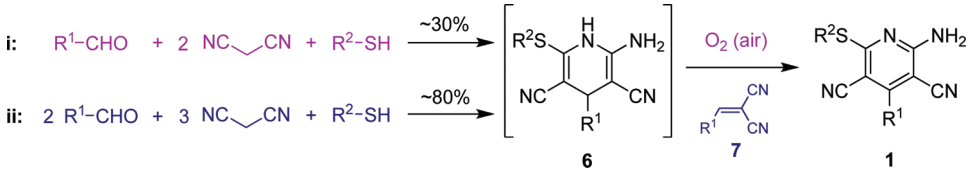
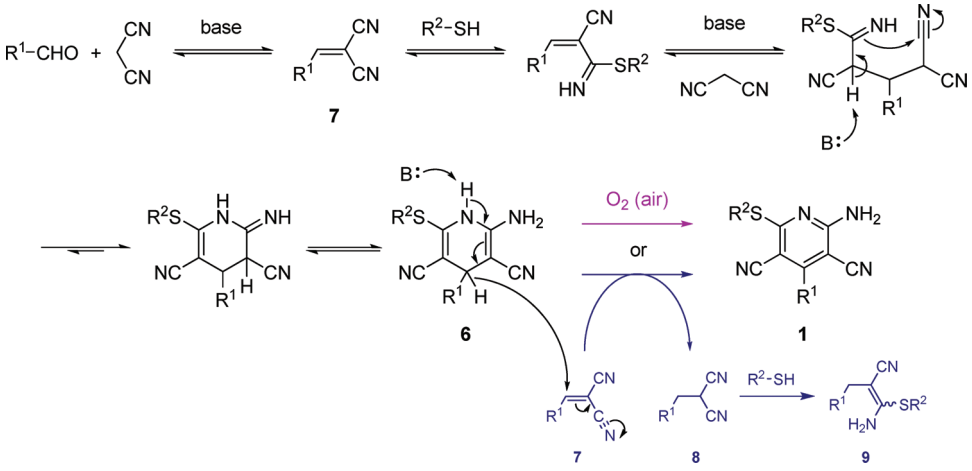


FIGURE 1. General structure of pyridine-3,5-dicarbonitriles **1** (R^1, R^2 = alkyl, aryl) and examples of such compounds displaying potent biological activity (**2**–**5**).

SCHEME 1. Multicomponent Synthesis of Pyridine-3,5-dicarbonitriles



SCHEME 2. Likely Mechanism of the MCR Synthesis of Pyridine-3,5-dicarbonitriles[8,9]



the most unresolved in terms of the mechanisms involved. Two processes are known to contribute to this last step: aerobic oxidation of **6** plays a minor role apparently being limited by the low solubility of oxygen in reaction solvent (ethanol), whereas the major pathway is a base-catalyzed net transfer of molecular hydrogen to the Knoevenagel adduct **7** (Scheme 2), initially deduced by Evdokimov et al.,[10] and involving a formal hydride transfer from C-4 of the 1,4-dihydropyridine to **7**. The predominance of the latter process effectively cuts the product yield in half by consuming a reaction intermediate and thus accounts for the inefficiency of this MCR noted earlier. Though the reaction yield was doubled when an additional equivalent of **7** was generated in situ,[9] isolation of its reduced form **8** was not achieved previously, although the thiol addition product **9** was isolated from the reaction mixture.[9a]

According to a recent report,[10] this MCR can be promoted by using an ionic liquid, 1-methyl-3-butylimidazolium hydroxide, [bmIm]OH, as opposed to the usual amine base catalyst. Yields of **1** between 62 and 92% were reported, even without in situ formation of the extra equivalent of intermediate **7**, indicating that a different pathway, particularly with respect to the final oxidation of the penultimate 1,4-dihydropyridine **6**, must be involved under these conditions. We thought this observation warranted further investigation in order to better understand the influence of [bmIm]OH on the reaction.

A further phenomenon associated with the MCR is arrest of the final oxidation step when a sterically hindered

(9) (a) Evdokimov, N. M.; Magedov, I. V.; Kireev, A. S.; Kornienko, A. *Org. Lett.* **2006**, *8*, 899–902. (b) Evdokimov, N. M.; Kireev, A. S.; Yakovenko, A. A.; Antipin, M. Yu.; Magedov, I. V.; Kornienko, A. *J. Org. Chem.* **2007**, *72*, 3443–3453.

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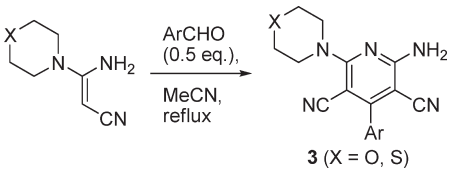
SCHEME 3. Reported Synthesis of Related 6-Amino Compounds 3



aldehyde such as 2,6-dichlorobenzaldehyde is used.[9−12] In such cases, the 1,4-dihydropyridine **6** is stable and can be easily isolated, requiring subsequent chemical oxidation to **1**.[8] Interestingly, in a related reaction[4] (Scheme 3) which must initially result in formation of the 1,4-dihydropyridine, high yields of the pyridines were reported in all cases—including that of 2,6-dichlorobenzaldehyde—with no detection of the 1,4-dihydropyridine products noted at all. We were thus prompted to seek to understand the mechanism of oxidation to pyridines **3** under these conditions in the search for a procedure which might overcome the limitations previously encountered in the related MCR (Scheme 1).

In this paper, we present our recent investigations into the utility of the two types of catalyst (ionic base and organic base) in the MCR leading to pyridine-3,5-dicarbonitriles **1** (Scheme 1), with respect to the optimization of reaction conditions and mechanistic insight, which resulted in a modified protocol enabling direct synthesis of pyridine-3,5-dicarbonitriles from sterically demanding aldehydes.

Results and Discussion

Studies the Effects of Ionic and Nonionic Base Catalysts. Analysis of the improved [bmIm]OH-promoted MCR developed by Ranu et al.[10] was initially hampered by apparent instability of the ionic liquid, as in our hands, a pure sample could not be obtained using the reported procedure.[11] We subsequently found that [bmIm]OH decomposes rapidly when dry but is moderately stable when a small water content is maintained (more details are included in the Supporting Information). Having successfully isolated a clean sample, we observed that the yield of a model MCR still did not exceed 50% under the reported conditions[10] (curve 1, Figure 2a). Furthermore, in this case, generating an extra equivalent of **7** using the 2:3:1 ratio of reactants did not markedly improve the product yield (curve 2, Figure 2a). Unlike the amine base-catalyzed system in which the yield was essentially doubled by this change (Figure 2c), we only observed a slight enhancement of conversion (by about 10%) under [bmIm]OH catalysis. In addition, since a relatively large quantity of the ionic liquid (50 mol %) was reported as necessary, we systematically evaluated the effects of different amounts of catalyst upon the outcome of the reaction. Interestingly, it was found that there was an optimal range of catalyst amount (30−70 mol %) for both ratios (Figure 2a).

Due to the difficulties encountered regarding the preparation and stability of [bmIm]OH, we instead considered a related and more readily available ionic base catalyst, tetrabutylammonium hydroxide (TBAH), and found it is almost

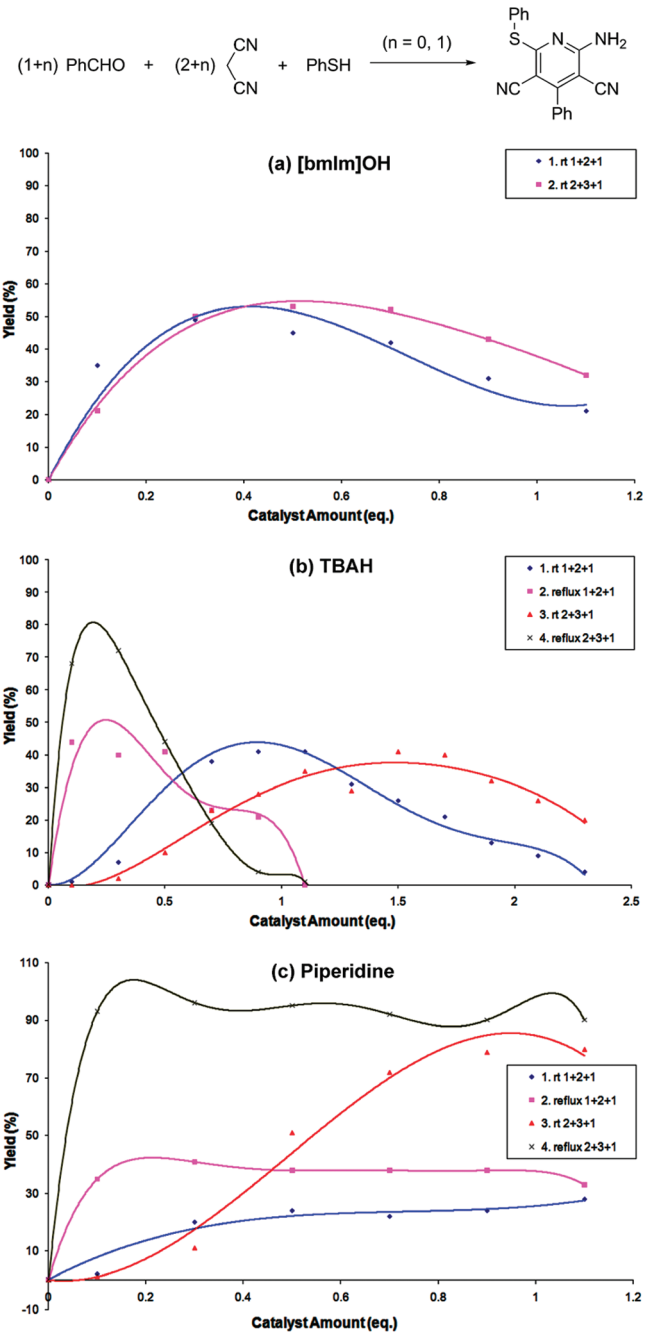
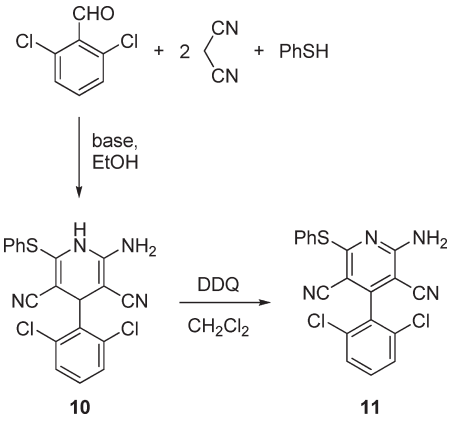


FIGURE 2. Investigation of catalyst amount on outcome of the model MCR, analyzed by HPLC: (a) [bmIm]OH, (b) TBAH, (c) piperidine.

as effective as the ionic liquid. Similarly to [bmIm]OH, TBAH showed an optimal range over which it exerted the best effect on promoting the reaction: between 50−110 mol % in the 1:2:1 reaction or 110−170 mol % in the 2:3:1 case (curves 1 and 3, Figure 2b). All reactions considered thus far were performed at rt. However, the optimal amount of TBAH was reduced to 10−50 mol % for both reactant ratios when the MCR was carried out under reflux (curves 2 and 4, Figure 2b), and the yield was improved significantly in the 2:3:1 reaction. Interestingly, in situ formation of an extra 1 equiv of Knoevenagel adduct **7** generally showed less effect on the conversion in the MCRs with either ionic species

(11) (a) Ranu, B. C.; Banerjee, S. *Org. Lett.* **2005**, *7*, 3049–3052. (b) Mehnert, C. P.; Dispenziere, N. C.; Cook, R. A. *Chem. Commun.* **2002**, 1610–1611.
(12) Reddy, T. R. K.; Mutter, R.; Heal, W.; Guo, K.; Gillet, V. J.; Pratt, S.; Chen, B. *J. Med. Chem.* **2006**, *49*, 607–615.

SCHEME 4. MCR Derived from a Sterically Hindered Aldehyde



as catalyst, suggesting that **7** might play a less significant role in oxidation of the penultimate 1,4-dihydropyridines in the presence of these ionic catalysts.

In contrast to the ionic base-mediated reactions where yields diminished sharply above the optimal catalyst range, little variation was detected above 10 mol % with piperidine at reflux (curves 2 and 4, Figure 2c). The higher temperature of reflux resulted in the best yields in both cases (1:2:1 and 2:3:1 reactions). At rt, an increased quantity of 30 or 70 mol % of piperidine was required to effect the best conversions for 1:2:1 and 2:3:1 MCRs, respectively, though yields did not reach those of the reflux reactions (curves 1 and 3, Figure 2c).

As expected, the combination of 2:3:1 resulted in a significant improvement in yield, essentially doubling product formation regardless of the temperature. In contrast to the ionic base-catalyzed systems, these observations suggested that Knoevenagel intermediate **7** plays the more significant role as oxidant in the final step—oxidation of the 1,4-dihydropyridine—under amine base catalysis.

In summary, in our hands, we found an ionic liquid, [bmIm]OH, was not as effective in promoting the MCR as reported,[10] which may perhaps be explained by the unstable nature of this catalyst. However, our results suggested there might be different mechanisms involved in the final oxidation of 1,4-dihydropyridine **6** depending on the catalyst used (ionic or nonionic base), an observation we wished to explore in more detail. The key reaction intermediate **7** seems to play a significant role in the final oxidation in the organic base-catalyzed reaction while exerting a markedly weaker effect on the reaction yield with ionic base catalysis. Meanwhile, whereas high temperature was found to improve the MCR in all cases, it is not necessary for the reaction to proceed as previously assumed.[7−9] Pyridine products were detected in good yield at rt with appropriate quantities of either catalyst.

Optimization of MCR for Sterically Hindered Aldehydes. Our focus then turned toward cases where the MCR is arrested at the 1,4-dihydropyridine stage, corresponding to use of more sterically demanding aldehydes such as 2,6-dichlorobenzaldehyde (Scheme 4). According to our earlier mechanistic studies,[8] Knoevenagel adduct **7** is the major oxidant mediating final oxidation of the 1,4-dihydropyridine **6**. Therefore, we suspected that steric crowding originating from the aldehyde starting material—thereby blocking close approach of **6** and **7** where *ortho*-substituents are present—might be a reason for arrest of the MCR at the 1,4-dihydropyridine stage. Several reports[9−12] of this observation have been made, yet a direct pyridine synthesis involving 2,6-dichlorobenzaldehyde was reported more recently[4] (Scheme 3). Compared with the standard MCR conditions (Scheme 1), a significant difference was that acetonitrile was employed in place of ethanol as solvent in the direct method (Scheme 3). During investigation of MCRs from a handful of 2,6-disubstituted benzaldehydes, we had observed that the 1,4-dihydropyridines **6** are only sparingly soluble in acetonitrile, whereas the final pyridines **1** are fully soluble; neither species is soluble in ethanol, and both dissolve readily in DMSO. It was thought solubility may be a factor influencing the final oxidation step, and therefore, to attempt direct synthesis of pyridine-3,5-dicarbonitriles from sterically hindered aldehydes, acetonitrile and DMSO were employed as solvents for the MCR so that a comparison could be made.

TABLE 1. Optimization of Reaction Conditions for the MCR from Sterically Hindered Aldehydes[a]

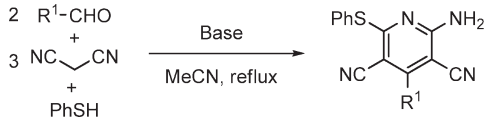
			MeCN		DMSO		EtOH	
catalyst[b]	T[c] (°C)	time (h)	1:2:1	2:3:1	1:2:1	2:3:1	1:2:1	2:3:1
TBAH	rt	6	12	24	7	1	11	18
TBAH	reflux	1	15	76	3	4	6	36
TBAH	reflux	18	24	76	41	40	7	41
[bmIm]OH	rt	6	2	0	1	0	6	1
[bmIm]OH	reflux	1	15	35	15	21	28	47
[bmIm]OH	reflux	18	33	30	31	53	14	49
piperidine	reflux	3	11	42	21	28	1	5
piperidine	reflux	24	37	70	49	62	6	42
column:			**A**	**B**	**C**	**D**	**E**	**F**

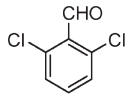
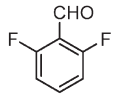
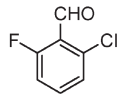
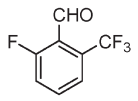
[a] All yields are HPLC yields. [b] TBAH and [bmIm]OH were used at 50 mol %, piperidine at 30 mol %. [c] In DMSO, 90 °C was used, not reflux temperature.

Of the three solvents investigated, formation of the desired product **11** was particularly pronounced in acetonitrile (columns A and B, Table 1) regardless of catalyst, temperature, and reactant ratio, thereby explaining the direct pyridine synthesis in this solvent noted above (Scheme 3).[4] It also indicated that there is a discernible solvent effect on the outcome of the MCR, aside from any differences in solubility. In DMSO (column D) and ethanol (column F), similar yields were observed in the 2:3:1 MCRs, except with piperidine as catalyst where DMSO performed noticeably better. There was hardly any formation of **11** in ethanol with a reactant ratio of 1:2:1 (column E), which explains the previously documented failure of direct synthesis of such products from sterically hindered aldehydes.[9−12]

Of the two ionic catalysts, [bmIm]OH was found to be less effective than TBAH in most cases, perhaps due to the observed instability of the ionic liquid. Dramatic improvement of reaction yield was detected with both ionic catalysts when the reaction was heated—1 h at reflux was sufficient in acetonitrile and ethanol, though optimum conversion required 18 h in DMSO. In ethanol and acetonitrile, the yield was enhanced noticeably by the in situ formation of an extra 1 equiv of the Knoevenagel adduct (2:3:1 reactions), in contrast to only modest improvement detailed earlier for the MCRs derived from unhindered aldehydes (Figure 2); in DMSO, this effect was not as marked, suggesting the Knoevenagel adduct makes a smaller relative contribution to the oxidation step in this solvent. The nonionic, organic base

TABLE 2. Synthesis of Pyridine-3,5-dicarbonitriles from Sterically Hindered Aldehydes



Entry	Aldehyde	Product	Isolated Yield (%) Piperidine (30mol%)	Isolated Yield (%) TBAH (50mol%)
1		**11**	57	67
2		**12**	56	54
3		**13**	48	49
4		**14**	50	40
5		**15**	5	6

piperidine resulted in similar yields to TBAH, although it demanded a longer reaction time (24 h).

The best conditions identified in the above investigation (acetonitrile, 2:3:1, TBAH, 1 h reflux; or acetonitrile, 2:3:1, piperidine, 24 h reflux; Table 1) were then tested further by employing a small set of sterically demanding aldehydes in the MCR (Table 2). Generally, similar isolated yields were obtained using either catalyst. 2,6-Disubstituted benzaldehydes led to the pyridine products **11**−**14** directly in fairly good yields. In contrast, the most hindered aldehyde, trimethylacetaldehyde (entry 5, Table 2), proved very poorly reactive under these conditions, which suggests that there is a sterically controlled limitation to this MCR, as we had suspected. Nonetheless, an improved set of conditions for the reaction, allowing wider tolerance in the range of aldehyde building blocks, had been successfully established.

Mechanistic Studies of the Final Oxidation Step. In order to examine the oxidation step more closely, especially with regard to the effect of different catalysts, a more detailed investigation was carried out. First, to address the extent of 1,4-dihydropyridine oxidation by Knoevenagel adduct **7** in the MCR with an unhindered aldehyde (benzaldehyde), we prepared the reduced form of **7**, benzylmalononitrile (**8**, R^1 = Ph) according to a literature procedure.[13] The previously characterized enaminonitrile side product **9** (R^1 = R^2 = Ph) was also prepared as reported.[10] The relative concentrations of these species, together with pyridine product **1**, were determined by HPLC under different reaction conditions.

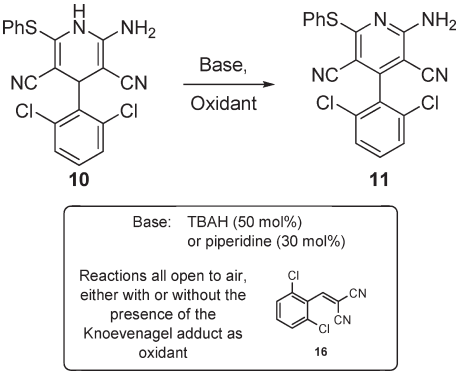
(13) Diez-Barra, E.; de la Hoz, A.; Moreno, A.; Sánchez-Verdú, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2589–2592.

TABLE 3. Investigation of Final Oxidation Stage in the MCR Employing Benzaldehyde

	ratio[a]	catalyst[b]	time (h), T (°C)	product[c] (%) **1**	**8**	**9**
1	1:2:1	piperidine	3, reflux	49	43	5
2	2:3:1	piperidine	3, reflux	91	88	7
3	1:2:1	TBAH	1, rt	46	50	4
4	2:3:1	TBAH	1, rt	6	132	0

[a] Benzaldehyde/malononitrile/thiophenol. [b] 0.3 equiv of piperidine, 0.5 equiv of TBAH. [c] HPLC yields. Reactions were carried out in ethanol.

SCHEME 5. Oxidation of the Hindered 1,4-Dihydropyridine 10



According to Evdokimov's earlier report,[9a] pyridine product **1** and enaminonitrile **9** were detected in a 1:1 ratio using the standard protocol, with an amine catalyst (entry 1, Table 3). However, we found that **1** was formed in an equimolar amount to benzylmalononitrile **8** in this reaction, confirming the suspected role of **7** as major oxidant.[9] Although enaminonitrile **9** was reportedly isolated in a yield of 34%,[9a] only a small amount of this structure was observed by HPLC in the present study. Compound **9** was isolated from the reaction mixture to confirm its identity and obtained as a mixture of regioisomers in only 5% yield. When TBAH was employed in place of piperidine, similar results were obtained in the 1:2:1 reaction, but the 2:3:1 case proved markedly different, with only a 6% yield of product detected. The large amount of benzylmalononitrile **8** seen in this reaction mixture was difficult to rationalize, though a significant quantity of **7** was also present, indicating that under these conditions (2:3:1 with TBAH catalysis; entry 4), the reaction had largely been arrested at the Knoevenagel adduct stage.

In order to further aid our understanding of the oxidation step, a sample of the stable, hindered 1,4-dihydropyridine **10** was synthesized using the standard protocol in ethanol (Scheme 1). Its conversion into **11** was monitored directly by HPLC, either with or without the presence of related Knoevenagel adduct **16** and with either TBAH or piperidine as catalyst (Scheme 5). These procedures were all carried out at reflux and left open to the air; the reactions were studied initially in acetonitrile since this solvent is the most amenable to oxidation of **10**. Results in the presence of **16** were assumed to represent the sum of contributions to the oxidation from both air and the Knoevenagel adduct; without **16** present, only aerobic oxidation could occur. Thus, the extent of oxidation mediated by the Knoevenagel adduct was

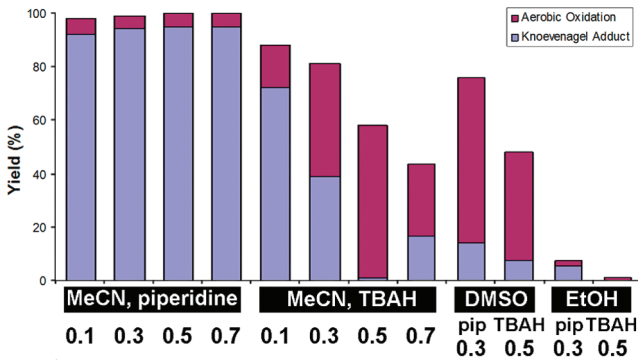


FIGURE 3. Contributions to oxidation of the sterically hindered 1,4-dihydropyridine **10**.

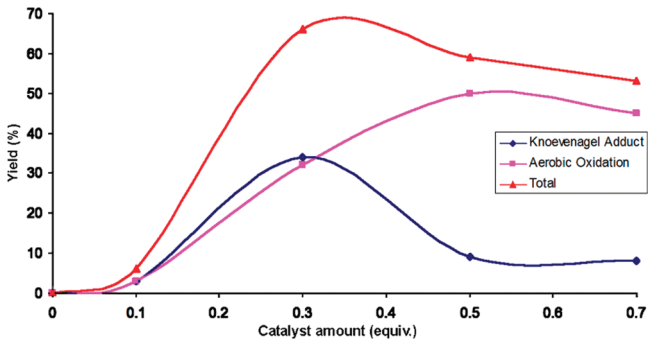


FIGURE 4. MCR from sterically hindered aldehyde with various amounts of TBAH catalyst.

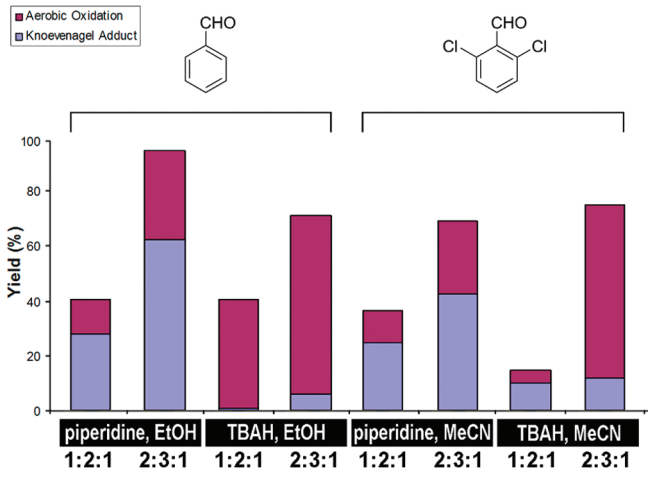


FIGURE 5. Distribution of relative contribution from Knoevenagel adduct and aerobic oxygen to the final oxidation stage of the MCR.

estimated from the difference of the two yields, under each set of conditions studied (Figure 3).

Under piperidine catalysis, oxidation mediated by Knoevenagel adduct **16** clearly played the major role, with the amount of catalyst making a negligible difference to the outcome (Figure 3). In contrast, where TBAH was used to promote the reaction, aerobic oxidation made a significant contribution, particularly with larger amounts of catalyst where it is the major pathway, although overall yield decreased in line with findings described earlier (Figure 2). Thus, the nature of the base catalyst employed dictates the major pathway followed during the final oxidation step. Piperidine led to more effective conversions in acetonitrile but the difference was less pronounced in other solvents. High conversions were observed in DMSO regardless of catalyst, with aerobic oxidation making the major contribution in both cases, and suggesting the solubility of oxygen and/or **10** might be a factor in the oxidation stage of the MCR. Confirming our findings from earlier optimization of the MCR, ethanol was proven to be the poorest solvent for the oxidation process.

Whereas the Knoevenagel adduct intermediate was unequivocally the major oxidant in the presence of piperidine, the ionic catalyst TBAH showed much more variation in results as the amount of base was increased. To further probe the selectivity of oxidant in the presence of this catalyst, the MCR utilizing 2,6-dichlorobenzaldehyde was carried out with varying amounts of TBAH (Figure 4). A 2:3:1 ratio of aldehyde, malononitrile, and thiophenol was reacted in acetonitrile under the optimized conditions. Similarly to the individual oxidation reaction (Scheme 5), the relative contribution from the Knoevenagel adduct varied and dropped sharply above 30 mol % of TBAH. As is evident, aerobic oxidation played the major role in the oxidation step above this amount; and as observed in the related MCR with benzaldehyde, TBAH was most effective—in terms of total yield—over an optimal range of 30−50 mol %.

Finally, we carried out a set of MCRs both open to air and under N_2, in order to deduce the relative contribution of each oxidation pathway to the total yield of the reaction. The contribution of aerobic oxidation was considered to be the difference in yields of equivalent reactions with either inclusion of exclusion of air. MCRs were carried out with benzaldehyde in ethanol, and with 2,6-dichlorobenzaldehyde in acetonitrile, and the effects of catalyst, solvent, and reactant ratio were assessed.

In ethanol with piperidine as catalyst (the "standard protocol"), the yield was only suppressed by about one-third when anaerobic conditions were employed (columns I and II, Figure 5). However, with TBAH as catalyst (columns III and IV), there was almost no product formed with exclusion of oxygen, even in the case of a 2:3:1 combination of reagents. These results provide further support for observations above (Figure 4), wherein the stronger ionic base was found to promote aerobic oxidation and suppress the alternate, Knoevenagel adduct-mediated pathway. Similar results were found in the MCRs carried out in acetonitrile (columns V−VIII, Figure 5), except for the 1:2:1 case catalyzed by TBAH where a very low yield was obtained, mostly from oxidation via the Knoevenagel adduct.

Conclusions

Two different types of base (ionic base and amine base) as catalyst for the MCR were investigated. With typical, reactive aldehydes, the established procedure using an amine base in ethanol was found to be more effective, though ionic base catalysis resulted in comparable yields in a shorter time when acetonitrile was used as solvent. The first direct MCR synthesis of pyridine-3,5-dicarbonitriles from sterically hindered aldehyde building blocks has been achieved by changing the solvent from ethanol to acetonitrile. Solvent

was found to have a significant influence on the outcome of the reaction.

Mechanistically, the two types of catalyst were proven to show a different selectivity of oxidant in the final step of the MCR, oxidation of the penultimate 1,4-dihydropyridine product **6** (Scheme 1). The ionic base strongly promoted aerobic oxidation above 30 mol %, whereas below this quantity the two possible pathways made a similar contribution. In contrast, the dominant oxidation process under amine base catalysis was net transfer of H_2 to the Knoevenagel adduct **7** present as a reaction intermediate. In support of this mechanism, the reduced benzylmalononitrile byproduct **8** was detected in similar yield to the desired pyridine compound **1** at the end of the MCR.

Experimental Section

HPLC Conditions. Method A . Ace 3 μm C18 column, 12.5 × 4.6 cm; 40−70% MeOH in water over 10 min, then 70−90% MeOH in water over 3 min, hold 2 min; flow rate 1.0 mL/min; 5 μL injection; UV detection at 254 nm.

Method B . Ace 3 μm C18 column, 12.5 × 4.6 cm; 70% MeOH in water over 7 min; flow rate 1.0 mL/min; 5 μL injection; UV detection at 254 nm.

Method C . Alltima HP C18 3 μm column, 15 × 4.6 cm; 40−70% MeCN in water over 20 min; 70−90% MeCN in water over 5 min; flow rate 1.0 mL/min; 20 μL injection; UV detection at 254 nm.

Investigation of Catalyst Amount on Outcome of Model Reaction (Figure 2). Malononitrile (38.2 μL, 0.6 mmol for 1:2:1; 57.3 μL, 0.9 mmol for 2:3:1) and thiophenol (31.3 μL, 0.3 mmol) were added to a solution of benzaldehyde (30.3 μL, 0.3 mmol for 1:2:1; 60.6 μL, 0.6 mmol for 2:3:1) in ethanol (0.5 mL), followed by the relevant amount of the appropriate catalyst (as detailed in Figure 2). After addition, the volume of the reaction mixture was adjusted to 1000 μL with ethanol, and the mixture was either stirred at rt or heated to reflux, as necessary. Reactions catalyzed by TBAH or [bmIm]OH were carried out for 1 h, while 3 h was employed with piperidine as catalyst. After reaction, MeCN (1000 μL) was added resulting in a clear solution. For reactions **a1**, **a2**, and **c2**, a 10 μL aliquot of the reaction mixture was added to 990 μL of MeCN to provide solutions for HPLC analysis (method C). For reactions **b1**, **b2**, and **b3**, a 10 μL aliquot of the reaction mixture was added to 5990 μL of MeCN to provide solutions for HPLC analyis (method C). For reactions **b4**, **c1**, and **c3**, a 10 μL aliquot of the reaction mixture was added to 990 μL of MeCN to provide solutions for HPLC analysis (method A). For reactions **c4**, a 10 μL aliquot of the reaction mixture was added to 1140 μL of MeCN to provide solutions for HPLC analysis (method A).

Optimization of Reaction Conditions for the MCR from Sterically Hindered Aldehydes (Table 1). The model reaction was carried out between 2,6-dichlorobenzaldehyde (53.0 mg, 0.3 mmol for 1:2:1; 106.0 mg, 0.6 mmol for 2:3:1), malononitrile (38.2 μL, 0.6 mmol for 1:2:1; 57.3 μL, 0.9 mmol for 2:3:1), and thiophenol (31.3 μL, 0.3 mmol) with related catalyst (50 mol % for TBAH and [bmIm]OH; 30 mol % for piperidine) in the relevant solvent (with the reaction mixture adjusted to 1000 μL in each case). The mixture was stirred at either rt, reflux (MeCN and EtOH), or 90 °C (DMSO) for the time displayed in Table 2. After reaction, DMSO (1000 μL) was added to provide a clear solution. An aliquot of this solution was diluted in MeCN for HPLC analysis. Details of dilution ratio and HPLC methods used in each case are listed in the Supporting Information.

General Procedure for the Preparation of Compounds 11−15 (Table 2). Malononitrile (3 mmol) and thiophenol (1 mmol) were added to a solution of aldehyde (2 mmol) in acetonitrile (5 mL). The catalyst—either piperidine (0.3 mmol) or TBAH (40% w/v aq solution, 0.5 mmol)—was then added. The reaction mixture was refluxed for the appropriate time (24 h with piperidine catalysis, or 1 h with TBAH), after which time it was cooled then the solvent evaporated. The crude mixture was purified by flash column chromatography (FC) on silica gel, as indicated.

2-Amino-4-(2,6-dichlorophenyl)-6-phenylsulfanylpyridine-3,5-dicarbonitrile (11). The crude product was purified by FC in ethyl acetate−hexane (1:5): yield 57% with piperidine and 67% with TBAH; yellow powder; mp 182−183 °C; ν_{max} (solid)/cm^{-1} 3330.0, 3222.8, 2946.0, 2851.4, 2218.3, 1999.8, 1953.4, 1639.6, 1613.8, 1548.8, 1530.1, 1470.6, 1444.1, 1426.5, 1396.9, 1367.8, 1317.8, 1284.3, 1256.3, 1190.7, 1150.4, 1126.5, 1076.5, 1018.7, 927.9; δ_H/ppm (250 MHz, $CDCl_3$) 5.54 (2H, br s), 7.44−7.59 (8H, m); δ_C/ppm (62.8 MHz, $CDCl_3$) 88.4, 96.7, 113.5, 113.9, 126.8, 128.7, 129.4, 130.1, 131.5, 132.1, 133.7, 135.8, 154.2, 159.0, 168.9; *m*/*z* (ES+), 397 ([M + H]$^+$); HRMS observed 397.0094 (required for $C_{19}H_{11}SN_4Cl_2$ [M + H]$^+$ 397.0081).

2-Amino-4-(2,6-difluorophenyl)-6-phenylsulfanylpyridine-3,5-dicarbonitrile (12). The crude product was purified by FC in ethyl acetate−hexane (1:5): yield 56% with piperidine and 54% with TBAH; yellow powder; mp 172−173 °C; ν_{max} (solid)/cm^{-1} 3360.2, 2209.5, 2168.6, 1637.4, 1620.7, 1591.4, 1485.8, 1469.1, 1391.8, 1247.0, 1230.6, 994.9, 813.6; δ_H/ppm (250 MHz, DMSO-d_6) 7.40−7.82 (8H, m), 8.09 (2H, br s); δ_C/ppm (62.8 MHz, DMSO-d_6) 88.6, 94.4, 111.1 (t, J = 19.5), 113.0 (dd, J = 2.0, 21.5), 114.5, 114.8, 127.1, 130.0, 130.4, 134.6 (t, J = 10.0), 135.4, 147.8, 158.9 (dd, J = 6.0, 250), 159.9, 167.1; *m*/*z* (ES+), 365 ([M + H]$^+$); HRMS obsd 365.0679 (required for $C_{19}H_{11}SN_4F_2$ [M + H]$^+$ 365.0672).

2-Amino-4-(2-chloro-6-fluorophenyl)-6-phenylsulfanylpyridine-3,5-dicarbonitrile (13). The crude product was purified by FC in ethyl acetate−hexane (1:5): yield 48% with piperidine and 49% with TBAH; yellow powder; mp 175−176 °C; ν_{max} (solid)/cm^{-1} 3464.2, 3330.6, 3214.0, 2216.8, 1610.3, 1548.5, 1527.7, 1474.5, 1447.9, 1403.9, 1311.9, 1251.1, 1021.5, 902.2; δ_H/ppm (250 MHz, $CDCl_3$) 5.52 (2H, br s), 7.29−7.69 (8H, m); δ_C/ppm (62.8 MHz, $CDCl_3$) 89.3, 97.5, 114.3 (d, J = 34.5), 115.4 (d, J = 21.5), 121.5 (d, J=19.0), 126.6 (d, J = 3.0), 127.2, 129.9, 130.6, 133.2 (d, J = 9.5), 133.7, 134.0, 136.2, 151.1, 159.4, 159.7 (d, J = 252), 169.3; *m*/*z* (ES+), 381 ([M + H]$^+$); HRMS obsd 381.0388 (required for $C_{19}H_{11}SN_4ClF$ [M + H]$^+$ 381.0377).

2-Amino-4-(2-fluoro-6-(trifluoromethyl)phenyl)-6-phenylsulfanylpyridine-3,5-dicarbonitrile (14). The crude product was purified by FC in ethyl acetate−hexane (1:5): yield 50% with piperidine and 40% with TBAH; yellow powder; mp 192−193 °C; ν_{max} (solid)/cm^{-1} 3492.1, 3338.6, 3224.2, 2215.9, 1630.7, 1603.7, 1554.7, 1528.3, 1504.4, 1474.2, 1421.7, 1317.8, 1260.1, 1229.8, 1156.4, 1022.1; δ_H/ppm (250 MHz, DMSO-d_6) 6.40 (2H, br s), 7.45−7.96 (8H, m); δ_C/ppm (100 MHz, DMSO-d_6) 89.2, 97.6, 113.4, 113.7, 120.3 (d, J = 21.5), 122.5 (dq, J=3.0, 275), 122.7−123.0 (m), 126.7, 129.4, 130.2, 132.8 (d, J=9.0), 135.8, 150.4, 158.6, 158.9 (d, J = 250), 168.6; *m*/*z* (ES+), 415 ([M + H]$^+$); HRMS obsd 415.0645 (required for $C_{20}H_{11}SN_4F_2$ [M + H]$^+$ 415.0641).

2-Amino-4-*tert*-butyl-6-phenylsulfanylpyridine-3,5-dicarbonitrile (15). The crude product was purified by FC in CH_2Cl_2−ethyl acetate−hexane (2:1:2): yield 5% with piperidine and 6% with TBAH; yellow powder; mp 145−146 °C; ν_{max} (solid)/cm^{-1} 3428.8, 3333.9, 3218.0, 2981.2, 2200.3, 1624.2, 1534.9, 1503.2, 1475.4, 1440.2, 1384.8, 1370.2, 1304.0, 1244.1, 1169.9, 1125.7; δ_H/ppm (250 MHz, DMSO-d_6) 1.60 (9H, s), 3.97 (2H, br s), 7.30−7.62 (5H, m); δ_C/ppm (62.8 MHz, DMSO-d_6) 29.9, 85.4, 91.8, 117.0, 117.3, 125.4, 127.4, 127.6, 129.3, 129.6, 135.0, 161.0, 166.5, 168.5; *m*/*z* (ES+), 309 ([M + H]$^+$); HRMS obsd 309.1162 (requires for $C_{17}H_{17}SN_4$ [M + H]$^+$ 309.1174).

Investigation of Final Oxidation Stage of the MCR Employing Benzaldehyde (Table 3). To a solution of benzaldehyde (30.3 μL,

0.3 mmol for entries 1 and 3; 60.6 μL, 0.6 mmol for entries 2 and 4) in ethanol (0.5 mL) were added malononitrile (38.2 μL, 0.6 mmol for entries 1 and 3; 57.3 μL, 0.9 mmol for entries 2 and 4), thiophenol (31.3 μL, 0.3 mmol), and catalyst (0.09 mmol of piperidine for entries 1 and 2; 0.15 mmol of 40% w/v aq TBAH for entries 3 and 4). The volume of the reaction mixture was adjusted to 1000 μL with ethanol. Reactions catalyzed by piperidine were refluxed for 3 h, whereas those catalyzed by TBAH were stirred at rt for 1 h. After reaction, MeCN (1000 μL) was added to obtain a clear solution. For entries 1 and 2, a 10 μL aliquot of the reaction mixture was added to MeCN (990 μL) to provide solutions for HPLC analysis (Method A). For entries 3 and 4, a 5 μL aliquot of the reaction mixture was added to MeCN (995 μL) to provide solutions for HPLC analysis (Method A).

Contribution to Oxidation of the Sterically Hindered 1,4-Dihydropyridine 10 (Figure 3). In the first set of reactions, compound **10** (39.9 mg, 0.1 mmol), the catalyst (as displayed in Figure 3), and **16** (23.3 mg, 0.1 mmol) were combined in the relevant solvent (1 mL). Reactions in ethanol and MeCN were heated to reflux, and reactions in DMSO were heated at 90 °C. The reaction time was 6 h in all cases. A second set of reactions were carried out with the omission of compound **16**. In all cases, MeCN (1000 μL) was added at the end of the reaction, and then a 25 μL aliquot of the resultant clear solution was added to MeCN (975 μL) to provide solutions for HPLC analysis (method B). Results from the first set represent the contribution from both aerobic oxygen and Knoevenagel adduct, while the second set represents the contribution from oxygen only. Therefore, for each set of reactions, the contribution to oxidation from the Knoevenagel adduct could be calculated.

MCR from Sterically Hindered Aldehyde with Varying Amounts of TBAH Catalyst (Figure 4). In the first set of MCRs, 2,6-dichlorobenzaldehyde (106.0 mg, 0.6 mmol), malononitrile (57.3 μL, 0.9 mmol), and thiophenol (31.3 μL, 0.3 mmol) were combined in MeCN (0.5 mL). TBAH (40% w/v aq solution) was added in various amounts (as shown in Figure 4) and the reaction mixture adjusted to 1000 μL with MeCN. After the mixture was refluxed for 1 h and cooled to rt, a 30 μL aliquot of the solution was added to MeCN (970 μL) to provide solutions for HPLC analysis (method A). This set of MCRs was repeated under a N_2 atmosphere in degassed solvent, and after these reactions, a 10 μL aliquot of the final reaction mixture was added to MeCN (990 μL) to provide solutions for HPLC analysis (method A).

Distribution of Contribution from Knoevenagel Adduct and Oxygen to the Final Oxidation Step of the MCR (Figure 5). Benzaldehyde or 2,6-dichlorobenzaldehyde (0.3 or 0.6 mmol), malononitrile (0.6 or 0.9 mmol), and thiophenol (0.3 mmol) were reacted in ethanol (1 mL) or acetonitrile (1 mL) in the combinations detailed in Figure 5 and in the presence of the catalyst shown (piperidine or TBAH). With piperidine (30 mol %) as catalyst, the MCR was refluxed for 3 h (EtOH) or 24 h (MeCN). With TBAH (40% w/v aq solution, 50 mol % for 1:2:1 case; 30 mol % for 2:3:1) as catalyst, the MCR was refluxed for 1 h in all cases. Two sets of reactions were performed: one open to the air and one in degassed solvent under an N_2 atmosphere. For each pair of experiments, the yield of the reaction open to air was assumed to represent the sum of contributions from aerobic oxidation and Knoevenagel adduct-mediated oxidation; the yield of the reaction with exclusion of air was taken to represent the contribution of Knoevenagel adduct mediated oxidation alone. For all reaction mixtures, MeCN (degassed, 1000 μL) was added, and a 4 μL aliquot then added to MeCN (996 μL) to provide solutions for HPLC analysis (method A). Data for MCRs open to air were obtained from Figure 2 (reactions derived from benzaldehyde) or Table 1 (2,6-dichlorobenzaldehyde as building block).

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Supporting Information Available: Synthesis of compounds **1**, **7**−**10**, and **16**; spectral characterization for all compounds (**1**, **8**, and **9**, where R^1, R^2 = Ph; **10**−**16**); extended information on the preparation of the ionic liquid [bmIm]OH; HPLC details for Table 1; and representative HPLC traces indicating selected key findings. This material is available free of charge via the Internet at http://pubs.acs.org.