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Air-oxidized products of multi-component reactions between 3-amino-1,2,4-triazole, aromatic aldehydes and isonitriles

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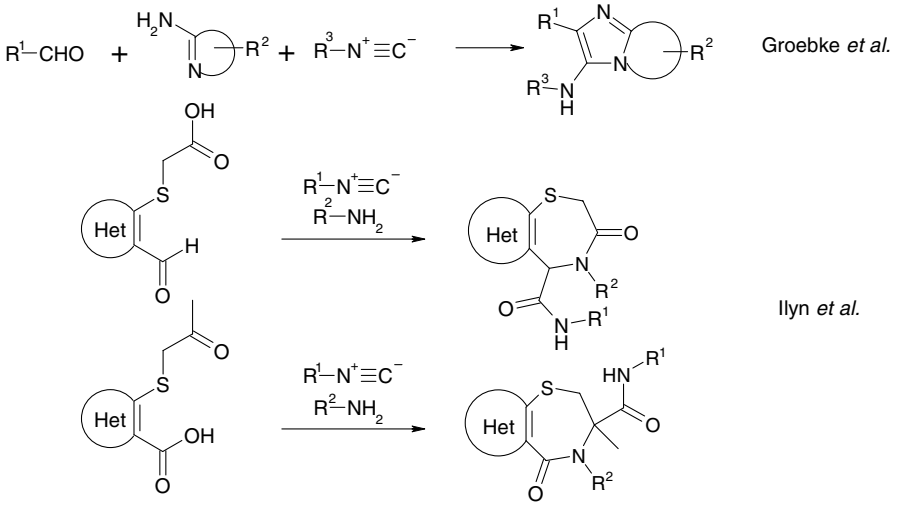
Abstract—The Groebke-type multi-component reaction (MCR) between 3-amino-1,2,4-triazole, aromatic aldehydes and isonitriles has been studied from the viewpoint of convenient generation of combinatorial arrays of imidazo[1,2-*b*][1,2,4]triazoles. However, it was established that the desired heterocyclic structures can be produced in moderate to good yields in an oxidized form, when benzylic isonitriles are used. Oxidation occurred at the benzylic position to produce *N*-alkylidene-4*H*-imidazo[1,2-*b*][1,2,4]triazol-6-amines that proved to be unusually stable towards acid hydrolysis and reduction. The presence of an easily oxidized benzylic position in the target structures is thought to be the prerequisite for successful Groebke-type MCR of 3-amino-1,2,4-triazole.

Continued interest in Ugi multi-component reactions[1] is driven partly by the emergence of elegant intramolecular versions of this four-component process in which two reacting entities are incorporated into one reactant molecule. The Groebke reaction of 2-aminoazines and azoles[2,3] as well as the annelation reactions of a number of heterocycle-containing aldehydo- and keto acids recently reported by us[4] (Scheme 1) are notable examples



Scheme 1. Examples of intramolecular multi-component reactions.

Keywords: Combinatorial chemistry; Intramolecular Ugi reaction; Air oxidation; Imidazo[1,2-*b*][1,2,4]triazoles.
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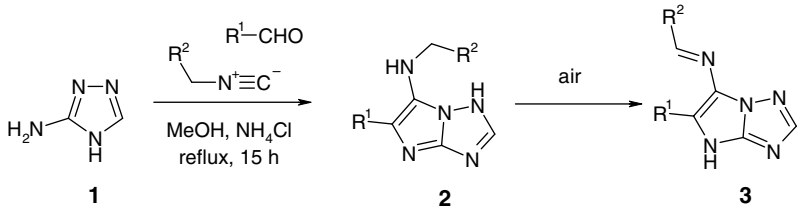


Scheme 2. MCR between 3-amino-1,2,4-triazoles, aldehydes and aliphatic isonitriles studied in this work.

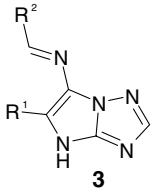
of the complexity-generating power of intramolecular MCRs offering convenient access to a wide variety of novel molecular scaffolds.

Despite the high promise Groebke-type reactions hold for compound library production, there have not been many reports on combinatorial development of these processes, most likely due to the fact that individual synthetic protocols often suffer from low yields of the target compounds and/or provide an opportunity for unwanted side-reactions to occur.[5] Recently, we reported the results of our studies on the optimization of an MCR protocol for 2-aminopyrimidine condensation with aldehydes and isonitriles.[6] Our further efforts have been devoted to developing a similar reaction of 3-amino-1,2,4-triazole **1** (one example of which was reported to produce the expected imidazo[1,2-*b*][1,2,4]triazoles **2**,[3] Scheme 2) into a reliable process that would enable the production of compound arrays in a combinatorial fashion. Herein, we present the results of these studies.

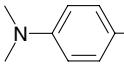
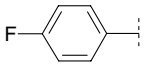
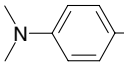
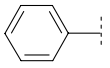
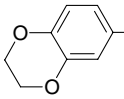
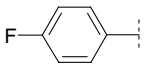
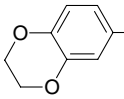
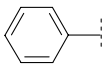
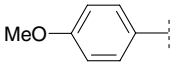
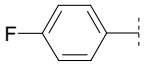
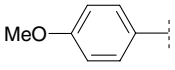
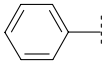
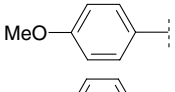
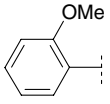
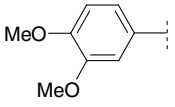
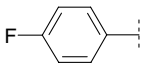
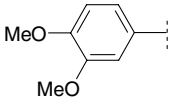
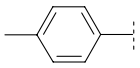
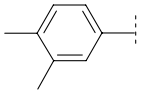
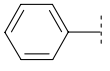
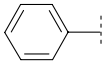
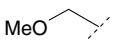
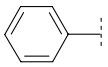
A number of aliphatic isonitriles chosen for our optimization studies were combined in methanol with 3-amino-1,2,4-triazole and a variety of substituted benzaldehydes (Table 1) and heated at reflux for 15 h in the presence of solid ammonium chloride (the mildly acidic catalyst often employed to catalyze the Ugi MCR[6,7]). At the end of that period, LC MS analysis of the cooled reaction mixture indicated complete disappearance of the starting materials. However while for simple aliphatic isonitriles (such as isobutyl and 2-(methoxy)ethyl) the product mixture was complex and did not allow isolation of the pure imidazo[1,2-*b*][1,2,4]triazoles **2** in appreciable yield, for benzylic isonitriles, the reaction mixture consisted mostly of a product with an *m*/*z* value lacking two mass units compared to the anticipated imidazo[1,2-*b*][1,2,4]triazoles **2**[8] and presumably resulting from oxidation of the latter (the 'M-2' product). The methanolic solutions were diluted with water and the resulting precipitates were collected by filtration[9] and air dried. Crystallization from methanol provided analytically pure compounds in moderate to good yields (Table 1).

It was natural to expect the conversion of the initially formed **2** into the 'M-2' product via oxidative removal of the two nitrogen-bound hydrogen atoms. However, when the isolated products were analyzed by ^{1}H and ^{13}C NMR, their identity was established as *N*-alkylidene-4*H*-imidazo[1,2-*b*][1,2,4]triazol-6-amines **3**,[10] obviously resulting from oxidation at the benzylic C–H bond (Scheme 2). Additional evidence came from sin-

Table 1. *N*-alkylidene-4*H*-imidazo[1,2-*b*][1,2,4]triazol-6-amines **3** prepared in this study



3

Compound	R^1	R^2	Yield (%)
3a			54
3b			32
3c			46
3d			46
3e			50
3f			52
3g			48
3h			48
3i			62
3j			38
3k			0[a]
3l			0[a]

[a] No oxidized imidazo[1,2-*b*][1,2,4]triazol-6-amine **3** was detected in the reaction mixture by LC MS analysis. The nonoxidized product **2** was present as a minor component of a complex mixture of products.

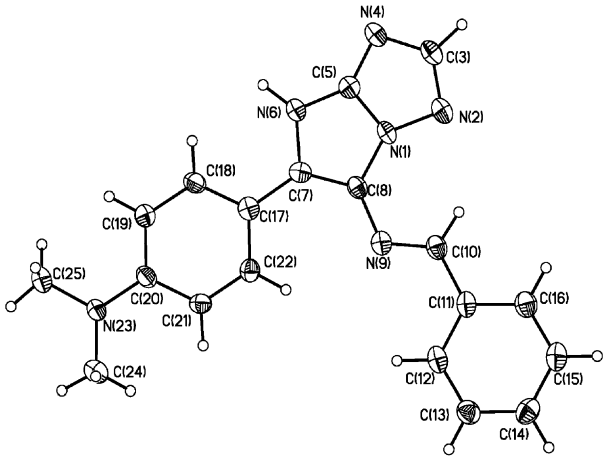


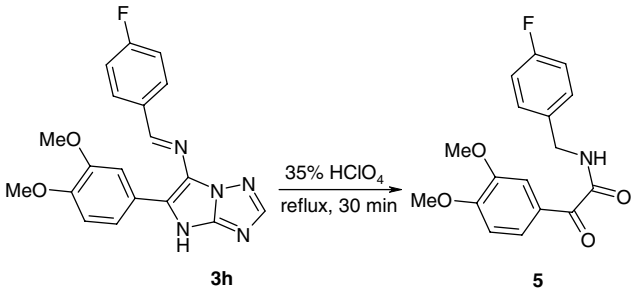
Figure 1. X-ray structure of compound **3b**.

gle-crystal X-ray analysis of a representative compound (**3b**, Fig. 1).[11]

Compounds **3** represent an unusual case of stable and chemically robust imines: attempted hydrolysis (1:1 aq HCl, reflux, 18 h) or reduction ($NaBH_4$, MeOH, rt, 18 h) resulted in the formation of only small amounts of background decomposition products. Treatment of a representative compound (**3h**) with stronger acid (35% $HClO_4$, reflux, 30 min) resulted in complete decomposition of the imidazo[1,2-*b*][1,2,4]triazole nucleus and quantitative conversion to ketoamide **5** (Scheme 3).

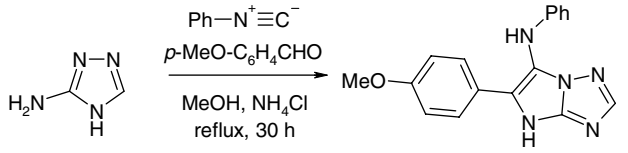
Based on these results, we reason that the use of benzylic isonitriles is the prerequisite for successful Groebke-type MCR of 3-amino-1,2,4-triazoles, in which case further oxidation at the benzylic position promotes efficient product formation. Therefore, the use of simple aliphatic isonitriles (vide supra) that lack such a position did not lead to appreciable formation of the MCR products. Likewise, when phenylisonitrile was used in several control runs of the same process, the respective (nonoxidized) imidazo[1,2-*b*][1,2,4]triazole **6**[12] was isolated consistently in low yield (7–10%, Scheme 4).

In conclusion, we have demonstrated that the MCR between 3-amino-1,2,4-triazole, aromatic aldehydes and isonitriles was efficient when benzylic type isonitriles



3h **5**

Scheme 3. Hydrolysis of representative *N*-alkylidene-4*H*-imidazo[1,2-*b*]-[1,2,4]triazol-6-amine **3h**.



1 **6**, 7-10%

Scheme 4. Aromatic isonitrile usage in the MCR under investigation.

were used and permitted air-oxidation of the initial MCR products into *N*-alkylidene-4*H*-imidazo[1,2-*b*]-[1,2,4]triazol-6-amines.

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8. The nonoxidized imidazo[1,2-*b*][1,2,4]triazoles **2** were sometimes present in the reaction mixtures and disappeared after prolonged exposure of the methanolic solutions to ambient atmosphere, as indicated by repeated LC MS analysis.
9. Additional extraction of the MeOH–water phase with ethyl acetate was required in some cases.
10. Analytical data for selected compounds: Compound **3b**—yellow solid, mp = 144–146 °C (dec); ^{1}H NMR (300 MHz, d_6-DMSO, 25 °C): δ 12.43 (br s, 1H, imidazole–N*H*), 9.43 (s, 1H, N=C*H*–Ph), 8.00 (br s, two signals overlapped, including N=C*H*–N, 3H), 7.92 (d, $J = 5.8$ Hz, 2H), 7.51 (m, 2H), 6.87 (d, $J = 7.9$ Hz, 2H), 3.00 (s, 6H, N(CH_3)$_2$); ^{13}C NMR (75 MHz, d_6-DMSO): δ 153.6, 152.5, 150.0, 148.8, 136.9, 130.5, 128.9, 128.0, 127.6, 127.5, 122.1, 116.6, 112.0, 39.8 (obscured by the DMSO signal); LCMS *m*/*z* 331 (M+1); HRMS *m*/*z* (EI) found: 330.3950; $C_{19}H_{18}N_6$ requires 330.3955. Compound **3h**—beige solid, mp = 132–134 °C; ^{1}H NMR (300 MHz, d_6-DMSO, 25 °C): δ 12.70 (br s, 1H, imidazole–N*H*), 9.44 (s, 1H, N=C*H*–Ar), 8.06 (s, 1H, N=C*H*–N), 7.99 (dd, $^3J_{H-H} = 8.6$ Hz, $^4J_{C-F} = 5.8$ Hz, 2H), 7.81 (unresolved d, 1H), 7.71 (unresolved dd, $J = 8.5$ Hz, 1H), 7.36 (dd, $^3J_{H-H} = 8.6$ Hz, $^3J_{C-F} = 8.9$ Hz, 2H), 7.14 (d, $J = 8.5$ Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 154.0, 152.8, 149.0, 148.8, 148.7, 133.4, 130.0, 129.9, 122.9, 121.9, 119.8, 116.3, 116.0, 112.0, 110.5, 55.6, 55.5; LCMS *m*/*z* 366 (M+1); HRMS *m*/*z* (EI) found: 365.3704; $C_{19}H_{16}FN_5O_2$ requires 365.3701. Compound **3i**—yellow solid, mp = 156–158 °C (dec); ^{1}H NMR (300 MHz, d_6-DMSO, 25 °C): δ 12.69 (br s, 1H, imidazole–N*H*), 9.41 (s, 1H, N=C*H*–Ar), 8.04 (s, 1H, N=C*H*–N), 7.87 (s, 1H), 7.81 (d, $J = 7.5$ Hz, 2H),

7.70 (d, $J = 8.1$ Hz, 1H), 7.30 (d, $J = 7.5$ Hz, 2H), 7.11 (d, $J = 8.1$ Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 154.0, 153.9, 148.9, 148.8, 148.7, 141.0, 134.1, 129.6, 127.7, 125.8, 123.1, 122.0, 119.6, 111.9, 110.5, 55.6, 55.4, 21.1; LCMS m/z 362 (M+1); HRMS m/z (EI) found: 361.4070; $C_{20}H_{19}N_5O_2$ requires 361.4067.

11. Crystallographic data (excluding structure factors) for structure **3b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 614188. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk].
12. Analytical data for **6**: off-white solid, mp = 125–127 °C; ^{1}H NMR (300 MHz, d_6-DMSO, 25 °C): δ 12.26 (br s, 1H, imidazole–N*H*), 8.13 (s, 1H, N=C*H*–N), 7.84 (s, 1H, PhN*H*), 7.69 (d, $J = 8.6$ Hz, 2H), 7.13 (t, $J = 7.9$ Hz, 2H), 7.00 (d, $J = 8.6$ Hz, 2H), 6.71 (t, $J = 7.2$ Hz, 1H), 6.61 (d, $J = 7.9$ Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 158.9, 153.2, 148.2, 145.8, 129.2, 127.1, 124.8, 121.7, 118.5, 114.4, 114.3, 113.3, 55.2; LCMS m/z 306 (M+1); HRMS m/z (EI) found: 305.3422; $C_{17}H_{15}N_5O$ requires 305.3420.