Towards molecular diversity: dealkylation of *tert*-butyl amine in Ugi-type multicomponent reaction product establishes *tert*-butyl isocyanide as a useful convertible isonitrile†

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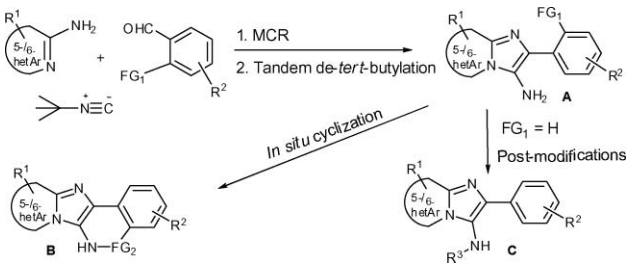
With the development of a novel microwave-assisted one-pot tandem de-*tert*-butylation of *tert*-butyl amine in an Ugi-type multicomponent reaction product, *tert*-butyl isocyanide as a useful convertible isonitrile has been explored for the first time affording access to molecular diversity of pharmaceutically-important polycyclic N-fused imidazo-heterocycles.

The preparation of chemical libraries is an essential prerequisite for lead discovery, lead optimization, and targeted drug design. The class of multicomponent reactions (MCRs),[1] especially isocyanide-based, is an excellent tool for the generation of chemical libraries. However, the diversity of products from iscocyanide-based MCRs is restricted by the limited availability and synthetic-troublesomeness of isocyanides. The use of convertible isocyanides,[2] an excellent concept introduced by Armstrong, and its combination with UDC (Ugi/De-BOC/Cyclize) strategy[3] affords rapid access *via* the Ugi product to a large library with scaffold- and functionality-diversities. This approach has thus gained immense importance in the generation of molecular diversity and therapeutic agents.[4] The problematic removal of alkyl amine (or aryl amine) derived from the isocyanide component in the Ugi-MCR product, which is crucial for *in situ* cyclization or functionality-interconversion, has led to the development of several convertible isonitriles.[2c–h] Recently, an Ugi-type multicomponent reaction (also referred to as Groebke–Blackburn or Groebke–Blackburn–Bienaymé reaction) has exhibited its potential in the preparation of therapeutically-relevant N-fused imidazoles.[5,6] To offer a convertible isocyanide in this Ugi-type MCR, the dealkylation of the derived alkyl amine in the MCR product was found to be critical. It requires a particular alkyl group in the isonitrile component, which in post-MCR protonolytic dealkylation can generate a highly stable carbocation such as isooctyl in the case of 1,1,3,3-tetramethylbutyl isocyanide (Walborsky reagent). It is also necessary to use the dealkylating agent in a large excess or as solvent.[5g,7] Besides, 1,1,3,3-tetramethylbutyl isocyanide is expensive and thus not applicable to bulk- and solid-phase library-synthesis. The use of *tert*-butyl isocyanide, which is economical, commercially available, stable and storable, as a convertible isonitrile has been attempted.[7a,8] But, the de-*tert*-butylation of the *tert*-butyl amine-containing MCR product was found to be ineffective in methods mediated by various Brønsted acids such as HCl, AcOH, conc. HCl and H_2SO_4. The reaction under reflux in neat TFA is complicated by uncontrollable over-trifluoroacetylation of primary amine, and thus requires stringent alkaline hydrolysis in the subsequent step. Furthermore, the reaction sequence is not suitable for the *in situ* generation of molecular diversity. The over-trifluoroacetylation of the derived amine in de-*tert*-butylation can be avoided only by its internal trapping with tethered electrophile.[9] To the best of our knowledge, there is no report of de-*tert*-butylation which does not require internal trapping, is one-step and amenable to access to molecular diversity. We present herein the development of a novel tandem one-step dealkylation of derived *tert*-butyl amine in an Ugi-type MCR product (Scheme 1). This has established first time *tert*-butyl isocyanide as a useful convertible isonitrile affording one-pot preparation of therapeutically-relevant diverse polycyclic N-fused heterocycles including N-fused imidazole-amines (**A**) and tetracyclic heterocycles (**B**). The diversity of compounds **A** has been found to be extendable *via* various post-modifications at the primary amino group into their derivatives (**C**).



Scheme 1 Development of tandem de-*tert*-butylation in MCR product affording *tert*-butyl isocyanide as a useful converting isonitrile towards the preparation of diverse N-fused imidazoles (**A**, **B** and **C**).

Recently, we have developed efficient methods of Groebke–Blackburn MCR catalyzed by $ZrCl_4$ for the synthesis of N-fused imidazoles.[5d,e] Our initial investigations centered on developing a tandem one-step dealkylation of the derived *tert*-butyl amine in the MCR product formed by this reaction using *tert*-butyl isocyanide. We envisioned that for Brønsted acid-mediated protonolytic elimination of imidazole-amine, controlling parameters might be the pK_a of acid (HX), size of anion (X^-), using a solvent capable of transient stabilizing ion pair [^{t}Bu$^+$ X^-], and the availability of sufficient activation energy. With this thought, a systematic screening of acids, solvents and reaction conditions was carried out. The results are summarized in Table 1. HBF_4 in microwave irradiation was found to be the most effective dealkylating

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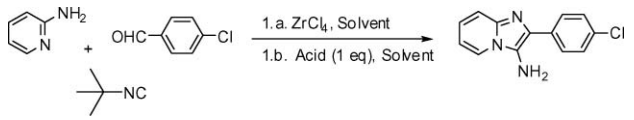
† Electronic supplementary information (ESI) available: General experimental procedure and characterization data for products. See DOI: 10.1039/c0ob00022a

Table 1 Screening of protic acids, solvents and conditions[a]

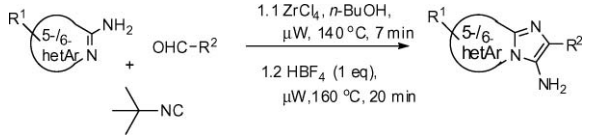


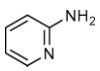
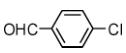
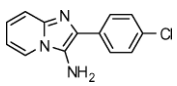
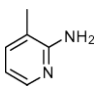
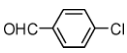
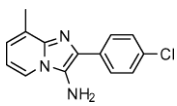
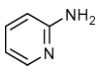
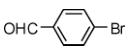
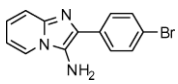
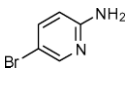
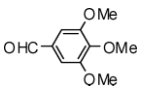
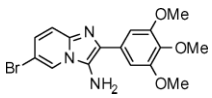
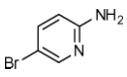
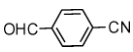
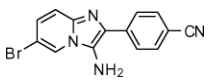
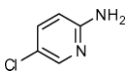
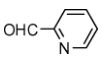
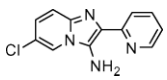
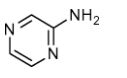
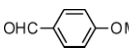
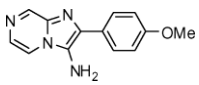
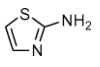
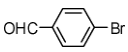
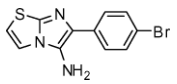
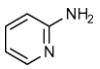
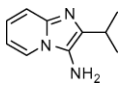
Entry	Acid	pK_a (in H_2O)	Solvent	Yield (%)[b] Conventional	μW
1	TFA	–0.25	*n*-BuOH	0	0
2	CH_3SO_3H	–2.6	*n*-BuOH	21	60
3	HBF_4	–0.4	*n*-BuOH	35	90
4	HCl	–8.0	*n*-BuOH	28	81
5	HBr	–9.0	*n*-BuOH	26	76
6	HBF_4		PEG-400	—	78
7	HBF_4		DMSO	—	72
8[c]	HBF_4		*n*-BuOH	—	89
9[c]	HBF_4		PEG-400	—	74
10[c]	HBF_4		DMSO	—	33

[a] Reactants and reagents: azine (1 mmol), aldehyde (1 mmol), *tert*-BuNC (1 mmol), $ZrCl_4$ (10 mol%), *n*-BuOH (1 mL) and Brønsted acid (1 mmol). Conditions in conventional heating: 1.a. 50 °C, 2 h; 1.b. 110 °C, 15 h. μW conditions: 1.a. 140 °C, 7 min; 1.b. 160 °C, 20 min. [b] Isolated yields. [c] 4-Bromobenzaldehyde was used in place of 4-chlorobenzaldehyde.

agent, although HCl exhibited a similar dealkylation activity. The correlation of dealkylation activity of acids with their acidity (pK_a in water) reveals that there must be parameter(s) other than acidity responsible for dealkylation efficiency, and they may be the size and shape of counter anions. Inorganic acids are better dealkylating agents than organic acids. While *n*-BuOH, PEG-400 and DMSO as solvents showed similar results for the multicomponent reaction, *n*-BuOH was found to be superior to other solvents for the de-*tert*-butylation affording a cleaner reaction, easier isolation and higher yield of final products. This observation was also evident in a different reaction of 2-aminopyridine with 4-bromobenzaldehyde and *tert*-butyl isocyanide (Entries 8–10, Table 1). In conventional heating, the MCR proceeded well, but the de-*tert*-butylation suffered from very slow and incomplete reaction. In contrast, the microwave irradiation promoted the de-*tert*-butylation with much enhanced reaction rate and higher yield of product. The variation in equivalence of HBF_4 revealed that one equivalent was optimal for its best dealkylation activity. The MCR–de-*tert*-butylation performed in a domino[10] fashion resulted in decreased activities of both $ZrCl_4$ and HBF_4. The mutually exchanged use of $ZrCl_4$ and HBF_4 in this tandem protocol caused little progress of the multicomponent reaction and the de-*tert*-butylation. This implies that $ZrCl_4$ and HBF_4 are efficient catalyst and promoter for their respective use. The de-*tert*-butylation was also found to undergo non-significantly, while catalyzed by Lewis acids (20 mol%) such as $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$ and $CeCl_3{\cdot}7H_2O$. The effectiveness of the HBF_4-promoted de-*tert*-butylation procedure was also tested in a single step. N-*tert*-Butyl-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-amine, prepared by our earlier developed procedure,[5e] in these de-alkylation reaction conditions provided the product in 88% yield, which reflected an almost identical result to Table 1, entry 3. The actual reason for HBF_4 in optimized conditions being the most efficient de-*tert*-butylating protocol is not clear at the present stage. However, the overall results of screening (Table 1) indicate that plausible favorable factors are the enhanced acidity and

Table 2 One-pot MCR-tandem de-*tert*-butylation: synthesis of N-fused imidazole-amines[a]



Entry	Amidine	Aldehyde (R^2CHO)	Product	Yield [b](%)
1				90
2				92
3				89
4				94
5				80
6				88
7				95
8				70
9				82

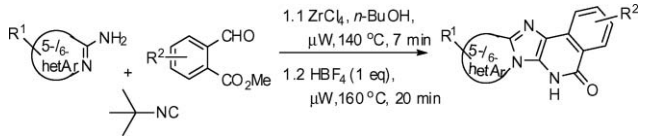
[a] Reactants and reagents: azine (1 mmol), aldehyde (1 mmol), *tert*-BuNC (1 mmol), $ZrCl_4$ (10 mol%), *n*-BuOH (1 mL) and 40% aqueous HBF_4 (1 mmol). [b] Isolated yields.

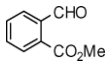
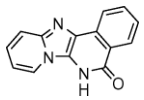
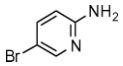
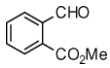
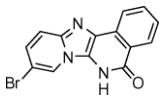
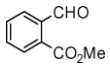
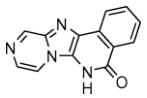
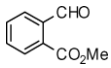
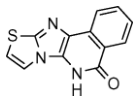
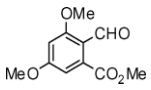
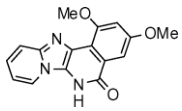
reactivity in microwave irradiation, and the increased transition state-stabilization of the ion pair ($^tBu^+X^-$) by like-size of counter anion and by solvation with *n*-BuOH *via* hydrogen bond and electrostatic interaction.

With the optimized tandem MCR–de-*tert*-butylation method in hand, we next set out to explore its scope. To our delight, various heterocyclic-2-amidines and aldehydes in this methodology produced diverse N-fused imidazole–primary amines in good to high yields (Table 2). The experimental procedure is simple and straightforward.[11] The sensitive functionalities such as halogens (Cl, Br), methoxy and cyano remained tolerated.

We were then interested in *in situ* cyclization of primary amine functionality generated by de-*tert*-butylation in MCR products with tethered internal functional group. For this, we chose

Table 3 One-pot MCR–de-*tert*-butylation–cyclization: synthesis of N-fused isoquinolinone-imidazole-heterocycles[a]



Entry	Amidine	Aldehyde	Product	Yield [b](%)
1				85
2				72
3				89
4				87
5				80

[a] Reactants and reagents: azine (1 mmol), aldehyde (1 mmol), *tert*-BuNC (1 mmol), $ZrCl_4$ (10 mol%), *n*-BuOH (1 mL) and 40% aqueous HBF_4 (1 mmol). [b] Isolated yields.

phthalaldehydic esters as the aldehyde component. Their Ugi-type multicomponent reaction with heterocyclic-2-amidines and *tert*-butyl isocyanide and the tandem dealkylation by the developed protocol formed the *in situ* cyclized products isoquinolinone-imidazole-heterocycles in good to high yields (Table 3). This novel one-pot process of MCR-tandem dealkylation-*in situ* cyclization, which involves six-centered-three component reactions, is much amenable for rapid and economical preparation of large arrays of isoquinolinono-tetracycles in parallel format. The post-modification of Ugi-type MCR products at their secondary amino group (NH-*tert*-butyl or NH-isooctyl) without dealkylation was found difficult,[7] as revealed also in our attempted investigations. The present protocol of one-pot MCR-de-*tert*-butylation is useful in generation of further molecular diversity *via* various post-modifications at primary amino group of products (Table 2). For example, the derivatives that we have prepared using normal procedures are acylamide (Ugi reaction), urea (carbamoylation), N-arylalkyl (nucleophilic substitution), imine, and N-aryl (Pd-catalysed N-arylation). In reported studies of developing a convertible isocyanide in the Groebke–Blackburn MCR, the dealkylation was either complicated or specific. Whereas, our developed protocol of dealkylation of *tert*-butyl amine uses only one equiv. HBF_4 (which is less corrosive) and n-butanol as solvent (which is greener), and is a one-step reaction, compatible with MCR conditions in tandem-mode and well matched to one-pot preparation of isoquinolinone-imidazole-heterocycles. This novel protocol has led to the establishment of *tert*-butyl isocyanide as a useful convertible isonitrile. It is remarkable that among commercially available isonitriles *tert*-butyl isocyanide is economical, according to the Sigma-Aldrich price. Thus, the method is amenable for bulk-scale and solid phase syntheses towards the easy generation of scaffold- and substitution/functionality-diversities.

Conclusion

In conclusion, we have developed a novel microwave-assisted tandem protocol of de-*tert*-butylation of derived *tert*-butyl amine in an Ugi-type MCR product, which has afforded to the successful implementation of *tert*-butyl isocyanide as a useful convertible isonitrile. The method provides access to a diverse array of medicinally-relevant N-fused heterocycles. This new finding can be extended to many multicomponent reactions using *tert*-butyl isocyanide as a convertible isonitrile for generating molecular diversity, which is under our current investigation.

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11 **Representative experimental procedure (Table 2, entry 1)**: To a mixture of 2-aminopyridine (0.09 g, 1 mmol) and 4-chlorobenzaldehyde (0.14 g, 1 mmol) in *n*-BuOH (1 mL) taken in a microwave vial were added *tert*-butyl isocyanide (0.08 g, 0.11 mL, 1 mmol) and $ZrCl_4$ (0.023 g, 10 mol%). The vessel was sealed with a cap and the mixture was then irradiated in a monomode microwave synthesizer (Biotage Initiator™ EXP) at 140 °C for 7 min. After cooling to r.t. in the microwave cavity, the vial cap was removed and to the reaction mixture was added 40% aqueous HBF_4 (0.2 mL, 1 mmol). The vial was resealed and then irradiated at 160 °C for 20 min. To the resultant mixture was added aqueous ammonia solution (10%) to basify (pH = 8). The mixture was then extracted with EtOAc (60 mL) and the solution was washed with H_2O (3 × 10 mL). The organic layer was dried (anhy. Na_2SO_4), filtered, and concentrated under reduced pressure. The column chromatographic purification of the crude product over silica gel (mesh size: 60–120) with EtOAc–hexane as eluent afforded 2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-amine in 90% yield as yellow solid; mp = 146–148 °C; IR (KBr) ν_{max} = 3310, 2932, 1646, 1492, 1270, 1091, 767 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 5.22 (br s, NH_2), 6.85 (t, J = 6.7 Hz, 1H), 7.08 (dd, J = 7.2, 8.3 Hz, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 8.06 (d, J = 8.4 Hz, 2H), 8.25 (d, J = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 111.5, 116.9, 122.9, 123.0, 126.6, 127.2, 128.1 (2CH), 128.7 (2CH), 130.7, 134.3, 139.3; MS (APCI) m/z: 244 (MH^+). Anal. found: C, 63.8; H, 4.05; N, 17.4. Calcd. for $C_{13}H_{10}ClN_3$: C, 64.1; H, 4.1; N, 17.2%. This experimental procedure was followed for all compounds (Table 2). **General procedure for synthesis of compounds (Table 3)**: The resultant mixture obtained after reaction following the above procedure was made basic (pH = 8) with addition of aqueous ammonia solution (10%). The precipitated solids were then filtered and washed with water and EtOAc. The pure products were obtained by crystallization from EtOH–EtOAc. The structures of the products were identified by ^1H and ^{13}C NMR, mass and IR spectroscopies, and confirmed by elemental analysis or HRMS. The compounds, which were reported in literature, showed identical spectroscopic data.

