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tert-Butyl isocyanide revisited as a convertible reagent in the Groebke–Blackburn reaction

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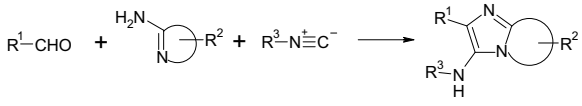
ABSTRACT

tert-Butyl isocyanide can serve as the convertible reagent in Groebke–Blackburn multi-component reactions. The effective removal of the *tert*-butyl group from the resulting imidazo[1,2-*a*]azines and -azoles is achieved on a gram scale in two steps without chromatographic purification.

The Groebke–Blackburn multi-component reaction (GB-MCR)[1–3] of 2-aminoazines and -azoles with aldehydes and isocyanides has received increased attention as a powerful tool for generating large arrays of drug-like fused imidazo[1,2-*a*]azines and -azoles in a combinatorial, diversity-controlled fashion (Scheme 1).[4] The diversity in the final products, if limited by the availability of the requisite isocyanides, can be extended further by the use of a convertible isocyanide, such as 1,1,3,4-tetramethylbutylisocyanide (Walborsky reagent[5]), removal of the *N*-isooctyl group and subsequent derivatization at the primary amino group via Pd-catalyzed arylation, acylation, carbamoylation, and reductive alkylation, as demonstrated by us[6] and others[7] (Scheme 2).

For preparation of combinatorial libraries of hundreds to thousands of compounds based on this methodology, larger quantities of the Groebke–Blackburn type core building blocks must be synthesized, thus requiring larger quantities of the somewhat expensive Walborsky reagent. Presumably, the *N*-isooctyl group is removed by a strong Brønsted acid via formation of the stable (tertiary) carbocation.[7] Therefore, other tertiary alkyl isocyanides (such as *t*-Bu) would be natural alternatives to consider. Although *t*-BuNC is a much more economical alternative to the Walborsky reagent, unfortunately, the resultant (*tert*-butyl)amino Groebke–Blackburn reaction products have been shown to undergo TFA-induced cleavage at a much slower rate (also complicated by the trifluoroacetylation of the primary amino group) compared to isooctylamino products.[7] Herein, we report an efficient two-step procedure for solution-phase de-*tert*-butylation of various Groebke–Blackburn reaction products obtained using *tert*-butyl isocyanide.



Scheme 1. Reaction of 2-aminoazines and -azoles with aldehydes and isocyanides (the Groebke–Blackburn reaction).

The starting imidazo[2,1-*b*]-1,3,4-thiadiazoles **1** and imidazo-[1,2-*a*]azines **2–4** were synthesized according to the recently reported procedure using an equimolar quantity of TMSCl as the Lewis acid promoter for the reaction (Scheme 3).[8] In our preliminary experiments, Brønsted acids such as HCl in MeOH or dioxane, glacial acetic acid, concentrated HCl or H_2SO_4 led to inefficient removal of the *tert*-butyl group from GB-MCR products **1–4**. However, neat TFA under reflux was found to convert these compounds in 3 h, cleanly and effectively, into the respective trifluoroacetamides **5–8**. The latter were then subjected to alkaline hydrolysis and the corresponding primary amines **9–12** were isolated in good yields after crystallization from isopropanol (Table 1).[9] All of the reactions described were run on 5–10 mmol scale resulting in the yields indicated. While derivatization of the

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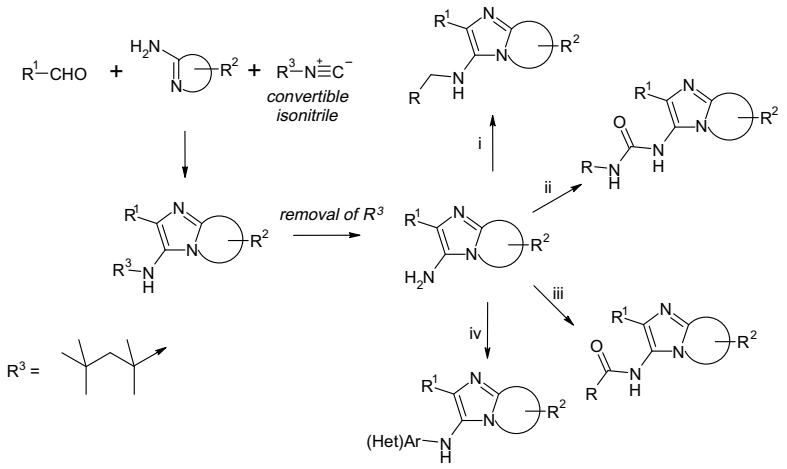
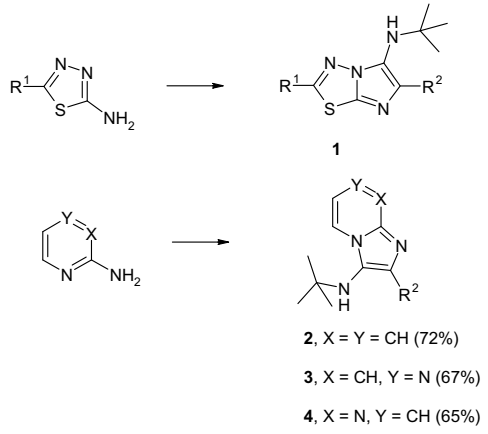


Scheme 2. Extended diversity in Groebke–Blackburn reaction products achieved via the use of a convertible isocyanide. Reagents and conditions: (i) RCHO, $NaBH_3CN$, DMF–AcOH, 25 °C, 50 h;[7] (ii) RNCO, DMF, 25 °C, 24 h;[7] (iii) RCOCl, DMF–pyridine, 25 °C, 24 h;[7] (iv) (Het)ArX, $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, sealed tube, 100 °C, 16 h.[6]



Scheme 3. Preparation of the starting imidazo[2,1-*b*]-1,3,4-thiadiazoles **1**[8] and imidazo[1,2-*a*]azines **2–4**. Reagents and conditions: (i) 1 equiv R^2CHO, MeCN, reflux, 2 h; (ii) TMSCl (1 equiv), MeCN/DCM, rt, 30 min; (iii) *t*-BuNC.

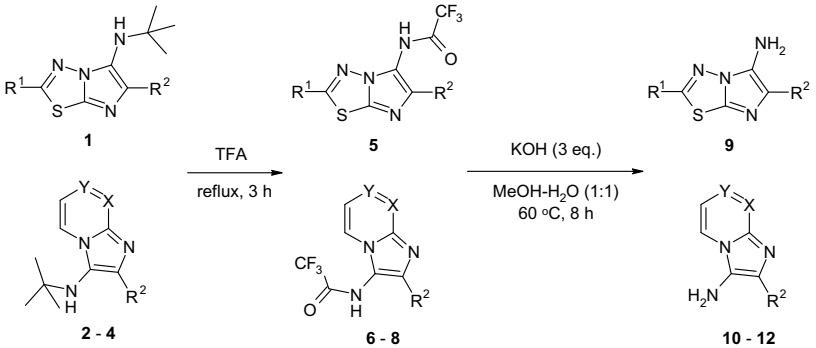
primary amines **10–12** has already been described,[7] newly synthesized compounds **9b–g** have been used to prepare a small library of amides and ureas **13**. Representative examples of such compounds are given in Figure 1.[10]

The inevitable intermediacy of the trifluoroacetamides in this two-step *tert*-butyl group removal can be used as an advantage. For example, we have performed a multigram synthesis of the *N*-protected imidazo[1,2-*a*]pyridine-based amino acid **6b**[11] (Scheme 4) that we are now finding useful in developing solid-supported library synthesis.[12]

In conclusion, we have developed an efficient two-step protocol for *tert*-butyl group removal from various bicyclic imidazolyl amines. These findings establish that readily available *tert*-butyl isocyanide can serve as a more economic convertible isocyanide alternative to Walborsky's reagent in Groebke–Blackburn multicomponent reactions, and is suitable for multigram preparations.

General procedure: A solution of the *tert*-butyl amine (10 mmol) in TFA (10 mL) was heated under reflux for 3 h. The solution was cooled to rt, concentrated in vacuo, and the residue was dissolved

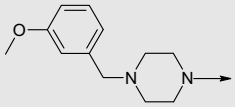
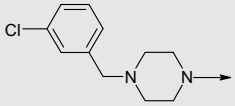
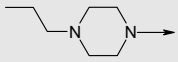
Table 1
Two-step removal of the *tert*-butyl group from imidazo[2,1-*b*]-1,3,4-thiadiazoles **1** and imidazo[1,2-*a*]azines **2–4**



Entry	Starting material	R^1	R^2	Step 1 product	Yield (%)	Step 2 product	Yield[b] (%)
1	**1a**	Boc–N⟨ ⟩N–	Ph	**5a**	92	**9a**[a]	46
2	**1b**	–N⟨ ⟩	Ph	**5b**	89	**9b**	73

(*continued on next page*)

Table 1 (*continued*)

Entry	Starting material	R^1	R^2	Step 1 product	Yield (%)	Step 2 product	Yield[b] (%)
3	**1c**	Me	4-FC_6H_4	**5c**	Quant.	**9c**	78
4	**1d**		Ph	**5d**	92	**9d**	35
5	**1e**		4-FC_6H_4	**5e**	86	**9e**	65
6	**1f**		Ph	**5f**	97	**9f**	58
7	**1g**		Ph	**5g**	67	**9g**	56
8	**2a**[c]	–	*i*-Pr	**6a**	84	**10a**	55
9	**3**[c]	–	*i*-Pr	**7**	77	**11**	43
10	**4**[c]	–	*i*-Pr	**8**	90	**12**	57

[a] The product of Boc-cleavage.
[b] Yield after crystallization from isopropanol. The actual yield may be higher.
[c] X and Y are defined in Scheme 3.

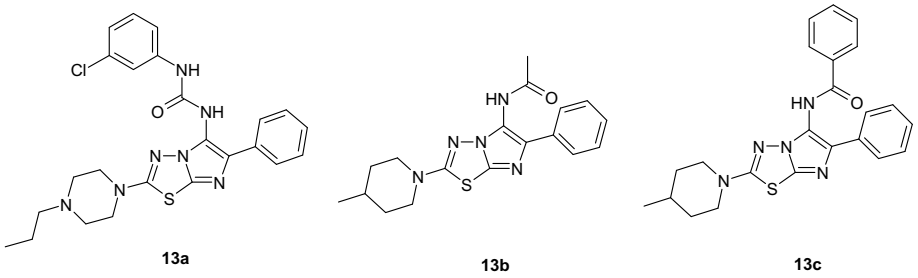
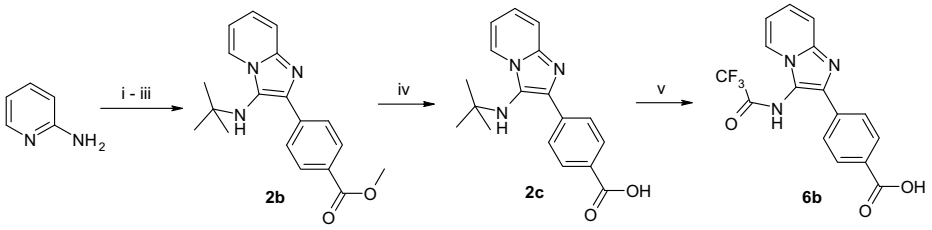


Figure 1. Representative compounds synthesized via derivatization of primary amines **9**.



Scheme 4. Large-scale preparation of 4-[3-(trifluoroacetylamino)imidazo[1,2-*a*]pyridin-2-yl]benzoic acid (**6b**). Reagents and conditions: (i) 1 equiv 4-$OHCC_6H_4COOMe$, MeCN, reflux, 2 h; (ii) TMSCl (1 equiv MeCN/DCM, rt, 30 min; (iii) *t*-BuNC (i–iii, 76%); (iv) aq KOH (1 equiv), rt, 4 h (93%); (v) TFA, reflux, 3 h (88%).

in water (50 mL). The solution pH was adjusted to neutral with $NaHCO_3$, and the resulting precipitate collected by filtration, washed with water, and air-dried. The solid trifluoroacetamide was dissolved in 50% aqueous methanol (100 mL) containing KOH (3 equiv) and the reaction mixture was stirred at 60 °C for 8 h. The precipitate that formed on cooling the reaction mixture to rt was collected by filtration, washed with water and air-dried. The crude product was purified by crystallization from isopropanol.

Acknowledgment

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9. *Characterization data for selected primary amines*: Compound **9b**—beige solid, mp = 153–155 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.77 (d, J = 7.7 Hz, 2H), 7.30 (t, J = 7.3 Hz, 2H), 7.07 (t, J = 7.7 Hz, 1H), 4.92 (br s, 2H, NH_2), 3.78 (d, J = 12.0 Hz, 2H), 3.12 (d, J = 12.0 Hz, 2H), 1.60–1.75 (m, 3H), 1.16–1.30 (m, 2H), 0.94 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.3, 158.7, 144.6, 133.1, 133.0, 127.7, 127.6, 114.5, 47.9, 34.3, 29.5, 20.3; LCMS (M+H$^+$) 314. Anal. Calcd for $C_{16}H_{19}N_5S$: C, 61.32; H, 6.11; N, 22.34. Found: C, 61.39; H, 6.15; N, 22.40. Compound **9c**—pale yellow solid, mp = 178–180 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.85 (dd, J = 5.9, 8.4 Hz, 2H), 7.17 (t, J = 8.8 Hz, 2H), 5.19 (br s, 2H, NH_2), 2.69 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.4 (d, J_{C-F} = 243.8 Hz), 160.5, 152.6, 143.4, 130.6 (d, J_{C-F} = 17.0 Hz), 128.4 (d, J_{C-F} = 6.9 Hz), 114.6 (d, J_{C-F} = 27.3 Hz), 104.6, 15.9; LCMS (M+H$^+$) 248. Anal. Calcd for $C_{11}H_9FN_4S$: C, 53.21; H, 3.65; N, 22.57. Found: C, 53.16; H, 3.59; N, 22.54. Compound **11**—brown sticky solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.75 (d, J = 5.9 Hz, 1H), 8.37–8.51 (m, 1H), 6.92–7.06 (m, 1H), 4.92 (br s, NH_2 + bound H_2O), 3.30 (m, 1H), 1.29 (d, J = 6.2 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 147.5, 140.6, 133.1, 130.8, 123.6, 108.7, 95.7, 24.9, 21.9; LCMS (M+H$^+$) 177. Anal. Calcd for $C_9H_{12}N_4$: C, 61.34; H, 6.86; N, 31.79. Found: C, 61.40; H, 6.91; N, 31.83.
10. *Characterization data*: Compound **13a**—white solid, mp = 176–178 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.36 (s, 1H), 7.82 (d, J = 7.7 Hz, 2H), 7.67 (br s, 1H), 7.35 (t, J = 7.4 Hz, 2H), 7.32 (s, 1H), 7.23 (dd, J = 16.5, 8.1 Hz, 2H), 6.95 (d, J = 7.8 Hz, 1H), 3.45 (br s, 4H), 3.19 (m, 4H, obscured by residual H_2O signal), 2.31 (t, J = 7.1 Hz, 2H), 1.47 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.1, 153.3, 141.3, 137.6, 135.7, 134.2, 133.3, 129.9, 128.1, 126.3, 125.3, 121.5, 118.1, 117.6, 116.8, 59.7, 51.6, 48.1, 19.5, 11.7; LCMS (M+H$^+$) 496; Anal. Calcd for $C_{24}H_{26}ClN_7OS$: C, 58.11; H, 5.28; N, 19.77. Found: C, 58.07; H, 5.22; N, 19.73. Compound **13b**—white solid, mp = 148–150 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.01 (s, 1H), 7.74 (d, J = 7.5 Hz, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.26 (t, J = 7.4 Hz, 1H), 3.85 (m, 2H), 3.15 (t, J = 12.2 Hz, 2H), 2.13 (s, 3H), 1.54–1.70 (m, 3H), 1.30–1.65 (m, 2H), 0.97 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.9, 164.4, 137.1, 133.3, 132.4, 128.4, 127.0, 125.4, 117.8, 48.7, 32.7, 29.8, 22.6, 21.5; LCMS (M+H$^+$) 356. Anal. Calcd for $C_{18}H_{21}N_5OS$: C, 60.82; H, 5.95; N, 19.70%. Found: C, 60.79; H, 5.91; N, 19.67. Compound **13c**—white solid, mp = 144–146 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.07 (d, J = 7.1 Hz, 2H), 7.77 (d, J = 7.7 Hz, 2H), 7.61 (d, J = 7.4 Hz, 1H), 7.54 (t, J = 7.5 Hz, 2H), 7.33 (d, J = 7.7 Hz, 2H), 7.19 (t, J = 7.4 Hz, 1H), 3.78 (d, J = 12.6 Hz, 2H), 3.11 (d, J = 12.6 Hz, 2H), 1.60–1.78 (m, 3H), 1.17–1.32 (m, 2H), 0.96 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.3, 164.1, 137.7, 135.1, 133.9, 133.0, 132.0, 126.4, 125.3, 117.6, 95.6, 56.1, 48.5, 32.7, 29.8, 21.5, 18.5; LCMS (M+H$^+$) 419. Anal. Calcd for $C_{23}H_{23}N_5OS$: C, 66.16; H, 5.55; N, 16.77. Found: C, 66.21; H, 5.59; N, 16.83.
11. *Characterization data*: Compound **2c**—off-white solid, mp = 151–153 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.20 (br s, 1H, COOH), 8.87 (d, J = 6.6 Hz, 1H), 8.26 (d, J = 8.1 Hz, 2H), 8.09 (d, J = 8.1 Hz, 2H), 7.92 (m, 2H), 7.47 (t, J = 7.3 Hz, 1H), 5.31 (s, 1H), 1.01 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.7, 137.5, 132.8, 132.4, 131.3, 129.5, 128.3, 128.2, 126.0, 116.1, 112.3, 56.5, 29.6; LCMS (M+H$^+$) 310. Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.91; H, 6.23; N, 13.62. Compound **6b**—yellowish solid, mp = 135–137 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (d, J = 6.9 Hz, 1H), 8.07 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 9.1 Hz, 1H), 7.60 (t, J = 7.4 Hz, 1H), 7.22 (t, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.3, 158.5 (q, J_{C-F} = 37.4 Hz), 139.2, 138.8, 129.4, 128.2, 127.6, 125.5, 125.0, 122.6, 116.4 (q, J_{C-F} = 148.9 Hz), 116.5, 111.2; LCMS (M+H$^+$) 350. Anal. Calcd for $C_{16}H_{10}F_3N_3O_3$: C, 55.02; H, 2.89; N, 12.03. Found: C, 54.98; H, 2.83; N, 11.98.
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