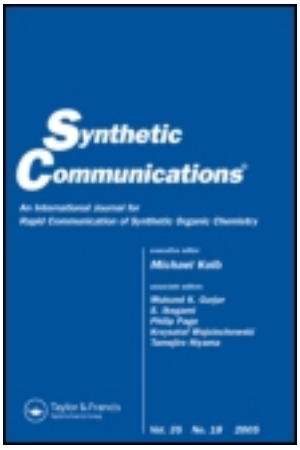
This article was downloaded by: [University of York]
On: 19 May 2013, At: 19:21
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954
Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Novel Practical Deprotection of N-Boc Compounds Using Fluorinated Alcohols

Jason Choy [a], Saul Jaime-Figueroa [a], Laurence Jiang [a] & Paul Wagner [a]
[a] Roche Palo Alto, Palo Alto, California, USA
Published online: 14 Oct 2008.

To cite this article: Jason Choy , Saul Jaime-Figueroa , Laurence Jiang & Paul Wagner (2008): Novel Practical Deprotection of N-Boc Compounds Using Fluorinated Alcohols, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:21, 3840-3853

To link to this article: http://dx.doi.org/10.1080/00397910802238718

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.tandfonline.com/page/terms-and-conditions

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae, and drug doses should be

independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Downloaded by [University of York] at 19:21 19 May 2013

Synthetic Communications®, 38: 3840–3853, 2008
Copyright © Taylor & Francis Group, LLC
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802238718

Taylor & Francis
Taylor & Francis Group

Novel Practical Deprotection of N-Boc Compounds Using Fluorinated Alcohols

Jason Choy, Saul Jaime-Figueroa, Laurence Jiang, and Paul Wagner
Roche Palo Alto, Palo Alto, California, USA

Downloaded by [University of York] at 19:21 19 May 2013

Abstract: The thermolytic deprotection of N-Boc compounds was accomplished using TFE (2,2,2-trifluoroethanol) or HFIP (hexafluoroisopropanol) as solvents. Even though the cleavage of the t-butylcarbamate (Boc) group can be achieved at solvent reflux temperature, the deprotection process was significantly accelerated under microwave-assisted conditions. The practicality of this methodology was demonstrated on alkyl, aryl, and heteroaromatic N-Boc-amines.

Keywords: Boc-deprotection, hexafluoroisopropanol, microwave, trifluoroethanol

Among various nitrogen protecting groups in organic chemistry, the *t*-butoxycarbonyl (Boc) group is perhaps one of the most widely used because of its exceptional stability toward a variety of reagents and reaction conditions.[1a] As a result, removal of the Boc group remains of prime importance in organic synthesis. Cleavage of Boc on nitrogen is generally achieved under acidic conditions;[1a,1b] however, basic,[2] thermolytic,[3] and microwave-assisted conditions[1b,4] are also described in the literature. In one of the Roche chemistry projects, a new, practical method was discovered to cleanly deprotect Boc-nitrogens using 2,2,2-trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP) as a solvent in quantitative yields. The reaction conditions are neutral and do not require additional reagents (apart from solvents). Thus, the product is recovered by a simple solvent evaporation without any workup, and in some cases, no further purification is needed.

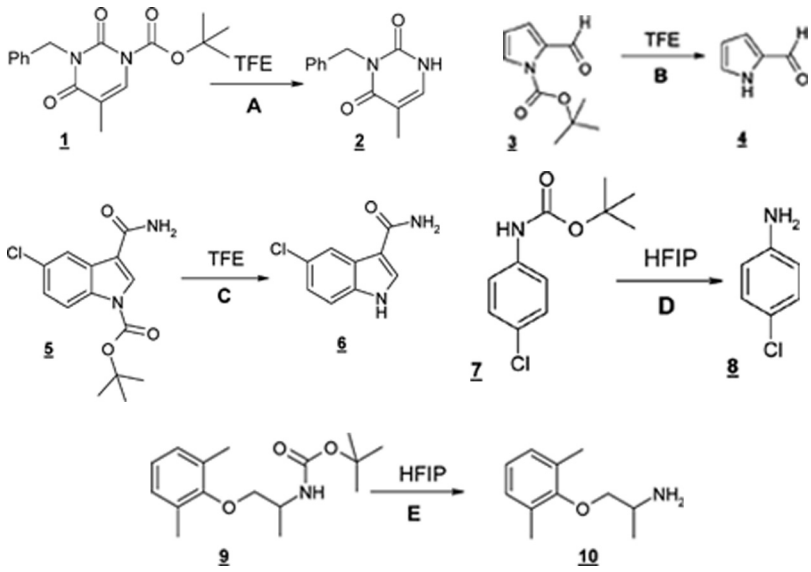
Received February 6, 2008.
Address correspondence to Saul Jaime-Figueroa, Roche Palo Alto, 3431 Hillview Ave., Palo Alto, CA 94304. E-mail: saul.jaime@roche.com

Compared to other solvents, TFE and HFIP are unique because of their high ionizing power, strong hydrogen bond donor power, and mild acidic character ($pK_a = 12.4$ and $pK_a = 9.3$ respectively).[5] These outstanding features encouraged us to explore their use in the deprotection of N-Boc compounds.

Initially, the cleavage of the Boc group was conducted at the solvent reflux temperature. Although the deprotection process was successful under these conditions, long reaction times were often required to achieve this transformation (see Table 1). To expedite reaction times, the cleavage was examined under microwave-assisted conditions,[6] and the results are shown in Table 1. These results suggest that although microwave heating

Downloaded by [University of York] at 19:21 19 May 2013

Table 1. Deprotection of different N-Boc-compounds



Entry	Reflux	Yield[a]%	Microwave	Yield[a] (%)
A	1 h	83	5 min/100 °C	97
B	6 h	65	0.5 h/100 °C	91
C	12 h	99	1 h/100 °C	98
D	36 h	81	1 h/150 °C	80
E	ND	—	2 h/150 °C	81

is not essential in this process, the reactions are significantly accelerated with this protocol.

In an effort to explore the role of the solvent in this deprotection process, N-Boc-4-chloroaniline (**7**) was subjected to experiments in different solvents. Thus, TFE and HFIP were replaced with solvents such as acetone, acetonitrile, tetrahydrofuran, chloroform, and toluene under the same conditions as those indicated in Table 1, entry D (microwave, 150 °C, 1 h). Using these solvents, unreacted Boc-aniline (**7**) was cleanly recovered in most cases with a minor amount of the product (**8**) detected by NMR (<10%). When nonfluorinated alcohols such as MeOH or EtOH were used as solvents, the unreacted N-Boc-aniline (**7**) was again the main component in the resulting crude mixture with some of the deprotected product (<25% by NMR). However, in this case, the corresponding methyl or ethyl-carbamates were also observed as side products.

To study the generality and scope of this methodology, the deprotection of a series of alkyl, aryl, and heteroaromatic N-Boc-amines was initiated. First, the deprotection of a series of N-Boc indoles was performed, varying the electronic nature of the substituents on the indole ring. In all cases, the product was obtained in essentially quantitative yields, and the results are summarized in Table 2.

Encouraged by these findings, the deprotection of a series of anilines was then explored using the same protocol. The results are summarized in Table 3. Anilines with electron-withdrawing substituents (**7a** and **7b**, Table 3) were found to react faster than those with electron-donating groups (**7c**, **7d**, and **7f**, Table 3). The reaction conditions employed were found to be compatible with other protecting groups such as –NCbz, –NAlloc, and –OTIPS (entries 15–20, Table 3).

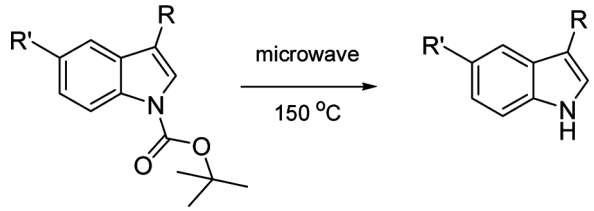
To extend the synthetic potential of this deprotection method, this protocol was further expanded to a wide range of N-Boc amines, and the results are shown in Table 4. In all cases, the deprotection product was obtained in good to excellent yields.

It was again confirmed that these reaction conditions were compatible with other protecting groups including –OAc and –OTBDMS (entries 4 and 5, Table 4). More important, compounds that are sensitive to typical acidic conditions (TFA and HCl) such as **5d** and **23** gave the corresponding deprotected product in excellent yields.

In general, hexafluoroisopropanol is a more reactive solvent than trifluoroethanol for these deprotection reactions. Thus, the use of HFIP over TFE on the same substrate under similar conditions consistently reduced reaction times (see odd vs. even entries, Tables 2 and 3). On the basis of the reactivity differences between TFE and HFIP, the selective, sequential Boc deprotection of compound **25** was explored. As outlined

Downloaded by [University of York] at 19:21 19 May 2013

Table 2. Deprotection of indoles under microwave assisted conditions using TFE and HFIP as solvents



Entry	N-Boc	R	R′	Solvent	Time	Product	Yield[a]%
1	**5**	–$CONH_2$	–Cl	TFE	5 min	**6**	98
2				HFIP	5 min	**6**	97
3	**5a**	–H	–H	TFE	15 min	**6a**	99
4				HFIP	5 min	**6a**	97
5	**5b**	–CHO	–H	TFE	5 min	**6b**	91
6				HFIP	5 min	**6b**	96
7	**5c**	–H	–Cl	TFE	1 h	**6c**	98
8				HFIP	5 min	**6c**	94
9	**5d**	–H	–OMe	TFE	1 h	**6d**	95
10				HFIP	15 min	**6d**	98
11	**5e**	–H	–CN	TFE	1 h	**6e**	98
12				HFIP	5 min	**6e**	98
13	**5f**	–H	–NO_2	TFE	15 min	**6f**	91
14				HFIP	5 min	**6f**	99
15	**5g**	–H	–NH_2	TFE	15 min	**6g**	81
16				HFIP	15 min	**6g**	70

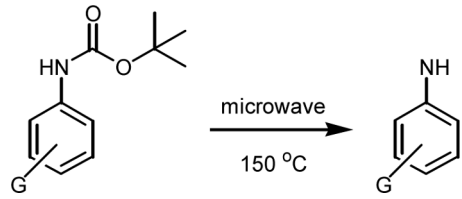
[a]Isolated yields after chromatography.

Downloaded by [University of York] at 19:21 19 May 2013

in Scheme 1, TFE was used to selectively remove the indole Boc moiety on **25** in good yields. Further treatment of **26** with HFIP efficiently completed the cleavage of the remaining N-Boc group on the piperazine ring. On the other hand, if selectivity is not required, both Boc groups can be removed simultaneously from **25** using HFIP as a solvent.

In summary, a practical and high-yielding method to deprotect N-Boc compounds using TFE or HFIP has been discovered. Under this protocol, the product is isolated by a simple solvent evaporation and minimal workup conditions. HFIP was found to be more reactive than TFE under similar conditions, and this difference in reactivity

Table 3. Deprotection of anilines under microwave-assisted conditions using TFE and HFIP as solvents



Entry	N-Boc	G	Solvent	Time	Product	Yield[a]%
1	**7**	4-Cl	TFE	1.5 h	**8**	98
2			HFIP	1 h	**8**	80
3	**7a**	4-Br,3-Cl	TFE	1 h	**8a**	97
4			HFIP	15 min	**8a**	77
5	**7b**	4-NO_2	TFE	1 h	**8b**	95
6			HFIP	5 min	**8b**	76
7	**7c**	4-OMe	TFE	2 h	**8c**	98
8			HFIP	0.5 h	**8c**	85
9	**7d**	3-OMe	TFE	1 h	**8d**	95
10			HFIP	0.5 h	**8d**	89
11	**7e**	2-I	TFE	1 h	**8e**	98
12			HFIP	1 h	**Dec.**	—
13	**7f**	4-NH_2	TFE	3 h	**8f**	93
14			HFIP	0.5 h	**8f**	97
15	**7g**	3-OTIPS	TFE	2 h	**8g**	81
16			HFIP	0.5 h	**8g**	81
17	**7h**	4-NHCbz	TFE	2 h	**8h**	99
18			HFIP	2 h	**8h**	86
19	**7i**	4-NHAlloc	TFE	1 h	**8i**	98
20			HFIP	0.5 h	**8i**	98

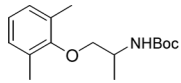
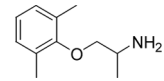
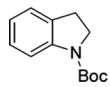
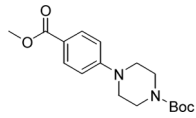
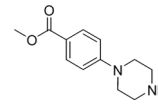
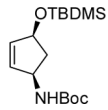
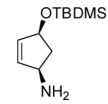
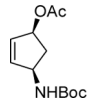
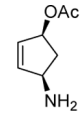
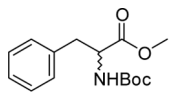
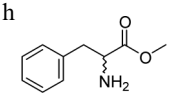
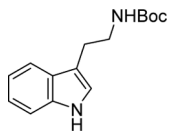
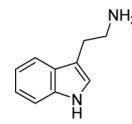
[a]Isolated yield after chromatography.

may allow the selective removal of different Boc groups in the same molecule. The mild reaction conditions are compatible with many protecting groups such as –OTIPS, –OTBDMS, –OAc, –OBn, –NCbz, and –NAlloc. This methodology can be applied when substrates are sensitive to deprotection under typical acidic conditions (TFA or HCl).

The extension of this methodology to the saponification of *t*-butyl-esters has proven successful, and this work is currently under further investigation.

Downloaded by [University of York] at 19:21 19 May 2013

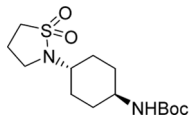
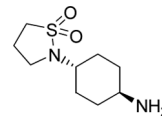
Table 4. Deprotection of various N-Boc compounds using HFIP as a solvent and under microwave-assisted conditions

Entry	N-Boc substrate	Conditions	Product	Yield[a] (%)
1		**9** 150 °C/2 h		**10** 81
2		**11** 150 °C/2 h		**12** 85
3		**13** 150 °C/5 h		**14** 91
4		**15** 150 °C/1 h		**16** 98
5		**17** 100 °C/4 h[b]		**18** 85
6		**19** 150 °C/0.5 h		**20** 89
7		**21** 150 °C/1 h		**22** 88

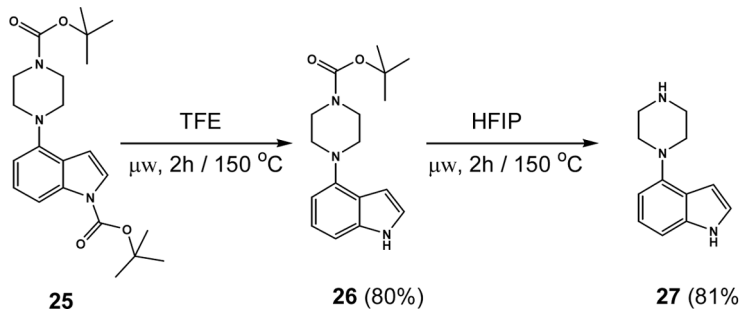
(*Continued*)

Downloaded by [University of York] at 19:21 19 May 2013

Table 4. Continued

Entry	N-Boc substrate	Conditions	Product	Yield[a] (%)
8		**23** 150 °C/1 h		**24** >95[c]

[a]Isolated yields after chromatography.
[b]At 150 °C side products are formed and yield is low.
[c]Crude yield (pure by NMR).



Scheme 1. Regioselective deprotection of compound **25**.

EXPERIMENTAL

The experiments under microwave-assisted conditions were performed in a Biotage-Initiator™ Sixty microwave instrument. ^{1}H NMR and ^{13}C NMR were measured on Bruker Avance DPX-300 NMR or Bruker Avance AMX-300 NMR spectrometers, operating at a proton (^{1}H) frequency of 300.13 MHz and carbon (^{13}C) frequency of 75.43 MHz. Because starting materials **1**,[7a] **3**,[8] **7g**,[9] **7h**,[10] 17[11] and **25**[12] are known compounds in the literature, their experimental data are not presented here. The N-Boc substrates **5a**–**g**, **7a**–**f**, **11**, **13**, **19**, and **21** were procured commercially.

Downloaded by [University of York] at 19:21 19 May 2013

Downloaded by [University of York] at 19:21 19 May 2013

Typical Experimental Procedure for Deprotection of N-Boc Compounds

A solution of the N-Boc protected amine (1 mmol) in TFE or HFIP (5 mL) was placed in a sealed microwave vial. The reaction mixture was heated (100 or 150 °C) in a Biotage–Initiator^{TM} Sixty microwave instrument with stirring until the disappearance of the starting material was observed. After cooling to room temperature, the mixture was evaporated to dryness under reduced pressure. The crude product was purified by flash-column chromatography.

Compound **2**[7a,7b,7c]: Mp 207–208 °C; ^{1}H NMR (DMSO-d_6) δ 11.00 (broad s, 1H), 7.35 (s, 1H), 7.22–7.34 (m, 5H), 4.97 (s, 2H), 1.80 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 164.15, 151.74, 137.81, 136.97, 128.65, 127.94, 127.41, 107.62, 43.20, 12.85; MS ESI: m/z (%) 217 ($M + H^+$, 100). Anal. calc. for $C_{12}H_{12}N_2O_2$: C, 66.64; H, 5.59; N, 12.95. Found: C, 66.66; H, 5.46; N, 13.01.

Compound **4**[13]: Mp = 44–45 °C; ^{1}H NMR ($CDCl_3$) δ 9.56–9.86 (broad s, 1H), 9.54 (s, 1H), 7.15 (s, 1H), 6.92–7.05 (m, 1H), 6.27–6.43 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 180.49, 132.92, 126.44, 121.40, 111.36. MS ESI: m/z (%) 96 ($M + H^+$, 100). HRMS ESI m/z 96.04388 ($M + H^+$). Calcd. 96.04439.

1-Boc-3-carboxamido-5-chloroindole (5)

To a solution of 3-carboxamido-5-chloroindole (0.5 g, 2.56 mmol) in acetonitrile (30 mL), 0.59 g (2.69 mmol) of (t-Boc)$_2$O and a catalytic amount of 4-DMAP (3 mg, 0.02 mmol) were added at room temperature. The reaction mixture was stirred for 4 h at the same temperature. The solid was collected by filtration and washed with cold MeCN (10 mL) to give 0.63 g (83%) of product (**5**) as a pale solid. Mp = 174–174.5 °C; ^{1}H NMR (DMSO-d_6) δ 8.52 (s, 1H), 8.24 (d, $J = 2.26$ Hz, 1H), 8.05 (d, $J = 8.67$ Hz, 1H), 7.93 (br. s., 1H), 7.39 (dd, $J = 9.04$, 2.26 Hz, 1H), 7.25 (br. s., 1H), 1.64 (s, 9H);^{13}C NMR (DMSO-d_6) δ 164.62, 148.45, 133.26, 129.71, 129.66, 127.95, 124.63, 121.13, 116.15, 114.13, 85.15, 27.56; MS ESI: m/z (%) 295 ($M + H^+$, 90). HRMS ESI m/z 295.08440 ($M + H^+$). Calcd. 295.08466.

Compound **6**: Mp 248–249 °C; ^{1}H NMR (DMSO-d_6) δ 11.72 (broad s, 1 H), 8.15 (d, $J = 2.26$ Hz, 1 H), 8.09 (d, $J = 3.01$ Hz, 1 H), 7.60–7.40 (broad s, 1H), 7.45 (d, $J = 8.67$ Hz, 1 H), 7.15 (dd, $J = 8.48$, 2.07 Hz, 1 H), 7.00–6.75 (broad s, 1 H);^{13} C NMR (DMSO-d_6) δ 166.42, 134.99, 130.17, 127.83, 125.43, 122.15, 120.55, 113.74, 110.54; MS ESI: m/z (%) 195 ($M + H^+$, 100). HRMS ESI m/z ($M + H^+$) 195.03188. Calcd. 195.03197.

Downloaded by [University of York] at 19:21 19 May 2013

Compound **6a**: Mp 50–51 °C; ^{1}H NMR ($CDCl_3$) δ s 8.08 (broad s, 1H), 7.65 (dd, 1H), 7.38 (m, 2H), 7.23–7.09 (m, 2H), 6.56–6.54 (m, 1H); ^{13}C NMR ($CHCl_3$-d) δ 135.74, 127.82, 124.10, 121.97, 120.72, 119.80, 111.00, 102.61; MS EI: m/z (%) 117 (M +, 100).

Compound **6b**: Mp 196–197 °C; ^{1}H NMR (DMSO-d_6) δ 12.14 (broad s, 1H), 9.95 (s, 1H), 8.30–8.09 (m, 2H), 7.56–7.20 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 185.34, 138.85, 137.43, 124.49, 123.84, 122.50 m 121.20, 118.54, 112.80; MS ESI: m/z (%) 146 ($M + H^+$; 100). HRMS ESI m/z ($M + H^+$) 146.05963. Calcd. 146.06004.

Compound **6c**: Mp 74–75 °C; ^{1}H NMR ($CDCl_3$), δ 8.13 (broad s, 1H, D_2O exch.), 7.61 (s, 1H), 7.31–7.12 (m, 3H), 6.50–6.48 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 134.11, 128.94, 125.51, 125.46, 122.31, 120.11, 111.97, 102.41; MS EI: m/z (%) 151 (M^+, 100%). HRMS ESI m/z ($M + H^+$) 152.02585. Calcd. 152.02615.

Compound **6d**: Mp 55–56 °C; ^{1}H NMR ($CDCl_3$), δ 8.03 (broad s, 1H, D_2O exch.), 7.28–6.84 (m, 4H), 6.49–6.47 (m, 1H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 154.19, 130.94, 128.27, 124.85, 112.35, 111.70, 102.38, 102.30, 55.85; MS ESI: m/z (%) 148 ($M + H^+$, 100%). HRMS ESI m/z ($M + H^+$) 148.07531. Calcd. 148.07569.

Compound **6e**: Mp 102–104 °C; ^{1}H NMR ($CDCl_3$), δ 8.68 (broad s, 1H, D_2O exch.), 8.00–7.99 (m, 1H), 7.49–7.40 (m, 2H), 7.36–7.34 (m, 1H), 6.64–6.62 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 137.50, 127.66, 126.48, 126.41, 124.87, 120.87, 112.02, 103.43, 102.79; MS EI: m/z (%) 142 (M^+, 100%). HRMS ESI m/z ($M + H^+$) 143.06006. Calcd. 143.06037.

Compound **6f**: Mp 141–142 °C; ^{1}H NMR ($CDCl_3$), δ 8.62 (d, 1H), 8.60–8.45 (broad s, 1H, D_2O exch.), 8.15–8.10 (m, 1H), 7.46–7.37 (m, 2H), 6.76–6.74 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 141.20, 139.03, 127.75, 126.95, 117.57, 116.83, 111.10, 104.05; MS EI: m/z (%) 162 (M^+, 100%). HRMS ESI m/z ($M + H^+$) 152.02585. Calcd. 152.02615. Anal. calc. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.11; H, 3.46; N, 17.14.

Compound **6g**: Mp 129–130 °C; ^{1}H NMR ($CDCl_3$), δ 7.98 (d, 1H), 7.21 (d, 1H), 7.14 (t, 1H), 6.96 (d, 1H), 6.68 (dd, 1H), 6.39 (s, 1H), 3.51 (broad s, 2H); ^{13}C NMR ($CDCl_3$) δ 139.54, 130.63, 128.77, 124.69, 112.95, 111.49, 105.52, 101.56; MS ESI m/z (%) 133 ($M + H^+$, 100%). HRMS ESI m/z ($M + H^+$) 133.07560. Calcd. 133.07602. Anal. calc. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.11; H, 3.46; N, 17.14.

Compound **8**: Mp 71–72 °C; ^{1}H NMR ($CDCl_3$), δ 7.04–7.16 (m, 2H), 6.54–6.67 (m, 2H), 3.65 (broad s., 2H); ^{13}C NMR ($CDCl_3$) δ 144.92, 129.10, 123.14, 116.21; MS ESI m/z (%) 128 ($M + H^+$, 100%). HRMS ESI m/z ($M + H^+$) 128.02576. Calcd. 128.02615.

Compound **8a**: Mp 63–64 °C; ^{1}H NMR ($CDCl_3$), δ 7.33 (d, $J = 8.67$ Hz, 1H), 6.79 (d, $J = 2.64$ Hz, 1H), 6.45 (dd, $J = 8.67$, 2.64 Hz, 1H), 3.74 (broad s, 2H); ^{13}C NMR ($CDCl_3$) δ 146.64, 134.62, 133.88, 116.38, 114.92, 109.75; MS ESI m/z (%) 205 ($M + H^+$, 53%). HRMS ESI m/z ($M + H^+$) 205.93645. Calcd. 205.93667.

Compound **8b**: Mp 147–148 °C; ^{1}H NMR ($CDCl_3$), δ 8.08 (d, $J = 9.04$ Hz, 2H), 6.63 (d, $J = 9.04$ Hz, 2H), 4.41 (broad s, 2H); ^{13}C NMR ($CDCl_3$) δ 153.41, 138.37, 126.34, 113.16; MS EI m/z (%) 138 (M^+, 47%). Anal. calc. for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.50; H, 4.40; N, 19.99.

Compound **8c**: Mp 59–60 °C; ^{1}H NMR ($CDCl_3$), δ 6.72–6.79 (m, 2H), 6.63–6.70 (m, 2H), 3.76 (s, 3H), 3.43 (broad s, 2H); ^{13}C NMR ($CDCl_3$) δ 152.78, 139.90, 116.40, 114.78, 55.72; MS ESI m/z (%) 124 ($M + H^+$, 100%). HRMS ESI m/z ($M + H^+$) 124.07530. Calcd. 124.07569.

Compound **8d**: Oil; ^{1}H NMR ($CDCl_3$), δ 7.08 (t, $J = 8.10$ Hz, 1H), 6.21–6.39 (m, 3H), 3.78 (s, 3H), 3.68 (broad s, 2H); ^{13}C NMR ($CDCl_3$) δ 160.72, 147.78, 130.10, 107.90, 103.92, 101.04, 55.07; MS ESI m/z (%) 124 ($M + H^+$, 100%). HRMS ESI m/z ($M + H^+$) 124.07526. Calcd. 124.07569.

Compound **8e**: Mp 56–57 °C; ^{1}H NMR ($CDCl_3$), δ 7.63 (dd, $J = 7.91$, 1.32 Hz, 1H), 7.04–7.19 (m, 1H), 6.75 (dd, $J = 8.10$, 1.51 Hz, 1H), 6.38–6.54 (m, 1H), 4.07 (broad s, 2H); ^{13}C NMR ($CDCl_3$) δ 146.71, 138.96, 129.31, 119.95, 114.70, 84.15; MS ESI m/z (%) 220 ($M + H^+$, 100%). HRMS ESI m/z ($M + H^+$) 219.96147. Calcd. 219.96177.

Compound **8f**: Mp 135–136 °C; ^{1}H NMR ($CDCl_3$), δ 6.58 (s, 4H), 3.35 (broad s, 4H); ^{13}C NMR ($CDCl_3$) δ 138.57, 116.70; MS ESI m/z (%) 109 ($M + H^+$, 100%). HRMS ESI m/z ($M + H^+$) 109.07565. Calcd. 109.07602.

Compound **8g**: Oil; ^{1}H NMR ($CDCl_3$), δ 7.00 (t, $J = 8.01$ Hz, 1H), 6.30–6.20 (m, 3H), 3.60 (broad s, 2H), 1.19–1.33 (m, 3H), 1.09–1.14 (d, $J = 6.78$ Hz, 18H); ^{13}C NMR ($CDCl_3$) δ 157.48, 148.03, 130.26, 110.76, 108.64, 107.40, 18.36, 13.48; MS ESI m/z (%) 266 ($M + H^+$, 100%). HRMS ESI m/z ($M + H^+$) 266.19327. Calcd. 266.19347.

Compound **8h**: Mp 86–87 °C; ^{1}H NMR ($CDCl_3$), δ, 7.30–7.46 (m, 5H), 7.16 (d, $J = 7.54$ Hz, 2H), 6.61–6.69 (m, 2H), 6.51 (broad s, 1H), 5.19 (s, 2H), 3.57 (broad s, 2H); ^{13}C NMR (DMSO-d_6) δ 153.97, 144.70, 137.35, 128.76, 128.56, 128.32, 128.26, 120.59, 114.34, 65.66; MESI m/z (%) 243 ($M + H^+$, 100%). HRMS ESI m/z ($M + H^+$) 243.11249. Calcd. 243.11280.

Compound **8i**: Mp = 52–53 °C; ^{1}H NMR ($CDCl_3$), δ 7.16 (d, $J = 7.91$ Hz, 2H), 6.69–6.59 (m, 2H), 6.50 (broad s, 1 H), 6.08–5.87 (m, 1H), 5.41–5.30 (m, 1H), 5.29–5.20 (m, 1H), 4.57–4.73 (m, 2H), 3.58 (broad s, 2H); ^{13}C NMR (DMSO-d_6) δ 153.82, 144.70, 134.00, 128.33,

Downloaded by [University of York] at 19:21 19 May 2013

120.66, 117.57, 114.32, 64.61; MS ESI m/z (%) 193 ($M+H^+$, 100%). HRMS ESI m/z ($M+H^+$) 193.09683. Calcd. 193.09715.

Compound **10**: Oil; ^{1}H NMR ($CDCl_3$), δ 7.06–6.86 (m, 3H); 3.59–3.51 (m, 1H), 3.70–3.62 (m, 1H), 3.46–3.29 (m, 1H), 2.30 (s, 6H), 1.72 (broad s, 2H), 1.18 (d, $J=6.78$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 155.49, 130.81, 128.88, 123.83, 78.23, 47.29, 19.78, 16.32; MS ESI m/z (%) 180 ($M+H^+$, 100%). HRMS ESI m/z ($M+H^+$) 180.13782. Calcd. 180.13829.

Compound **12**: Oil; ^{1}H NMR ($CDCl_3$), δ 7.14 (d, $J=6.78$ Hz, 1H), 7.04 (t, $J=7.72$ Hz, 1H), 6.77–6.70 (m, 1H), 6.67 (d, $J=7.91$ Hz, 1H), 3.57 (t, $J=8.48$ Hz, 2H), 3.05 (t, $J=8.29$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 151.57, 123.31, 127.19, 124.62, 118.64, 109.43, 47.32, 29.82; MS ESI m/z (%) 120 ($M+H^+$, 100%). HRMS ESI m/z ($M+H^+$) 120.08030. Calcd. 120.08078.

Compound **14**: Mp = 104–105 °C; ^{1}H NMR ($CDCl_3$), δ 7.92 (d, $J=9.04$ Hz, 2H), 6.87 (d, $J=9.04$ Hz, 2H), 3.87 (s, 3H), 3.34–3.23 (m, 4H), 3.08–2.94 (m, 4H), 1.74 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 167.15, 154.56, 131.18, 119.67, 113.60, 51.65, 54.16, 48.65, 47.50, 45.89; MS ESI m/z (%) 221 ($M+H^+$, 100%). HRMS ESI m/z ($M+H^+$) 221.12805. Calcd. 221.12845.

(4-*t*-Butyldimethylsilyloxycyclopent-2-enyl)carbamic Acid *tert*-Butyl Ester 15

To a solution of (4-hydroxycyclopent-2-enyl)-carbamic acid tertbutyl ester[11] (0.75 g, 3.76 mmol) in DMF (10 mL), imidazole (282 mg, 4.14 mmol) and *t*-butyldimethylsilyl chloride (624 mg, 4.14 mmol) were added at room temperature. After stirring for 12 h at the same temperature, the reaction mixture was diluted with EtOAc (100 mL) and washed with water (3×100 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, hexane-EtOAc, 8:2). 1.15 g (97%) of product **15** as an oil; ^{1}H NMR (DMSO-d_6), δ 7.02 (broad d, $J=8.29$ Hz, 1H), 5.64–5.79 (m, 2H), 4.71–4.65 (m, 1H), 4.29 (m, 1H), 2.52–2.66 (m, 1H), 1.37 (s, 9H), 1.26–1.36 (m, 1H), 0.85 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (DMSO-d_6) δ 155.33, 136.07, 134.43, 77.94, 75.51, 54.13, 42.28, 28.61, 26.15, 18.14, −4.30; MS ESI m/z (%) 314 ($M+H^+$, 65%). HRMS ESI m/z ($M+Na^+$) 336.19675. Calcd. 336.19654.

Compound **16**: Oil; ^{1}H NMR ($CDCl_3$), δ 5.86–5.81 (m, 1H), 5.80–5.74 (m, 1H), 4.75–4.66 (m, 1H), 3.78–3.69 (m, 1H), 2.72–2.60 (m, 1H), 1.96 (broad s, 2H), 1.38–1.22 (m, 1H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 137.92, 135.57, 76.37, 56.50, 45.88, 26.32, 18.19,

Downloaded by [University of York] at 19:21 19 May 2013

−4.21; MS ESI m/z (%) 214 ($M + H^+$, 25%). HRMS ESI m/z ($M + H^+$) 214.16183. Calcd. 214.16217.

Compound **18**: Oil; ^{1}H NMR ($CDCl_3$), δ 6.04–5.97 (m, 1H), 5.88–5.79 (m, 1H), 5.58–5.47 (m, 1H), 3.93–3.78 (m, 1H), 2.86–2.69 (m, 1H), 2.05 (s, 3H), 1.62 (broad s, 2H), 1.48–1.32 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 170.79, 141.32, 130.67, 78.46, 56.49, 41.80, 21.65; MS ESI m/z (%) 142 ($M + H^+$, 100%). HRMS ESI m/z ($M + H^+$) 142.08592. Calcd. 142.08626.

Compound **20**: Oil; ^{1}H NMR ($CDCl_3$), δ 7.10–7.34 (m, 5H), 3.75–3.71 (dd, $J = 7.93$, 5.20 Hz, 1H), 3.71 (s, 3H), 3.08 (dd, $J = 13.38$, 5.09 Hz, 1H), 2.84 (dd, $J = 13.56$, 7.91 Hz, 1H), 1.52 (broad s, 2H); ^{13}C NMR ($CDCl_3$), δ 175.34, 137.12, 129.16, 128.47, 126.73, 55.73, 51.87, 41.00; MS ESI m/z (%) 180 ($M + H^+$, 100%). HRMS ESI m/z ($M + H^+$) 180.10156. Calcd. 180.10191.

Compound **22**: Mp = 111–112 °C; ^{1}H NMR ($CDCl_3$), δ 8.35 (broad s, 1H), 7.64 (d, $J = 7.91$ Hz, 1H), 7.44–7.32 (m, 1H), 7.26–7.18 (m, 1H), 7.18–7.09 (m, 1H), 7.04 (d, $J = 2.26$ Hz, 1H), 1.36 (broad s, 2H), 3.11–3.01 (m,2H), 2.99–2.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 136.44, 127.49, 122.06, 121.96, 119.21, 118.87, 113.69, 111.16, 42.34, 29.49; MS ESI m/z (%) 161 ($M + H^+$, 100%). HRMS ESI m/z ($M + H^+$) 161.10693. Calcd. 161.10732.

N-Boc-*trans*-4-(1,1-dioxido-2-isothiazolidinyl)cyclohexylamine 23

3-Chloro-propanesulfonyl chloride (5.4 mL, 44 mmol) was added dropwise to a solution of N-Boc-trans-1,4-cyclohexanediamine (7.6 g, 35 mmol) and triethylamine (18.25 mL, 131 mmol) in dichloromethane (250 mL) at 5 °C. The reaction mixture was stirred at room temperature for 12 h. Then the organic solution was washed with an aqueous solution of sodium bicarbonate (10%, 250 mL) and water (200 mL). The organic phase was dried (Na_2 SO_4), filtered, and concentrated to give 11.52 g (91%) of N-Boc-trans-4-[(3′-chloropropanesulfonyl)amino]cyclohexylamine: ^{1}H NMR ($CDCl_3$), δ 4.35 (broad d, 1H), 4.18 (broad d, 1H), 3.68 (t, 2H), 3.40–3.16 (m, 2H), 3.18 (t, 2H), 2.32–2.23 (m, 2H), 2.06 (broad t, 2H), 1.43 (s, 9H), 1.44–1.15 (m, 2H); MS EI m/z (%) 354 (M +, 10%). To 250 mL of degassed absolute ethanol, 0.344 g (15 mmol) of sodium and after dissolution, 5.3 g (15 mmol) of the product from previous step were added. The mixture was refluxed for 5.5 h and cooled to 25 °C, and the solvent was removed under vacuum. Flash chromatography (SiO_2, hexane–EtOAc, 8:2) gave the title compound **23** (3.4 g, 71%): mp = 155–156 °C; ^{1}H NMR ($CDCl_3$), δ 4.38 (broad s, 1 H), 3.51–3.30 (m, 2 H), 3.26 (t, $J = 6.59$ Hz, 2 H), 3.16–3.07 (m, 2 H),

Downloaded by [University of York] at 19:21 19 May 2013

2.40–2.24 (m, 2 H), 2.13–1.86 (m, 4 H), 1.66–1.47 (m, 2 H), 1.43 (s, 9 H), 1.32–1.15 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 155.14, 79.29, 51.89, 48.73, 46.94, 41.19, 32.21, 29.38, 28.36, 18.68; MS ESI m/z (%) 319 ($M+H^+$, 100%). HRMS ESI m/z ($M+H^+$) 319.16846. Calcd. 319.16860.

Compound **24**: Oil; ^{1}H NMR ($CDCl_3$), δ 3.34–3.48 (m, 1H), 3.27 (t, $J=6.78$ Hz, 2H), 3.12 (t, 2H), 2.55–2.69 (m, 1H), 2.25–2.40 (m, 2H), 1.85–2.02 (m, 4H), 1.45–1.62 (m, 2H), 1.36 (broad s, 2H), 1.14–1.30 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 52.56, 49.75, 47.07, 41.54, 35.50, 29.41, 18.70; MS ESI m/z (%) 219 ($M+H^+$, 100%). HRMS ESI m/z ($M+H^+$) 219.11609. Calcd. 219.11618.

Compound **26**: Mp = 139–140 °C; ^{1}H NMR ($CDCl_3$), δ 8.27 (broad s, 1H), 7.25–7.07 (m, 3H), 6.60–6.54 (m, 2H), 3.67 (t, 4H), 3.19 (t, 4H), 1.50 (s, 9H); ^{13} C NMR ($CDCl_3$), δ 154.94, 145.53, 136.97, 122.87, 122.66, 121.36, 106.87, 106.18, 100.94, 76.60, 51.31, 43.69, 28.47; MS ESI m/z (%) 302 ($M+H^+$, 100%). HRMS ESI m/z ($M+H^+$) 302.18616. Calcd. 302.18630.

Compound **27**: Mp = 198–199 °C (dec.); ^{1}H NMR (DMSO-d_6), δ 10.99 (broad s, 1H), 7.21 (t, $J=2.73$ Hz, 1H), 7.04–6.90 (m, 2H), 6.41 (dd, $J=7.16$, 1.13 Hz, 1H), 6.35 (t, $J=2.17$ Hz, 1 H), 3.06–2.97 (m, 4H), 2.95–2.86 (m, 4H); ^{13}C NMR (DMSO-d_6), δ 145.99, 136.96, 123.25, 121.57, 120.78, 105.75, 105.30, 99.93, 52.28, 45.98; MS ESI m/z (%) 202 ($M+H^+$, 100%). HRMS ESI m/z ($M+H^+$) 202.13351. Calcd. 202.13387.

Downloaded by [University of York] at 19:21 19 May 2013

ACKNOWLEDGMENT

The authors thank Joseph Muchowski, who suggested the use of HFIP as an alternative fluorinated solvent in this study. We also thank Yanzhou Liu and Kate Comstock for assistance in the analysis of all the compounds by NMR and HRMS.

REFERENCES

1. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 3rd ed.; John Wiley and Sons: New York, 1999; (b) Ganesan, A.; Yurek-George, A.; Srinivasan, N. Rapid deprotection of N-Boc amines by TFA combined with freebase generation using basic ion-exchange resins. *Mol. Diversity* **2005**, *9*, 291–293.
2. (a) Chakrabarty, M.; Kundu, T. Mild deprotection of *tert*-butyl carbamates of NH-heteroarenes under basic conditions. *Synth. Commun.* **2006**, *36*, 2069–2077; (b) Tom, J. N.; Simon, M. W.; Frost, H. N.; Ewing, M. Deprotection of a primary Boc group under basic conditions. *Tetrahedron Lett.* **2004**, *45*, 905–906.

3. Rawal, V. H.; Cava, M. P. Thermolytic removal of t-butyloxycarbonyl (BOC) protecting group on indoles and pyrroles. *Tetrahedron Lett.* **1985**, *26*(50), 6141–6142.
4. Siro, J. G.; Martin, J.; Garcia-Navio, J. L.; Remuiñan, M. J.; Vaquero, J. J. Easy microwave assisted deprotection of N-Boc derivatives. *Synlett* **1998**, 147–148.
5. (a) Gladysz, J. A.; Curran, D. P.; Horvath, I. T. Selective and clean reactions in fluorinated alcohols; In *Handbook of Fluorous Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004; pp. 341–350; (b) Begue, J. P.; Bonnet-Delpone, D.; Crousse, B. Fluorinated alcohols: A new medium for selective and clean reactions. *Synlett* **2004**, *1*, 18–29.
6. For recent reviews of microwave-assisted organic reactions, see (a) Mavandadi, F.; Pilotti, A. The impact of microwave-assisted organic synthesis in drug discovery. *Drug Disc. Today* **2006**, *11*(3–4), 165–173; (b) Man, A. K.; Shahidan, R. Microwave-assisted chemical reactions. *J. Macromol. Sci. Pure Appl. Chem.* **2007**, *44*, 651–657; (c) Alcázar, J.; Diels, G.; Schoentjes, B. Microwave assisted medicinal chemistry. *Mini-Rev. Med. Chem.* **2007**, *7*, 345–369.
7. Jaime-Figueroa, S.; Zamilpa, A.; Guzmán, A.; Morgans, D. J. N-3-Alkylation of uracil and derivatives via N-1-Boc protection. *Synth. Commun.*, **2001**, *31*(24), 3739–3746; (b) Arias, L.; Guzmán, A.; Jaime-Figueroa, S.; López, F. J.; Morgans Jr., D. J.; Padilla, F.; Pérez-Medrano, A.; Quintero, C.; Romero, M.; Sandoval, L. Direct N(3) alkylation of uracil and derivatives via N(1)-{2-[(trimethylsilyl)ethoxy]methyl} protection. *Synlett* **1997**, *11*, 1233–1234; (c) Gambacorta, A.; Farah, M. E.; Tofani, D. HSAB Driven chemoselectivity in alkylation of uracil derivatives. A high yielding preparation of 3-alkylated and unsymmetrically 1,3-dialkylated uracils. *Tetrahedron* **1999**, *55*, 12615–12628.
8. Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. Hydrazines and azides via the metal-catalyzed hydrohydrazination and hydroazidation of olefins. *J. Am. Chem. Soc.* **2006**, *128*(35), 11693–11712.
9. Kondo, Y.; Kojima, S.; Sakamoto, T. General and facile synthesis of indoles with oxygen-bearing substituents at the benzene moiety. *J. Org. Chem.* **1997**, *62*(19), 6507–6511.
10. Hu, L.; Rafferty, M. F.; Ryder, T. R. Aniline derivatives as a calcium channel blockers. PCT Int. Appl. WO 9907689, A1 19990218, 1999.
11. Dauvergne, J.; Happe, A. M.; Jadhav, V.; Justice, D.; Matos, M.; McCormack, P. J.; Pitts, M. R.; Roberts, S. M.; Singh, S. K.; Snape, T. J.; Whittall, J. Synthesis of 4-azacyclopent-2-enones and 5,5-dialkyl-4-azacyclopent-2-enones. *Tetrahedron* **2004**, *60*(11), 2559–2567.
12. Madera, A. M.; Weikert, R. J. 2,4-Substituted indoles and their use as 5-HT_6 modulators. PCT Int. Appl. WO 2004026831, A1 20040401, 2004.
13. Gonzalez, C.; Greenhouse, R.; Tallabs, R.; Muchowski, J. M. Protecting groups for the pyrrole nitrogen atom: The 2-chloroethyl, 2-phenylsulfonylethyl, and related moieties. *Canadian J. Chem.* **1983**, *61*(8), 1697–702.

Downloaded by [University of York] at 19:21 19 May 2013