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Di-*tert*-butyl dicarbonate: a versatile carboxylating reagent

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ABSTRACT

Carbon nucleophiles generated by a non-nucleophilic base (LDA) were effectively trapped with di-*tert*-butyl dicarbonate (Boc-anhydride) to provide the corresponding *tert*-butyl aryl acetates, di-*tert*-butyl aryl malonates, unsymmetrical aryl malonates and *tert*-butyl benzoates in high yields. This reaction represents another useful way to prepare a variety of *tert*-butyl carboxylates and highlights the synthetic utility of di-*tert*-butyl dicarbonate as a versatile carboxylating reagent.

1. Introduction

Di-*tert*-butyl dicarbonate (Boc-anhydride) is a widely used reagent in organic chemistry. It is an extremely efficient reagent to introduce the *tert*-butoxycarbonyl (BOC) protecting group for the amine functionality.[1] It is also an efficient *tert*-butoxycarbonylating agent for alcohols and thiols.[2] Boc-anhydride has been used for the conversion of amines to corresponding isocyanates, carbamates and urea derivatives.[3] In some cases, it is used as an apparent dehydrating agent when it reacts with carboxylic acids,[4] primary nitroalkanes,[5] or with certain hydroxyl groups.[6] It's easy to introduce and cleave as a protecting group add to its value as a versatile reagent.

Compounds possessing *tert*-butyl carboxylate functionality are useful building blocks in organic synthesis, preferably due to their ease of de-protection to the corresponding carboxylic acid under acidic medium. Esterification of a carboxylic acid with *tert*-butanol, *tert*-butyl bromide or isobutylene is the most common method of synthesis of a *tert*-butyl ester. As part of a research program aimed at developing a one step organic transformation to achieve *tert*-butyl acetates of some nitrogen heterocycles, we decided to explore the possibility of using Boc-anhydride as a carboxylating agent. Hongmei Li and Jaume Balsells have demonstrated the synthesis of *tert*-butyl benzoates from haloarenes bearing multiple halogen substituents via selective metal–halogen exchange with lithium tri-*n*-butylmagnesium ate complex, followed by reacting with Boc-anhydride.[7] Interestingly the broad scope and synthetic utility of this reagent as a carboxylating agent has not been explored for substrates that could not produce triarenemagnesium ate complexes. Herein, we report Boc-anhydride as a mild and efficient carboxylating reagent by demonstrating the synthesis of *tert*-butyl aryl acetates, substituted di-*tert*-butyl malonates and *tert*-butyl benzoates by trapping the carbon nucleophiles generated by a non-nucleophilic base such as LDA[8] with Boc-anhydride.

2. Results and discussion

Our initial investigations were aimed at scrutinizing the feasibility of trapping Boc-anhydride with carbanions generated by LDA. Accordingly, the nitrogen heterocycle **1a** was treated with a freshly prepared solution of LDA (1.1 equiv)[9] in THF at −78 °C for 0.5 h and to the resulting solution was added Boc-anhydride (1.1 equiv). To our satisfaction, the product formed was found to be the expected *tert*-butyl acetate **2a** in 84% isolated yield (entry 1, Table 1). Subsequently, we investigated the scope of this reagent as a *tert*-butyl carboxylating agent on other nitrogen heterocycles (entries 2–11, Table 1) having an active methyl group as shown in Scheme 1. This procedure was found to exhibit excellent scope, and the reaction condition was found to be optimal as we could obtain most of the products in good to excellent yields as depicted in Table 1. Surprisingly, 3-cyano-4-picoline did not react with LDA under this reaction conditions and only starting material was recovered from the reaction mixture (entry 8, Table 1). While pyridine and quinoline substrates provided good yield of products, moderate yield was

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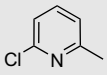
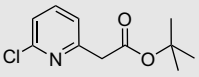
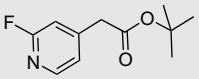
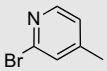
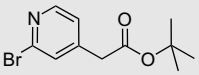
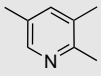
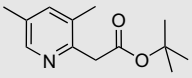
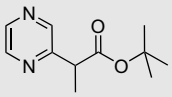
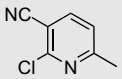
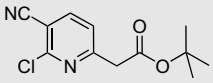
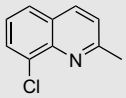
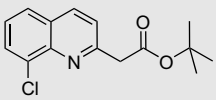
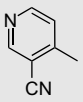
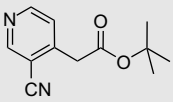
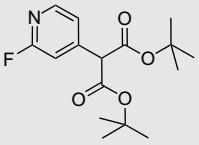
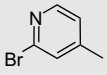
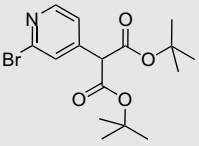
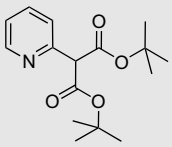
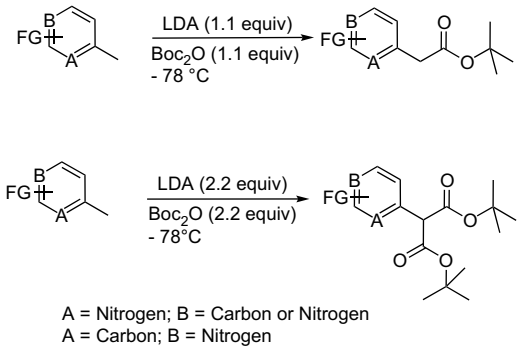
Table 1
Reaction of Boc-anhydride with carbon nucleophiles generated by LDA via Scheme 1

Entry	Substrate	Time (min)	Product	Yield[a] (%)
1	 **1a**	30	 **2a**	84
2	 **1b**	30	 **2b**	86
3	 **1c**	45	 **2c**	91
4	 **1d**	30	 **2d**	83
5	 **1e**	45	 **2e**	68
6	 **1f**	45	 **2f**	85
7	 **1g**	45	 **2g**	88
8	 **1h**	45	 **2h**	0[b]
9	 **1i**	30	 **2i**	93[c]
10	 **1j**	45	 **2j**	89[c]
11	 **1k**	45	 **2k**	81[c]

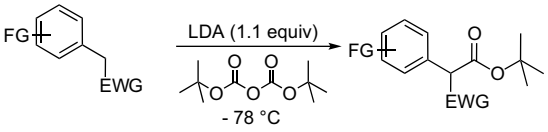
[a] Isolated yields.
[b] Starting material was recovered.
[c] Excess of LDA and Boc-anhydride (2.2 equiv each) were used.

obtained for pyrazine (entry 5, Table 1). Interestingly, the use of excess of LDA (2.2 equiv) and Boc-anhydride (2.2 equiv) led to the formation of di-*tert*-butyl malonates (entries 9–11, Table 1). It further emphasizes the synthetic utility of Boc-anhydride in producing the *tert*-butyl malonates of substrates possessing an active methyl group.



Scheme 1.

Having achieved the initial objective of *tert*-butyl acetate synthesis using Boc-anhydride as a carboxylating reagent, we proceeded to study the generality and efficacy of this method. With the optimal reaction conditions in hand, subsequently, we investigated the scope of this reaction on active methylene compounds (Scheme 2). A variety of active methylene compounds bearing multiple functional groups such as halo, methoxy, nitro, alkyl and trifluoromethoxy (entries 1–9, Table 2) participated effectively in this ester synthesis. Substrates having multiple reactive centres (entries 4 and 6, Table 2) were also studied. It is interesting to note that substrates having two reactive centers such as **3d** and **3f** gave exclusively **4d** and **4f** at −78 °C. Further, unlike in the case of active methyl substrates, the use of excess of LDA (2.2 equiv) and Boc-anhydride (2.2 equiv) failed to introduce a second *tert*-butyl carboxylate group on substrates possessing an active methylene group. As described in Table 2, this reaction was also found to be useful for the synthesis of *tert*-butyl benzoates (Scheme 3). Commercially available electron rich substrates such as **3j**–**3k** were reacted with Boc-anhydride under these conditions to provide the corresponding *tert*-butyl benzoates in good yields. The tolerance of functional group such as bromo under these conditions adds a synthetic advantage to this protocol (entries 10–12, Table 2).



Scheme 2.

3. Conclusion

In summary, carbanions generated by a non-nucleophilic base (LDA) were effectively trapped with di-*tert*-butyl dicarbonate to provide the corresponding *tert*-butyl carboxylates in high yields. This reaction represents another useful way to prepare a variety of *tert*-butyl aryl acetates, di-*tert*-butyl aryl malonates and *tert*-butyl benzoates and highlights the synthetic utility of di-*tert*-butyl dicarbonate as a versatile carboxylating reagent.

Table 2
Reaction of Boc-anhydride with carbon nucleophiles generated by LDA via Schemes 2 and 3

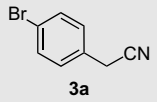
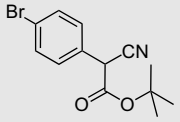
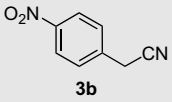
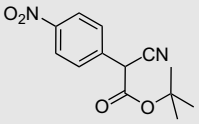
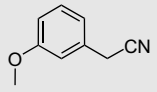
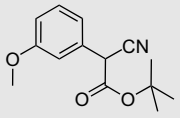
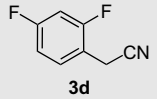
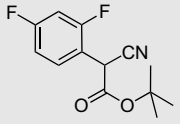
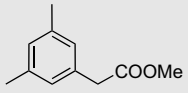
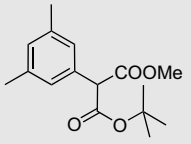
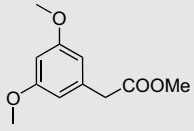
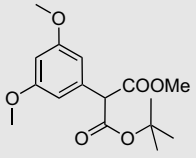
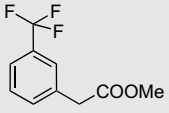
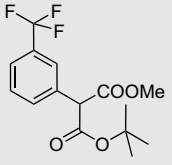
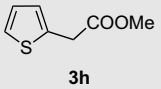
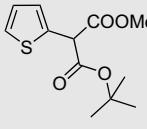
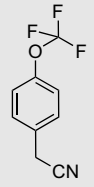
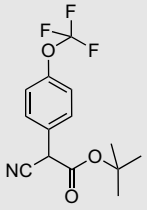
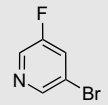
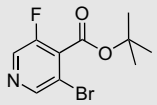
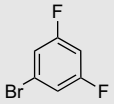
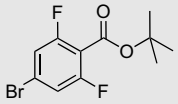
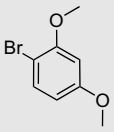
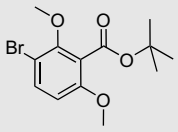
Entry	Substrate	Time (min)	Product[a]	Yield[b] (%)
1	 **3a**	60	 **4a**	89
2	 **3b**	90	 **4b**	90
3	 **3c**	60	 **4c**	86
4	 **3d**	60	 **4d**	88
5	 **3e**	70	 **4e**	92
6	 **3f**	70	 **4f**	85
7	 **3g**	70	 **4g**	91
8	 **3h**	70	 **4h**	84
9	 **3i**	70	 **4i**	87

Table 2 (*continued*)

Entry	Substrate	Time (min)	Product[a]	Yield[b] (%)
10	 **3j**	70	 **4j**	91
11	 **3k**	70	 **4k**	84
12	 **3l**	70	 **4l**	87

[a] Isolated yields.
[b] Excess LDA and Boc-anhydride (2.1 equiv each) were used.

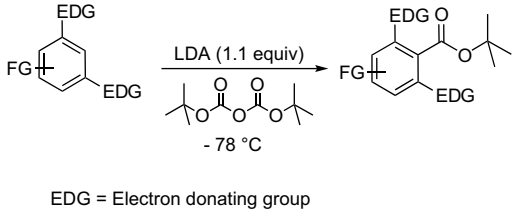
4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on 400-MHz and 100-MHz Bruker spectrometer, respectively, and elemental analysis was performed on a Thermo Finnigan FLASH EA 1112 CHN analyzer. ^{19}F NMR spectra were recorded on 376-MHz Bruker spectrometer. Melting points were recorded (uncorrected) on Buchi Melting Point B-545 instrument. Infrared spectra were recorded on a Thermo Scientific Nicolet 6700 FT-IR spectrometer. Coupling constants were reported wherever it was necessary in hertz (Hz). The mass spectra were recorded on Agilent LC/MSD SL 1100 instrument. Reactions were carried out in an oven dried three-necked round-bottomed flask. Yields in table refer to isolated yields of compounds with purity >95% as determined by ^{1}H NMR and HPLC analysis.

4.2. General procedure for the preparation of 2a–2g and 4a–4l

To a solution of diisopropylamine (0.12 mol) in THF (100 mL) at −78 °C was added *n*-BuLi (0.11 mol, 3 M solution in hexane) in drops over a period of 15 min and the resulting solution was stirred at −78 °C for additional 30 min. To the above LDA solution was added substrates **1a–1g** and **3a–3l** (0.10 mol) in THF (20 mL) in drops and the reaction mixture was stirred for 1 h. To this was added Boc-anhydride (0.11 mol) and the reaction mixture was slowly allowed to room temperature over a period of 2 h, and diluted with water (200 mL). The product was extracted with diethyl ether (2×100 mL). The combined organic layer was washed with water (100 mL), brine (50 mL) and dried over sodium sulfate. The



Scheme 3.

organic phase was concentrated under reduced pressure and the residue was purified by flash chromatography (1–5% EtOAc/hexane) to afford compounds **2a**–**2g** and **4a**–**4l** as colourless liquids.

The same protocol was used for the synthesis of **2i**–**2k**, except for the fact that 0.05 mmol of **1i**–**1k** were used.

*4.2.1. tert-Butyl (6-chloropyridin-2-yl)acetate (**2a**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.60; ν_{max} (liquid film) 1726, 1584, 1439, 1134 cm^{-1}; [Found: C, 58.09; H, 6.25; N, 6.12. $C_{11}H_{14}ClNO_2$ requires: C, 58.03; H, 6.20; N, 6.15%.] δ_H (400 MHz, $CDCl_3$) 7.63–7.59 (1H, t, Ph), 7.23–7.21 (2H, m, Ph), 3.73 (2H, s, CH_2COO^tBu), 1.44 (9H, s, COO^tBu); δ_C (100.6 MHz, DMSO-d_6) 169.3, 155.7, 150.6, 139.0, 122.5, 122.4, 81.5, 44.5, 28.0; MS (ESI) 228 $[M+H]^+$.

*4.2.2. tert-Butyl (2-fluoropyridin-4-yl)acetate (**2b**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.60; ν_{max} (liquid film) 1726, 1612, 1465, 1280, 1137, 854 cm^{-1}; [Found: C, 62.61; H, 6.74; N, 6.60. $C_{11}H_{14}FNO_2$ requires: C, 62.55; H, 6.68; N, 6.63%.] δ_H (400 MHz, $CDCl_3$) 8.18–8.16 (1H, d, *J* 5.1 Hz, Ph), 7.12–7.10 (1H, d, *J* 5.1 Hz, Ph), 6.88 (1H, s, Ph), 3.57 (2H, s, CH_2COO^tBu), 1.45 (9H, s, COO^tBu); δ_C (100.6 MHz, $CDCl_3$) 168.6, 165.1, 162.7, 149.1, 149.1, 147.5, 147.4, 129.1, 127.6, 122.5, 122.2, 110.3, 109.9, 81.9, 41.7, 41.7, 27.9; δ_F (376.5 MHz, $CDCl_3$) −68.34 (1F, s); MS (ESI) 212 $[M+H]^+$.

*4.2.3. tert-Butyl (2-bromopyridin-4-yl)acetate (**2c**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.60; ν_{max} (liquid film) 1725, 1588, 1416, 1380, 1140, 834 cm^{-1}; [Found: C, 48.60; H, 5.23; N, 5.13. $C_{11}H_{14}BrNO_2$ requires: C, 48.55; H, 5.19; N, 5.15%.] δ_H (400 MHz, $CDCl_3$) 8.32–8.31 (1H, d, *J* 5.0 Hz, Ph), 7.43 (1H, s, Ph), 7.20–7.18 (1H, dd, *J* 5.0, 1.2 Hz, Ph), 3.51 (2H, s, CH_2COO^tBu), 1.45 (9H, s, COO^tBu); δ_C (100.6 MHz, $CDCl_3$) 168.5, 149.9, 146.4, 142.3, 128.8, 123.6, 82.0, 41.4, 27.9; MS (ESI) 274 $[M+2]^+$.

*4.2.4. tert-Butyl (3,5-dimethylpyridin-2-yl)acetate (**2d**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.65; ν_{max} (liquid film) 1727, 1472, 1366, 1143, 884 cm^{-1}; [Found: C, 70.59; H, 8.70; N, 6.30. $C_{13}H_{19}NO_2$ requires: C, 70.56; H, 8.65; N, 6.33%.] δ_H (400 MHz, DMSO-d_6) 8.11 (1H, s, Ph), 7.37 (1H, s, Ph), 3.68 (2H, s, CH_2COO^tBu), 2.22 (3H, s, Ph*Me*), 2.19 (3H, s, Ph*Me*), 1.37 (9H, s, COO^tBu); δ_C (100.6 MHz, $CDCl_3$) 170.0, 150.7, 147.0, 138.6, 131.6, 131.5, 81.0, 42.7, 28.0, 18.6, 17.9; MS (ESI) 222 $[M+H]^+$.

*4.2.5. tert-Butyl 2-pyrazin-2-ylpropanoate (**2e**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.50; ν_{max} (liquid film) 1726, 1403, 1367, 1142, 1081, 847 cm^{-1}; [Found: C, 63.51; H, 7.83; N, 13.39. $C_{11}H_{16}N_2O_2$ requires: C, 63.44; H, 7.74; N, 13.45%.] δ_H (400 MHz, $CDCl_3$) 8.58–8.58 (1H, d, *J* 1.4 Hz, Ph), 8.53–8.52 (1H, dd, *J* 2.4, 1.6 Hz, Ph), 8.47–8.46 (1H, d, *J* 2.5 Hz, Ph), 3.90–3.85 (1H, q, Ph*CH*Me), 1.56–1.55 (3H, d, PhCH*Me*), 1.41 (9H, s, COO^tBu); δ_C (100.6 MHz, $CDCl_3$) 171.8, 156.0, 144.2, 143.9, 142.9, 81.4, 46.5, 27.9, 16.6; MS (ESI) 209 $[M+H]^+$.

*4.2.6. tert-Butyl (6-chloro-5-cyanopyridin-2-yl)acetate (**2f**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.65; ν_{max} (liquid film) 1727, 1585, 1366, 1142, 1072, 785 cm^{-1}; [Found: C, 57.10; H, 5.23; N, 11.01. $C_{12}H_{13}ClN_2O_2$ requires: C, 57.04; H, 5.19; N, 11.09%.] δ_H (400 MHz, $CDCl_3$) 7.97–7.95 (1H, d, *J* 8 Hz, Ph), 7.41–7.39 (1H, d, *J* 8 Hz, Ph), 3.82 (2H, s, CH_2COO^tBu), 1.46 (9H, s, COO^tBu); δ_C (100.6 MHz, $CDCl_3$) 168.0, 159.7, 152.0, 142.5, 122.6, 114.7, 108.9, 82.3, 44.7, 27.9; MS (ESI) 253 $[M+H]^+$.

*4.2.7. tert-Butyl (8-chloroquinolin-2-yl)acetate (**2g**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.70; ν_{max} (liquid film) 1725, 1625, 1408, 1135, 998, 755 cm^{-1}; [Found: C, 64.90; H, 5.89; N, 4.99. $C_{15}H_{16}ClNO_2$ requires: C, 64.87; H, 5.81; N, 5.04%.] δ_H (400 MHz, $CDCl_3$) 8.15–8.13 (1H, d, *J* 8.4 Hz, Ph), 7.83–7.81 (1H, dd, *J* 7.4, 1.2 Hz, Ph), 7.74–7.72 (1H, dd, *J* 8.2, 1.2 Hz, Ph), 7.52–7.50 (1H, d, *J* 8.4 Hz, Ph), 7.45–7.41 (1H, t, Ph), 4.05 (2H, s, CH_2COO^tBu), 1.49 (9H, s, COO^tBu); δ_C (100.6 MHz, $CDCl_3$) 169.6, 156.4, 144.0, 136.6, 133.2, 129.6, 128.3, 126.6, 126.1, 122.7, 81.4, 45.9, 28.0; MS (ESI) 278 $[M+H]^+$.

*4.2.8. Di-tert-butyl (2-fluoropyridin-4-yl)malonate (**2i**)*

Off-white solid; R_f (10% EtOAc/hexane) 0.70; mp 45.5–47.2 °C; ν_{max} (KBr) 1733, 1610, 1414, 1285, 1139, 849 cm^{-1}; [Found: C, 61.77; H, 7.19; N, 4.45. $C_{16}H_{22}FNO_4$ requires: C, 61.72; H, 7.12; N, 4.50%.] δ_H (400 MHz, $CDCl_3$) 8.22–8.21 (1H, d, *J* 5.1 Hz, Ph), 7.23–7.21 (1H, m, Ph), 7.01 (1H, s, Ph), 4.4 (2H, s, $CH(COO^tBu)_2$), 1.48 (18H, s, $CH(COO^tBu)_2$); δ_C (100.6 MHz, $CDCl_3$) 165.5, 164.9, 162.6, 147.6, 147.5, 147.4, 122.2, 122.1, 110.6, 110.2, 83.1, 59.2, 59.1, 28.0; δ_F (376.5 MHz, $CDCl_3$) −67.73 (1F, s); MS (ESI) 312 $[M+H]^+$.

*4.2.9. Di-tert-butyl (2-bromopyridin-4-yl)malonate (**2j**)*

White solid; R_f (10% EtOAc/hexane) 0.75; mp 64.8–66.2 °C; ν_{max} (KBr) 1739, 1731, 1588, 1456, 1369, 1134, 1085, 843 cm^{-1}; [Found: C, 51.67; H, 6.03; N, 3.70. $C_{16}H_{22}BrNO_4$ requires: C, 51.62; H, 5.96; N, 3.76%.] δ_H (400 MHz, $CDCl_3$) 8.37–8.35 (1H, d, *J* 5.1 Hz, Ph), 7.53 (1H, s, Ph), 7.33–7.32 (1H, dd, *J* 5.1, 1.2 Hz, Ph), 4.38 (1H, s, $CH(COO^tBu)_2$), 1.47 (18H, s, $CH(COO^tBu)_2$); δ_C (100.6 MHz, $CDCl_3$) 165.5, 149.9, 144.8, 142.2, 128.8, 123.5, 83.2, 58.9, 27.8; MS (ESI) 374 $[M+2]^+$.

*4.2.10. Di-tert-butyl (pyridin-2-yl)malonate (**2k**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.70; ν_{max} (liquid film) 1725, 1472, 1367, 1128, 757 cm^{-1}; [Found: C, 65.60; H, 8.03; N, 4.69. $C_{16}H_{23}NO_4$ requires: C, 65.51; H, 7.90; N, 4.77%.] δ_H (400 MHz, $CDCl_3$) 8.56–8.55 (1H, m, Ph), 7.73–7.68 (1H, m, Ph), 7.52–7.50 (1H, dd, *J* 7.9, 0.7 Hz, Ph), 7.25–7.21 (1H, m, Ph), 4.76 (1H, s, $CH(COO^tBu)_2$), 1.47 (18H, s, $CH(COO^tBu)_2$); δ_C (100.6 MHz, $CDCl_3$) 166.8, 153.8, 149.1, 136.4, 123.6, 122.7, 82.2, 62.7, 27.7; MS (ESI) 294 $[M+H]^+$.

*4.2.11. tert-Butyl (4-bromophenyl)(cyano)acetate (**4a**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.85; ν_{max} (liquid film) 1738, 1488, 1369, 1142, 1072, 1012, 829 cm^{-1}; [Found: C, 52.76; H, 4.81; N, 4.68. $C_{13}H_{14}BrNO_2$ requires: C, 52.72; H, 4.76; N, 4.73%.] δ_H (400 MHz, $CDCl_3$) 7.57–7.54 (2H, d, *J* 11.1 Hz, Ph), 7.34–7.31 (2H, d, *J* 11.1 Hz, Ph), 4.5 (1H, s, $CHCOO^tBu$), 1.48 (9H, s, COO^tBu); δ_C (100.6 MHz, $CDCl_3$) 163.3, 132.4, 132.2, 131.3, 129.4, 123.3, 115.5, 84.9, 44.2, 27.6; MS (ESI) 298 $[M+2]^+$.

*4.2.12. tert-Butyl cyano (4-nitrophenyl)acetate (**4b**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.8; ν_{max} (liquid film) 1738, 1523, 1370, 1346, 1142, 833 cm^{-1}; [Found: C, 59.60; H, 5.42; N, 10.58. $C_{13}H_{14}N_2O_4$ requires: C, 59.54; H, 5.38; N, 10.68%.] δ_H (400 MHz, $CDCl_3$) 8.30–8.28 (2H, d, *J* 8.8 Hz, Ph), 7.67–7.65 (2H, d, *J* 8.6 Hz, Ph), 4.76 (1H, s, $CHCOO^tBu$), 1.46 (9H, s, COO^tBu); δ_C (100.6 MHz, $CDCl_3$) 162.5, 148.3, 137.0, 129.0, 124.3, 114.8, 85.7, 44.4, 27.6; MS (ESI) 263 $[M+H]^+$.

*4.2.13. tert-Butyl cyano (3-methoxyphenyl)acetate (**4c**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.85; ν_{max} (liquid film) 1737, 1601, 1490, 1394, 1141, 1044, 769 cm^{-1}; [Found: C, 68.07; H, 7.00; N, 5.62. $C_{14}H_{17}NO_3$ requires: C, 68.00; H, 6.93; N, 5.66%.] δ_H (400 MHz, $CDCl_3$) 7.32–7.30 (1H, t, Ph), 7.03–6.91 (3H, m, Ph), 4.58 (1H, s, $CHCOO^tBu$), 3.83 (3H, s, OCH_3), 1.48 (9H, s, COO^tBu); δ_C (100.6 MHz, $CDCl_3$) 163.7, 160.0, 131.7, 130.2, 120.0, 115.9, 114.6, 113.3, 84.5, 55.3, 44.7, 27.6; MS (ESI) 248 $[M+H]^+$.

*4.2.14. tert-Butyl cyano (2,4-difluorophenyl)acetate (**4d**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.85; ν_{max} (liquid film) 1742, 1616, 1506, 1395, 1278, 1141, 967, 850 cm^{-1}; [Found: C, 61.70;

H, 5.23; N, 5.47. $C_{13}H_{13}F_2NO_2$ requires: C, 61.66; H, 5.17; N, 5.53%.] δ_H (400 MHz, $CDCl_3$) 7.52–7.46 (1H, m, Ph), 7.00–6.97 (1H, m, Ph), 6.96–6.88 (1H, m, Ph), 4.87 (1H, s, *CH*COO^{t}Bu), 1.48 (9H, s, COO^t*Bu*); δ_C (100.6 MHz, $CDCl_3$) 164.7, 164.6, 162.6, 162.2, 162.1, 161.4, 161.3, 158.9, 158.8, 130.6, 130.5, 130.5,115.0, 114.6, 114.4, 112.4, 112.3, 112.1, 112.1, 104.8, 104.5, 104.3, 85.2, 37.8, 37.8, 27.6; δ_F (376.5 MHz, $CDCl_3$) −107.32 (1F, d, J_{FF} 9.0 Hz), −112.12 (1F, d, J_{FF} 9.0 Hz); MS (ESI) 254 $[M+H]^+$.

*4.2.15. tert-Butyl methyl (3,5-dimethylphenyl)malonate (**4e**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.85; ν_{max} (liquid film) 1730, 1606, 1253, 1131, 849 cm^{-1}; [Found: C, 69.09; H, 8.03. $C_{16}H_{22}O_4$ requires: C, 69.04; H, 7.97%.] δ_H (400 MHz, $CDCl_3$) 6.98 (2H, s, Ph), 6.96 (1H, s, Ph), 4.48 (1H, s, *CH*COO^{t}Bu), 3.75 (3H, s, COO*Me*), 3.32 (6H, s, Ph*Me*), 1.47 (9H, s, COO^t*Bu*); δ_C (100.6 MHz, $CDCl_3$) 169.2, 167.2, 138.0, 132.8, 129.8, 128.9, 82.2, 58.6, 52.6, 27.8, 21.2; MS (ESI) 279 $[M+H]^+$.

*4.2.16. tert-Butyl methyl (3,5-dimethoxyphenyl)malonate (**4f**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.80; ν_{max} (liquid film) 1730, 1596, 1431, 1298, 1135, 783 cm^{-1}; [Found: C, 64.56; H, 6.93. $C_{15}H_{19}O_5$ requires: C, 64.50; H, 6.86%.] δ_H (400 MHz, $CDCl_3$) 6.54–6.53 (2H, d, *J* 2.2 Hz, Ph), 6.43–6.42 (1H, d, *J* 2.2 Hz, Ph), 4.47 (1H, s, *CH*COO^{t}Bu), 3.78 (6H, s, PhO*Me*), 3.75 (3H, s, COO*Me*), 1.46 (9H, s, COO^t*Bu*); δ_C (100.6 MHz, $CDCl_3$) 168.8, 166.8, 160.6, 134.9, 107.3, 100.2, 82.4, 58.8, 55.3, 52.6, 27.8; MS (ESI) 311 $[M+H]^+$.

*4.2.17. tert-Butyl methyl [3-(trifluoromethyl)phenyl]malonate (**4g**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.85; ν_{max} (liquid film) 1730, 1453, 1328, 1121, 700 cm^{-1}; [Found: C, 56.67; H, 5.43. $C_{15}H_{17}F_3O_4$ requires: C, 56.60; H, 5.38%.] δ_H (400 MHz, $CDCl_3$) 7.65 (1H, s, Ph), 7.62–7.59 (2H, m, Ph), 7.51–7.48 (1H, t, Ph), 4.61 (1H, s, *CH*COO^{t}Bu), 3.77 (3H, s, COO*Me*), 1.46 (9H, s, COO^t*Bu*); δ_C (100.6 MHz, $CDCl_3$) 168.3, 166.4, 133.9, 132.7, 131.0, 130.7, 128.9, 126.2, 126.2, 125.2, 125.0, 124.9, 122.5, 83.0, 58.5, 52.8, 27.7; MS (ESI) 319 $[M+H]^+$.

*4.2.18. tert-Butyl methyl 2-thienylmalonate (**4h**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.80; ν_{max} (liquid film) 1730, 1394, 1239, 1134, 700 cm^{-1}; [Found: C, 56.30; H, 6.34. $C_{12}H_{16}O_4S$ requires: C, 56.23; H, 6.29%.] δ_H (400 MHz, $CDCl_3$) 7.32–7.30 (1H, dd, *J* 5.2, 1.1 Hz, Ph), 7.09–7.07 (1H, m, Ph), 7.00–6.98 (1H, dd, *J* 5.1, 3.61 Hz, Ph), 4.85 (1H, s, *CH*COO^{t}Bu), 3.78 (3H, s, COO*Me*), 1.47 (9H, s, COO^t*Bu*); δ_C (100.6 MHz, $CDCl_3$) 168.1, 166.1, 133.8, 127.7, 126.4, 126.2, 82.2, 54.0, 52.9, 27.7; MS (ESI) 257 $[M+H]^+$.

*4.2.19. tert-Butyl cyano [4-(trifluoromethoxy)phenyl]acetate (**4i**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.85; ν_{max} (liquid film) 1740, 1508, 1253, 1142, 835 cm^{-1}; [Found: C, 55.89; H, 4.73; N, 4.60. $C_{14}H_{14}F_3NO_3$ requires: C, 55.82; H, 4.68; N, 4.65%.] δ_H (400 MHz, $CDCl_3$) 7.51–7.48 (2H, dd, *J* 8.6, 1.9 Hz, Ph), 7.29–7.29 (2H, m, Ph), 4.64 (1H, s, *CH*COO^{t}Bu), 1.48 (9H, s, COO^t*Bu*); δ_C (100.6 MHz, $CDCl_3$) 163.3, 149.6, 129.4, 129.0, 121.5, 119.0, 115.5, 85.0, 44.0, 27.6; MS (ESI) 302 $[M+H]^+$.

*4.2.20. tert-Butyl 3-bromo-5-fluoroisonicotinate (**4j**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.75; ν_{max} (liquid film) 1736, 1548, 1403, 1292, 1160, 1106, 885 cm^{-1}; [Found: C, 43.55; H, 4.10; N, 5.00. $C_{10}H_{11}BrFNO_2$ requires: C, 43.50; H, 4.02; N, 5.07%.] δ_H (400 MHz, $CDCl_3$) 8.58 (1H, s, Ph), 8.47 (1H, s, Ph), 1.62 (9H, s, COO^t*Bu*); δ_C (100.6 MHz, $CDCl_3$) 160.6, 156.3, 153.7, 147.8, 147.8, 137.2, 137.0, 132.1, 132.0, 116.9, 85.4, 28.0; δ_F (376.5 MHz, $CDCl_3$) −127.24 (1F, s); MS (ESI) 278 $[M+2]^+$.

*4.2.21. tert-Butyl 4-bromo-2,6-difluorobenzoate (**4k**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.85; ν_{max} (liquid film) 1728, 1613, 1415, 1307, 1111, 839 cm^{-1}; [Found: C, 45.15; H, 3,82. $C_{11}H_{11}BrF_2O_2$ requires: C, 45.08; H, 3.78%.] δ_H (400 MHz, $CDCl_3$) 7.14–7.13 (1H, t, Ph), 7.11–7.10 (1H, t, Ph), 1.58 (9H, s, COO^t*Bu*); δ_C (100.6 MHz, $CDCl_3$) 161.5, 161.4, 159.8, 158.9, 158.9, 124.4, 124.3, 124.2, 116.0, 116.0, 115.9, 115.8, 115.7, 115.7, 112.2, 83.8, 28.0; δ_F (376.5 MHz, $CDCl_3$) −109.94 (2F, s); MS (ESI) 295 $[M+2]^+$.

*4.2.22. tert-Butyl 3-bromo-2,6-dimethoxybenzoate (**4l**)*

Colourless liquid; R_f (10% EtOAc/hexane) 0.85; ν_{max} (liquid film) 1721, 1583, 1462, 1296, 1087, 742 cm^{-1}; [Found: C, 49.29; H, 5.45. $C_{13}H_{17}BrO_4$ requires: C, 49.23; H, 5.40%.] δ_H (400 MHz, $CDCl_3$) 7.47–7.45 (1H, d, *J* 8.9 Hz, Ph), 6.60–6.58 (1H, d, *J* 8.9 Hz, Ph), 3.90 (3H, s, PhO*Me*), 3.81 (3H, s, PhO*Me*), 1.59 (9H, s, COO^t*Bu*); δ_C (100.6 MHz, $CDCl_3$) 164.4, 156.4, 154.1, 133.6, 121.8, 108.5, 107.7, 82.5, 62.0, 56.2, 28.1; MS (ESI) 319 $[M+2]^+$.

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