Synthesis of ureas from titanium imido complexes using CO_2 as a C-1 reagent at ambient temperature and pressure

James C. Anderson and Rafael Bou Moreno*

Department of Chemistry, University College London, 20 Gordon Street, London, WC1H 0AJ UK

j.c.anderson@ucl.ac.uk

General experimental

All experimental procedures unless otherwise stated were carried out under an atmosphere of dry, oxygen free nitrogen. Those involving metal complexes were performed using standard Schlenk techniques. All glassware was rigourously flame-dried prior to use and a nitrogen atmosphere was maintained throughout the process. All reactions involving carbon dioxide were performed using a freshly prepared saturated solution of carbon dioxide. Degassed solutions and solvents were prepared by repeating a cycle of solidifying with a liquid nitrogen bath, applying *vacuum* (30 seconds) and melting three times. All carbon dioxide pressures were measured with a manometer at the head of the cylinder and performed in Schlenk flasks (NOTE: Pressurised glass flasks could susceptible to explosion under pressure conditions). NMR experiments were prepared using a glove box and pre-dried Young's Tap NMR tubes. Reactions at room temperature imply temperatures in the range 20 - 25 °C. Reaction solvents were purchased as HPLC grade and dried by passing them through activated alumina towers (dichloromethane, hexanes and toluene) or activated alumina and CaO towers (THF and Et_2O). All reagents were purchased and used without further purification unless otherwise stated. All amines, anilines, pyridines and phenols were redistilled or recrystallised according to literature procedures.[1] Column chromatography was performed using BDH 60 silica gel in the indicated solvent. Chromatography solvents were used as supplied without further purification. Column chromatography was monitored by thin layer chromatography (TLC) performed on Polgram SIL G/UV_{254} plastic backed plates in the indicated solvent and were visualised by combination of ultraviolet light (254 nm) and a visualising dip of potassium permanganate. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 298 K in $CDCl_3$, unless otherwise stated.

General method A: 2a with CO_2 to give 3a. To a degassed solution of **2a**[2] (349 mg, 1.00 mmol) in CH_2Cl_2 (20 mL), was added CO_2 (1.5 atmospheres). After stirring for 5 h, the brown solution was quenched with 2M HCl (20 mL) and stirred for another1 h. The biphasic mixture was neutralised with $NaHCO_3$. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The combined organic layers were dried ($MgSO_4$) filtered and concentrated in vacuo. Purification by flash column chromatography (Et_2O:hexanes, 20% to 50%) afforded **3a** (4 mg, 8%) as a white solid mp 238 - 240 °C (lit. 238 - 239 °C), that was judged >95% pure by NMR. Rf 0.14 (50%, Et_2O:hexanes). ^{1}H NMR δ 1.32 (9H, s, C(C*H*$_3$)$_3$), 4.05 (1H, s$_{br}$, N*H*). ^{13}C NMR δ 29.7 (*C*H$_3$), 50.3 (*C*(CH$_3$)$_3$), 157.0 (*C*O). Spectroscopic data was in agreement with the literature.[3]

10a with CO_2 to give 3a. **10a** (427 mg, 1.00 mmol) was treated with CO_2 according to General method A to give **3a** (7 mg, 14%), that was judged >95% pure by NMR.

10b with CO_2 to give 3b. **10b** (540 mg, 1.07 mmol) was treated with CO_2 according to General method A to give **3b** (189 mg, 98%) mp 234 - 232 °C (lit. 230 °C) , that was judged >95% pure by NMR. ^{1}H NMR δ 1.16 (12H, d, *J* = 5.6, CH(C*H*$_3$)$_2$), 3.07 (2H, sept, *J* = 5.6, C*H*(CH$_3$)$_2$), 6.80 - 7.25 (3H, m, C*H*$_{Ar}$), 7.72 (1H, s$_{br}$, N*H*). Spectroscopic data was in agreement with the literature.[4]

General method B: 10b with CO_2 then NaOEt to give 3b. To a degassed solution of **10b** (630 mg, 1.19 mmol) in CH_2Cl_2 (20 mL), was added CO_2 (1.5 atmospheres). After stirring for 5 h, the brown solution was quenched with NaOEt (812 mg, 12.0 mmol) and stirred for another 1 h. The pale orange mixture was quenched with 2M HCl (20 mL) and stirred for another 1 h. The biphasic mixture was neutralised with $NaHCO_3$. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The combined organic layers were dried ($MgSO_4$) filtered and concentrated in vacuo. Purification by flash column chromatography (Et_2O:hexanes, 20% to 50%) afforded **3b** (306 mg, 68%) as a white solid, that was judged >95% pure by NMR.

10b with CO_2 then $BnNH_2$ to give 11. **10b** (1.06 g, 2.00 mmol) was treated with CO_2 and $BnNH_2$(0.22 mL, 2.00 mmol) according to General method B to give **11** (114 mg, 18%) as a white solid, that was judged >95% pure by NMR. mp 185 - 186 °C (lit. 186 - 188). ^{1}H NMR δ 1.16 (12H, d, *J* = 5.6, CH(C*H*$_3$)$_2$), 3.31 (2H, sept, *J* = 5.6, C*H*(CH$_3$)$_2$), 4.39 (2H, d, *J* = 4.8, C*H*$_2$Ph), 4.50 (1H, s$_{br}$, N*H*), 5.97 (1H, s$_{br}$, N*H*), 7.15 - 7.35 (8H, m, C*H*$_{Ar}$). ^{13}C NMR δ 28.4 (CH(*C*H$_3$)$_2$), 44.2 (*C*H$_2$Ph), 124.2 (*C*H$_{Ar}$), 127.3 (*C*H$_{Ar}$), 127.6 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 129.2 (*C*$_{Ar}$), 130.7 (*C*$_{Ar}$), 139.2 (*C*H$_{Ar}$), 148.1 (*C*$_{Ar}$), 157.6 (*C*O). Missing primary carbon. Spectroscopic data was in agreement with the literature.[5]

General Method C: 2a with *t*-BuNCO then HCl to give 3a. To a bright orange solution of **2a**[1] (350 mg, 1.00 mmol) in dry dichloromethane (15 mL) at rt under N_2 a solution of freshly prepared t-BuNCO (99 mg, 1 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise over approximately 30 seconds. The bright orange solution turned immediately to a black mixture. After stirring the black mixture for 16 h, 2M HCl (aq) (20 mL) and acetone (20 mL) were added. The clear biphasic mixture was stirred vigorously for another 16 h before being neutralised with $NaHCO_3$. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography gave **3a** (98 mg, 62%) as a white solid, that was judged >95% pure by NMR.

2a with *t*-BuNCO then NaOEt to give 3a. 2a[1] (688 mg, 1.92 mmol) was treated with t-BuNCO according to General method C, but NaOEt (408 mg, 6.00 mmol) in EtOH (10 mL) was added and stirred for 1 h before quenching with 2M HCl to give **3a** (139 mg, 82%) as a white solid, that was judged >95% pure by NMR.

2a with *t*-BuNCO then $BnNH_2$ to give 12c. 2a[1] (576 mg, 1.69 mmol) was treated with t-BuNCO according to General method C, but $BnNH_2$ (0.65 mL, 6.00 mmol) was added and stirred for 1 h before quenching with 2M HCl to give **12c** (171 mg, 51%) as a white solid mp 109 - 112 °C (lit. 110 - 112 °C) , that was judged >95% pure by NMR. Rf 0.25 (66%, Et_2O:hexanes). ^{1}H NMR δ 1.33 (9H, s, C(CH_3)$_3$), 4.30 (2H, d, J = 5.6, CH_2Ph), 4.45 (1H, s$_{br}$, NH), 4.73 (1H, m, NH), 7.23 - 7.36 (5H, m, CH_{Ar}). ^{13}C NMR δ 29.5 (C(CH$_3$)$_3$), 44.4 (CH$_2$), 50.4 (C(CH$_3$)$_3$), 127.2 (CH$_{Ar}$), 127.5 (CH$_{Ar}$), 128.6 (CH$_{Ar}$), 139.5 (*ipso*-C), 157.5 (CO). Spectroscopic data in agreement with literature.[6]

Reaction of mixture of 10a and 10c with CO_2. To an orange solution of **10a** (2.14 g, 5.00 mmol) in dry CH_2Cl_2 (60 mL) at r.t., a solution of 2,6-(*i*-Pr)$_2$PhNH$_2$ (0.94 mL, 5.00 mmol) in dry CH_2Cl_2 (5 mL) was added. After stirring for 3 h., volatile solvents were removed in vacuo. The brown solid was dissolved in CH_2Cl_2 (3 mL) and washed with hexanes (60 mL) to give a dark brown solid (876 mg). ^{1}H NMR showed a 7 : 3 mixture (**10a** : **10b**). A solution of the brown solid (800 mg, 1.28 mmol of **10a**, 0.54 mmol **10b**) was degassed before CO_2 (1.5 atmospheres) was added. The brown solution was stirred for 5 h before it was quenched with 2M HCl (20 mL) and stirred for another 1 h. The biphasic mixture was neutralised with $NaHCO_3$. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The combined organic layers were dried ($MgSO_4$) filtered and concentrated in vacuo. Purification by flash column chromatography (Et_2O:hexanes, 20% to 50%) gave **12b** (118 mg, 36%) as a white solid mp 178 - 179 °C. Rf 0.39 (50%, Et_2O:hexanes). ^{1}H NMR δ 1.15 - 1.25 (12H, s$_{br}$, CH(CH_3)$_2$), 1.27 (9H, s, C(CH_3)$_3$), 3.32 (2H, sept, J = 6.9, CH(CH$_3$)$_2$), 7.20 (2H, d, J = 7.7, *m*-CH), 7.33 (1H, t, J = 7.7, *p*-CH). ^{13}C NMR δ 23.6

(C(*C*H_3)$_3$), 28.2 (*C*H(CH$_3$)$_2$), 29.2 (CH(*C*H$_3$)$_2$), 50.4 (*C*(CH$_3$)$_3$), 124.2 (*m*-*C*H), 128.9 (*p*-*C*H), 131.1 (*o*-*C*H), 148.0 (*ipso*-*C*), 156.7 (*C*=O). IR ν_{max} (solution in CHCl$_3$) 3421.3, 3011.5, 2967.0, 1662.5 (C=O), 1522.5, 1458.0, 1392.8, 1365.1, 1317.0 cm^{-1}. ESI/MS: *m/z* 277.2291 (M+H, 16%), 299.2320 (M+Na, 32%). HRMS: found (calcd for $C_{17}H_{29}N_2O$) m/z 277.2291 (277.2274). Spectroscopic data was in agreement with the literature.[7]

An identical experiment was performed, but this time the initial solution was stirred for 4 h to isolate a brown solid (1.26 g). ^{1}H NMR showed a 36 : 64 starting material : product mixture. A solution of the brown solid (1.20 mg, 0.96 mmol of starting material, 1.71 mmol product). Workup as above gave **12b** (55 mg, 21%) as a white solid, that was judged >95% pure by NMR.

NMR experiments. In a glove box complexes **10a** and **10b** and mesitylene (2 μL, internal standard) were dissolved in C_6D_6 (0.75 mL) and transferred to a Youngs tap NMR tube. Attachment of the Youngs tap NMR tube to a Schlenk line was followed by 3 freeze thaw cycles before finally filling with CO_2 (1.5 atm) and monitoring by NMR.

General method D: Formation of 10c and insitu reaction with CO_2 to give 3c. A solution of BnNH$_2$ (0.11 mL, 1.0 mmol) in dry CH_2Cl_2 (5 mL) was added to an orange solution of **10a** (427 mg, 1.00 mmol) in dry CH_2Cl_2 (30 mL) at rt and stirred for 2 h. The solution was degassed, CO_2 added (1.5 atm) and stirred for another 5 h at rt before it was quenched with 2M HCl (20 mL) and stirred for another 1 h. The biphasic mixture was neutralised with KHCO$_3$. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The combined organic layers were dried (MgSO$_4$,) filtered and concentrated in vacuo. Purification by flash column chromatography (Et$_2$O:hexanes, 10% to 50%) gave **3c** (20 mg, 20%) as a white solid mp 165 - 168 °C (Crystallised from CH_2Cl_2). ^{1}H NMR δ 4.37 (4H, d, *J* = 6.0, C*H*$_2$Ph), 4.79 (2H, s$_{br}$, N*H*), 7.18 - 7.35 (10H, m, C*H*$_{Ar}$). ^{13}C NMR δ 44.6 (*C*H$_2$Ph), 127.4 (*C*H$_{Ar}$), 127.5 (*C*H$_{Ar}$), 128.7 (*C*H$_{Ar}$), 138.1 (*C*$_{Ar}$), 158.0 (C=O). IR ν_{max} (solution in CHCl$_3$) 3447.0, 3007.8, 2962.6, 2927.5, 1670.2 (CO), 1530.5, 1264.5, 1097.7, 1027.5 cm^{-1}. ESI/MS: *m/z* 241.1324 (M+H$^+$, 54%), 263.1144 (M+Na$^+$,30%). HRMS found (calcd for $C_{15}H_{16}N_2O$) m/z 241.1324 (241.1335). Spectroscopic data was in agreement with the literature.[8]

Formation of 10d and insitu reaction with CO_2 to give 3d and 12d. According to General method using Ph(CH$_2$)$_2$NH$_2$ (0.13 mL, 1.00 mmol) gave **3d** (25 mg, 9%) as a white solid mp 139 - 140 °C (lit. 138 - 141 °C). ^{1}H NMR δ 2.73 (4H, t, *J* = 6.9, C*H*$_2$Ph), 3.39 (4H, q, *J* = 6.5, C*H*$_2$N), 4.15 (2H, s$_{br}$, N*H*), 7.15 - 7.32 (10H, m, C*H*$_{Ar}$). ^{13}C NMR δ 36.4 (*C*H$_2$Ph), 41.6 (*C*H$_2$N), 126.4 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 128.8 (*C*H$_{Ar}$), 139.2 (*ipso*-*C*$_{Ar}$), 157.9 (*C*O) whose spectroscopic data was in agreement with the literature,[9] and **12d** (32 mg, 15%) as a white solid mp 73 - 74 °C (lit. 70 - 71 °C). Rf 0.20 (66%,

Et_2O:hexanes). ^{1}H NMR δ 1.33 (9H, s, C(C*H*$_3$)$_3$), 2.82 (2H, t, *J* = 6.9, C*H*$_2$Ph), 3.41 (2H, q, *J* = 6.9, C*H*$_2$N), 4.30 (1H, s$_{br}$, N*H*), 4.37 (1H, m, N*H*), 7.19 - 7.36 (5H, m, C*H*$_{Ar}$). ^{13}C NMR δ 29.6 (C(*C*H$_3$)$_3$), 36.5 (*C*H$_2$Ph), 41.5 (*C*H$_2$N), 50.3 (*C*(CH$_3$)$_3$), 126.4 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 128.9 (*C*H$_{Ar}$), 139.4 (*ipso*-*C*), 157.5 (*C*=O) whose spectroscopic data in agreement with literature.[10]

General Method E: 10a with *N,N*-bis(trimethylsily) benzylamine. To a solution of **10a** (427 mg, 1.00 mmol) in CH_2Cl_2 (20 mL), a solution of *N,N*-bis(trimethylsily) benzylamine (251 mg, 1.00 mmol) in CH_2Cl_2 (2 mL) was added. The solution was then degassed before applying CO_2 (1.5 atm). The solution was stirred for 5 h before being quenched with 2M HCl (20 mL) and stirred for another 1 h. The biphasic mixture was neutralised with $NaHCO_3$. The two phases were separated and the aqueous layer was extracted with dichloromethane (2x20 mL). The combined organic layers were dried ($MgSO_4$) filtered and concentrated *in vacuo*. Purification by flash column chromatography (Et_2O:hexanes, 20% to 50%) gave **3a** (49 mg, 99%) as a white solid, that was judged >95% pure by NMR.

10a with *N,N*-bis(trimethylsilyl) 2-phenylethylamine. According to General method E, but using ***N,N***-bis(trimethylsilyl) 2-phenylethylamine (275 mg, 1.00 mmol) gave **3a** (48 mg, 97%) as a white solid, that was judged >95% pure by NMR.

10a with Et_3N. According to General method E, but using Et_3N (0.14 mL, 1.00 mmol) gave **3a** (32 mg, 37%) as a white solid, that was judged >95% pure by NMR.

General synthesis of symmetrical ureas 3a,c,d,e from $TiCl_4$ with varying molar equivalents of amine (Table 2). To a clear yellow solution of $TiCl_4$ (0.50 mL, 4.65 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C, was added amine (x mmol) dropwise over a period of 5 min. After stirring the orange mixture for a period of 0.5 h, the solid was removed by filtration to give a bright orange solution, pyridine (x mmol) was then added and the mixture was stirred for further 0.5 h. The dark red suspension was then filtered to give a dark orange solution which was degassed before applying CO_2 (1.5 atm). After stirring for 5 hours, the brown solution was quenched with 2M HCl (20 mL) and stirred for another 1 h. The biphasic mixture was neutralised with $NaHCO_3$. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (Et_2O:hexanes, 20% to 50%) afforded **3** (see Table 2) as a white solid, that was judged >95% pure by NMR.

Data for **3e** mp 225 - 228 °C (lit. 227 - 229 °C). ^{1}H NMR δ 1.05 - 1.20 (6H, m, C*H*$_2$), 1.34 (4H, qt, *J* = 11.9, 3.5, C*H*$_2$), 1.60 (2H, dt, *J* = 13.0, 3.8, C*H*$_2$), 1.69 (4H, dt, *J* = 13.8, 3.8, C*H*$_2$), 1.90 - 1.97

(4H, m, CH_2), 3.48 (2H, tt, J = 10.5, 3.8, CHN), 3.95 - 4.15 (2H, s$_{br}$, NH). ^{13}C NMR δ 25.0 (CH$_2$), 25.7 (CH$_2$), 34.0 (CH$_2$), 49.2 (CHN). Missing quaternary carbon (CO). Spectroscopic data was in agreement with the literature.[11]

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Figure S2. A view of the cation along the crystallographic three-fold axis. This axis passes through the carbon atom at the centre of the picture.