An Efficient Synthesis of Aryl Phenaceturates Using Acid Catalyzed Dicyclohexylcarbodiimide Esterification and Transient *N*-*tert*-Butoxycarbonylation

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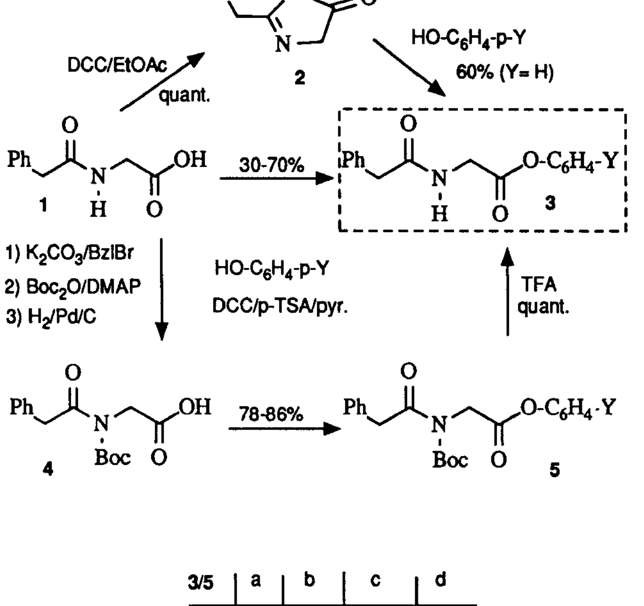
Application of the Holmberg procedure (DCC/pyridine/*p*-TSA$_{cat}$) improves the yield of the direct condensation of phenols with phenylacetylglycine (**1**). Moreover, *N*-*tert*-butoxycarbonylation of **1** impedes an intramolecular reaction leading to an oxazolone, and allows the formation of stable aryl *N*-Boc phenaceturates. Then, mild cleavage of the Boc group with four equivalents of trifluoroacetic acid furnishes the aryl phenylacetylglycinate. This indirect method is more efficient than its direct analog in the case of phenols possessing electron-withdrawing substituents.

For an ongoing project concerning the study of new *β*-lactamase substrates and inhibitors, an efficient synthesis of phenylacetylglycine aryl esters (aryl phenaceturates) was needed.[1] Phenyl and *p*-alkoxycarbonylphenyl phenaceturates are formed in aqueous solutions of potassium penicillin G which contain phenols as preservatives.[2,3] They have been synthesized in about 20% yield by heating a mixture of a phenol and the 2-benzyl-5-(4*H*)-oxazolone hydrobromide (**2**, HBr) obtained by treatment of phenaceturic acid (**1**) with phosphorous tribromide.[2,3] *ortho*-, *meta*- and *para*-Benzyloxycarbonylphenyl phenaceturates have also been prepared from the acid **1** and the corresponding benzyl hydroxybenzoate using 1,1′-carbonyldiimidazole as the activating agent.[4] Activated derivatives of hippurates (*N*-benzoylglycinates) and other *N*-acylglycine analogs,[5] such as **1**, are particularly prone to the formation of an oxazolone.



3/5	a	b	c	d
p-Y	H	NO$_2$	CO$_2$Et	SMe

Dissolution of phenaceturic acid (**1**) in hot ethyl acetate (10 mL per mmole) and addition of one equivalent of dicyclohexylcarbodiimide (DCC) leads to the quantitative formation of the 2-benzyl-5(4*H*)-oxazolone (**2**) and precipitation of the dicyclohexylurea. However, this oxazolone only reacts with phenol at 50 °C in a concentrated EtOAc solution to give the phenyl phenaceturate in 60% yield. Therefore we sought for a milder method compatible with fragile phenols. In the esterification of amino acids mediated by DCC, pyridine as solvent increases the reactivity of *ortho*-nitrophenol and reduces the amount of *N*-acylurea byproducts.[6] Furthermore, Holmberg and Hansen have observed that a strong acid, such as *p*-toluenesulfonic acid (*p*-TSA), improves the yields of the esterification reaction.[7] On the other hand, *N*-acylation of the acid **1** should give an imide which after activation could not cyclize.[8] Some secondary amides have been efficiently *N*-*tert*-butoxycarbonylated by using di-*tert*-butyl dicarbonate and 4-dimethylaminopyridine (Boc$_2$O/DMAP).[9]

Alkylation of cesium phenaceturate with benzyl bromide in DMF gave the benzyl phenaceturate. Then, treatment with Boc$_2$O/DMAP and hydrogenolysis of the benzyl protecting group furnished the *N*-*tert*-butoxycarbonylphenaceturic acid (**4**) in 80% overall yield. In the *tert*-butoxycarbonylation reaction, a small amount of a di-Boc derivative was isolated (see Experimental).

A comparative esterification of a series of phenols with phenaceturic acid (**1**) or its *N*-Boc derivative **4**, using the same DCC/*p*-TSA/pyridine conditions has been performed (Table 1). Substituted esters **5** are obtained in higher yields than esters **3**, particularly in the case of the acidic phenols (Y = NO$_2$ or CO$_2$Et). Moreover esters **5** are more stable than esters **3** and do not decompose on silica gel. Cleavage of the Boc protecting group from **5** with a slight excess of trifluoroacetic acid gives the aryl phenaceturate **3** in quantitative yield, without chromatographic purification. On the whole, the indirect route, which needs the synthesis of the *tert*-butoxycarbonylated acid **4**, is valuable in the case of phenols possessing electron-withdrawing substituents.

Phenylacetylglycine (**1**) was prepared following ref 4. The other reagents were obtained commercially and were used without purification. ^{1}H spectra were recorded on a Bruker AC 200E at 200 MHz and ^{13}C spectra at 50 MHz with TMS as internal standard. TLC was performed on silica gel 60F-254 (Merck) and visualized with UV light. Column chromatography was carried out on silica gel 60 (70–230 mesh). Unless otherwise stated, the eluent used is the same for TLC and for column chromatography purification.

Compounds **3b–d**, **4** and **5a–d** gave C, H, N ± 0.31%.

Benzyl *N*-Phenylacetylglycinate:

To a solution of *N*-phenylacetylglycine (**1**) (4.83 g, 25 mmol) in MeOH (100 mL) and water (10 mL) was added a solution of CsCO$_3$ (4.1 g, 12.5 mmol) in water (20 mL). The mixture was evaporated and the residue was dried (P$_2$O$_5$) under vacuum. To this solid was added DMF (60 mL), then benzyl bromide (3.3 mL, 27.5 mmol). The suspension was stirred at r.t. for 24 h, then DMF was removed at 45 °C under vacuum. The residue was distributed between CH$_2$Cl$_2$

Table 1. Yields of Aryl Phenaceturates **3** and **5**.

Product	Yield[a] (%)	Yield[b] (%)
3a	58	71
3b	30[c]	68
3c	31[c]	–
3d	71	–
5a	78	79
5b	82	86
5c	86	–
5d	84	–

[a] Yield of isolated product.
[b] Yield estimated by NMR.
[c] Phenaceturates of acidic phenols decompose on SiO_2.

and water. The organic phase was dried (Na_2SO_4) and evaporated. The crude product was purified by chromatography (CH_2Cl_2 followed by CH_2Cl_2/EtOAc, 95:5), affording 6.81 g (95% yield) of the desired product; R_f 0.22 (CH_2Cl_2/MeOH, 99:1); mp 92–93°C (EtOAc).

^1H NMR ($CDCl_3$): δ = 3.60 (s, 2H, $PhCH_2$), 4.02 (d, J = 5.5 Hz, 2H, NCH_2), 5.13 (s, 2H, OCH_2Ph'), 6.86 (br, 1H, NH), 7.21 and 7.26 (m, 10H, Ph and Ph').

^{13}C NMR ($CDCl_3$): δ = 41.2 (NCH_2), 43.0 ($PhCH_2$), 66.9 (CH_2OPh'), 127.1, 128.1, 128.3, 128.4, 128.7, 129.2, 134.4 and 135.0 (Ph and Ph'), 169.5 (COO), 171.1 (CON).

Anal: Calc. for $C_{17}H_{17}NO_3$ (283.31): C, 72.06; H, 6.05; N, 4.94. Found: C, 71.77; H, 6.05; N, 4.85.

Benzyl *N*-Boc-*N*-phenylacetylglycinate:

A solution of benzyl *N*-phenylacetylglycinate (0.68 g, 2.4 mmol), $(Boc)_2O$ (0.628 g, 2.88 mmol) and DMAP (29.3 mg, 0.24 mmol) in CH_3CN (6 mL) was stirred at r.t. overnight. The solvent was evaporated and the residue purified by chromatography (pentane/EtOAc, 97:3 then 97:5), giving 820 mg (89% yield) of the title product, as an oil; R_f 0.4 (pentane/EtOAc, 9:1).

^1H NMR ($CDCl_3$): δ = 1.38 (s, 9H, Boc), 4.28 (s, 2H, $PhCH_2$), 4.49 (s, 2H, NCH_2), 5.12 (s, 2H, OCH_2Ph'), 7.23 and 7.30 (m, 10H, Ph and Ph').

^{13}C NMR ($CDCl_3$): δ = 27.6 (Boc), 43.9 ($PhCH_2$), 45.5 (NCH_2), 66.8 (CH_2OPh'), 83.9 ($NCOO\underline{C}$), 126.7, 128.2, 128.3, 128.5, 129.5, 134.7 and 135.3 (Ph and Ph'), 151.9 (NCOO), 168.7 (COO), 173.7 (CON).

Anal: Calc. for $C_{22}H_{25}NO_5$ (383.43): C, 68.91; H, 6.57; N, 3.65. Found: C, 68.45; H, 6.44; N, 3.45.

A small amount, 40 mg (3.4% yield), of the di-Boc product: R_f 0.24 (pentane/EtOAc, 9:1) was also obtained as an oil.

^1H NMR ($CDCl_3$): δ = 1.39 (s, 9H, Boc), 1.43 (s, 9H, O-Boc), 4.52 (q, $J_{A,B}$ = 7.3 Hz, 2H, NCH_2), 5.16 (s, 2H, OCH_2Ph'), 5.62 (s, 1H, $PhC\underline{H}=C$), 7.31–7.36 (m, Ph and Ph').

^{13}C NMR ($CDCl_3$): δ = 27.6 and 27.7 (2 × *t*-Bu), 45.5 (NCH_2), 66.8 (OCH_2Ph'), 80.6 ($Ph\underline{C}H=C$), 82.0 ($OCOO\underline{C}$), 84.1 ($NCOO\underline{C}$), 127.7, 128.2, 128.4, 128.5, 129.6, 134.1 and 135.3 (Ph and Ph'), 150.2 (NCOO), 168.4 (COO), 170.3 (OCOO), 175.5 (=C(O)N).

MS (FAB): m/z = 490 $(M + Li)^+$, 390 $(M - Boc + H + Li)^+$, 290 $(M - 2Boc + 2H + Li)^+$.

***N*-Boc-*N*-phenylacetylglycine (4):**

A mixture of benzyl *N*-Boc-*N*-phenylacetylglycinate (0.65 g, 1.69 mmol) and 10% Pd/C (40 mg) in MeOH (40 mL) was hydrogenated at 50 lb/in² pressure at r.t. for 2 h. The reaction mixture was then filtered and evaporated. The crude product was purified by chromatography (CH_2Cl_2 followed by CH_2Cl_2/MeOH, 95:5), giving 473 mg (95% yield) of the title product **4**; R_f 0.36 (CH_2Cl_2/MeOH, 95:5).

^1H NMR ($CDCl_3$): δ = 1.48 (s, 9H, NBoc), 4.30 (s, 2H, $PhCH_2$), 4.51 (s, 2H, NCH_2), 7.25 and 7.34 (m, 5H, Ph), 10.0 (br, 1H, CO_2H).

^{13}C NMR ($CDCl_3$): δ = 27.7 (Boc), 43.9 ($PhCH_2$), 45.2 (NCH_2), 84.3 ($NCO_2\underline{C}$), 126.8, 128.3, 128.4, 129.5, and 134.5 (Ph), 151.8 (NCOO), 173.9 (CON), 175.0 (CO_2H).

Esterification Reactions; General Procedure:

To a mixture of a phenol and 1.5 equiv of acid **1** or **4** in anhydr. pyridine (1 mL/mmol) was added a catalytic amount of *p*-TsOH · H_2O (10 mg per mmol of phenol) and DCC (1.5 equiv). The resulting mixture was stirred at r.t. overnight, and then EtOAc and 10% HCl was added. The white precipitate (DCU) was filtered. The filtrate was separated and the organic phase was washed with water, dried (Na_2SO_4) and evaporated to give the crude product **3** or **5** which was purified by chromatography and crystallization.

Deprotection; General Procedure:

A solution of a *N*-Boc protected ester **5** in trifluoroacetic acid (4 equiv) was stirred at r.t. overnight and evaporated to remove the TFA. The obtained solid was dried over P_2O_5 and KOH under vacuum to give quantitatively the final product **3**.

3a: R_f 0.13 (CH_2Cl_2); mp 137–138°C (MeOH) (lit.[2] mp 132–133°C).

^1H NMR ($CDCl_3$): δ = 3.62 (s, 2H, $PhCH_2$), 4.22 (d, J = 5.4 Hz, 2H, NCH_2), 6.22 (br, 1H, NH), 7.04 (d, J_{AB} = 7.6 Hz, 2-H, 3-H and 5-H), 7.18–7.39 (m, 7H, 2-H, 6-H and Ph).

3b: R_f 0.12 (CH_2Cl_2); mp 142–143°C (MeOH).

^1H NMR ($CDCl_3$): δ = 3.62 (s, 2H, $PhCH_2$), 4.22 (d, J = 5.6 Hz, 2H, NCH_2), 5.93 (br, 1H, NH), 7.17–7.36 (m, 7H, 2-H, 6-H and Ph), 8.20 (d, J_{AB} = 8.9 Hz, 2H, 2-H and 5-H).

3c: R_f 0.14 (CH_2Cl_2); mp 126–127°C (MeOH).

^1H NMR ($CDCl_3$): δ = 1.38 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 3.66 (s, 2H, $PhCH_2$), 4.25 (d, J = 5.5 Hz, 2H, NCH_2), 4.36 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 7.14 (d, J_{AB} = 8.7 Hz, 2H, 2-H and 6-H), 7.28–7.39 (m, 5H, Ph), 8.06 (d, J_{AB} = 8.7 Hz, 2H, 3-H and 5-H).

3d: R_f 0.14 (CH_2Cl_2); mp 163–164°C (MeOH).

^1H NMR (acetone-d_6): δ = 2.49 (s, 3H, SCH_3), 3.60 (s, 2H, $PhCH_2$), 4.19 (d, J = 5.8 Hz, 2H, NCH_2), 7.00 (d, J_{AB} = 8.7 Hz, 2H, 3-H and 5-H); 7.21–7.32 (m, 7H, 2-H, 6-H and Ph), 7.36 (br, 1H, NH).

5a: R_f 0.50 (CH_2Cl_2); oil. ^1H NMR ($CDCl_3$): δ = 1.49 (s, 9H, Boc), 4.32 (s, 2H, $PhCH_2$), 4.70 (s, 2H, NCH_2), 7.04–7.34 (m, 9H, Ph and Ar).

5b: R_f 0.58 (CH_2Cl_2); oil.

^1H NMR ($CDCl_3$): δ = 1.52 (s, 9H, Boc), 4.33 (s, 2H, $PhCH_2$), 4.75 (s, 2H, NCH_2), 7.24–7.32 (m, 7H, 2-H, 6-H and Ph), 8.24 (d, J_{AB} = 9.0 Hz, 2H, 3-H and 5-H).

5c: R_f 0.42 (CH_2Cl_2); oil.

^1H NMR ($CDCl_3$): δ = 1.38 (t J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.51 (s, 9H, Boc), 4.33 (s, 2H, $PhCH_2$), 4.36 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 4.73 (s, 2H, NCH_2), 7.16 (d, J_{AB} = 8.7 Hz, 2H, 2-H and 6-H), 7.23–7.31 (m, 5H, Ph), 8.07 (d, $J_{5,6}$ = 8.7 Hz, 2H, 3-H and 5-H).

5d: R_f 0.42 (CH_2Cl_2); oil.

^1H NMR ($CDCl_3$): δ = 1.50 (s, 9H, Boc), 2.45 (s, 3H, SCH_3), 4.32 (s, 2H, $PhCH_2$), 4.70 (s, 2H, NCH_2), 7.00 (d, J_{AB} = 8.7 Hz, 2H, 3-H and 5-H), 7.22–7.30 (m, 7H, 2-H, 6-H and Ph).

(1) Xu, Y.; Pratt, R.F.; Cabaret, D.; Liu, J.; Wakselman, M., manuscript in preparation.
(2) Kern, S.F.; Terril, P.M.; Mann, M.M.; Jones, R.G. *Science* **1950**, *112*, 787.

(3) Simmons, B.D.L.; Frechette, M.; Ranz, R.J.; Chen, W.S. *Can. J. Pharm. Sci.* **1967**, *2*, 53.
(4) Govardhan, C.P.; Pratt, R.F. *Biochemistry* **1987**, *26*, 3385.
(5) De Jersey, J.; Willaden, P.; Zerner, B. *Biochemistry* **1969**, *8*, 1959.
Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1975**, 947.
(6) Bodansky, M.; Kondo, M.; Yang Lin, C.; Sigler, G.F. *J. Org, Chem.* **1974**, *39*, 444.
(7) Holmberg, K.; Hansen, B. *Acta Chem. Scand.* **1979**, *B33*, 410.
(8) Gunnarsson, K.; Ragnarsson, U. *Acta Chem. Scand.* **1990**, *44*, 944.
(9) Flynn, D.L.; Zelle, R.E.; Grieco, P.A. *J. Org. Chem.* **1983**, *48*, 2424.
M. Wakselman *di-tert-butyl dicarbonate* In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L.A., Ed; Wiley: in press.