

Cite this: *Chem. Commun.*, 2012, **48**, 8270–8272

www.rsc.org/chemcomm

COMMUNICATION

Protodecarboxylation of benzoic acids under radical conditions†

Sangwon Seo,^a John B. Taylor^b and Michael F. Greaney^{*a}

Received 8th May 2012, Accepted 29th May 2012

DOI: 10.1039/c2cc33306f

A new approach to protodecarboxylation is described that enhances the substrate scope for benzoic acids. The reaction uses oxidative radical conditions to decarboxylate a variety of acids in acetonitrile.

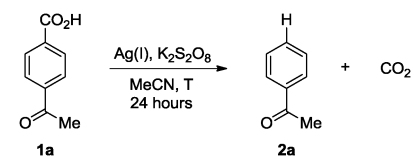
The decarboxylation of benzoic acids using transition metal catalysis has received considerable attention in recent years.¹ Decarboxylative metallation is at the heart of numerous C–C, C–X and C–H bond formations, all of which capitalise on the versatility of carboxylic acids as readily available starting materials. This latter transformation, protodecarboxylation, is important in syntheses that use a carboxylate to direct aromatic functionalisation,² but do not require the acid group in the final molecule.³ Moreover, the loss of CO₂ is often the key step in any decarboxylative coupling, and studying this step in protodecarboxylation has been a productive avenue for catalyst design and refinement.^{4–6}

Pioneering work from the groups of Goossen and Larrosa established Ag-catalysed protodecarboxylation at 120 °C as the current state of the art, having good substrate scope for heteroaromatic acids, but requiring an *ortho* substituent for benzoic acids.⁴ This requirement of an *ortho*-substituent, frequently a heteroatom, for benzoic acid protodecarboxylation is a significant restriction.⁷ Our interest in decarboxylative chemistry⁸ prompted us to address this issue, as we have recently developed an intramolecular decarboxylative C–H arylation that proceeds under oxidative radical conditions (K₂S₂O₈/Ag(i)).⁹ The reaction conditions we developed enabled decarboxylation of substrates that were resistant to conventional Pd/Cu or Ag co-catalysis. We were thus interested in applying this radical approach to protodecarboxylation with the aim of expanding the scope beyond *ortho*-substituted benzoic acids.

We selected the *para*-substituted 4-acetylbenzoic acid (**1a**) as a starting point and screened conditions using the combination of Ag(i) salts and K₂S₂O₈ in acetonitrile (Table 1). We were pleased to find that the reaction was productive using AgOAc (20 mol%) with excess K₂S₂O₈ at 100 °C, providing good

conversions to acetophenone. Raising the catalyst loading was counterproductive (entry 3), but raising the amount of K₂S₂O₈ was beneficial (entry 4). The reaction was effective for a variety of silver salts, with acetate, sulfate, carbonate, oxide and trifluoroacetate all being good (entries 1, 5, 6, 7 and 11). Silver halides, triflate and nitrate were poor (entries 8, 9, 10 and 12). Finally, we could reduce the reaction time to 1 h using microwave heating with little loss in yield (entry 13).

To investigate the scope of the reaction we examined a variety of functionalised carboxylic acids (Table 2), and were pleased to observe effective protodecarboxylation for a wide substrate range. *meta*-Substituted benzoic acids were equally effective as the *para*-substituted isomers, with good to excellent yields being obtained for ketones, esters, nitro, trifluoromethyl, fluoro and bromo substituents (**2a–2g**) in the *m* and *p*-positions. The reactions were generally clean when monitored by LC–MS, with unreacted starting material being the only other identifiable component. *p*-Iodobenzoic acid (**II**) was an exception, undergoing decomposition in the reaction and affording a rather low conversion to iodobenzene.¹⁰ We were pleased to see that benzoic

Table 1 Optimisation data^a


Entry	Catalyst loading (mol %)	Ag(i) catalyst	K ₂ S ₂ O ₈ (equiv.)	T/ °C	Yield 2a ^b (%)
1	20	AgOAc	3	100	71
2	20	AgOAc	3	120	69
3	40	AgOAc	3	100	45
4	20	AgOAc	5	100	84
5	10	Ag ₂ SO ₄	5	100	81
6	10	Ag ₂ CO ₃	5	100	67
7	10	Ag ₂ O	5	100	68
8	20	AgF	5	100	32
9	20	Ag(OTf)	5	100	< 10
10	20	AgI	5	100	< 10
11	20	Ag(TFA)	5	100	75
12	20	AgNO ₃	5	100	40
13 ^c	20	AgOAc	5	130	77
14	20	AgOAc	5	100	78 ^d

^a Conditions: **1a** (0.3 mmol), indicated amount of Ag(i) catalyst and K₂S₂O₈, MeCN (3.0 mL), 24 h. ^b Yield determined by ¹H NMR analysis using nitromethane as an internal standard. ^c Microwave heating for 1 h. ^d Isolated yield.

^a School of Chemistry, University of Manchester, Oxford Rd, Manchester M13 9PL, UK.

E-mail: michael.greaney@manchester.ac.uk

^b Syngenta, Jealott's Hill International Research Centre, Bracknell, RG42 6EY, UK

† Electronic supplementary information (ESI) available: Data for new compounds and experimental procedures. See DOI: 10.1039/c2cc33306f

Table 2 Substrate scope^a

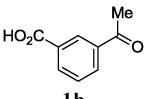
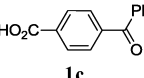
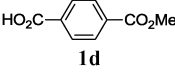
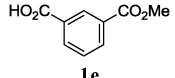
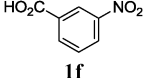
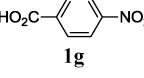
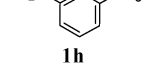
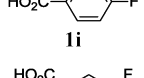
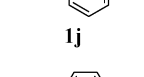
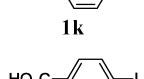
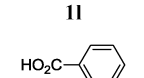
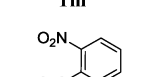
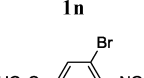
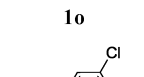
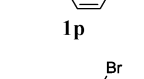
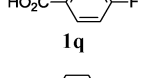
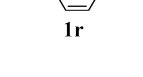
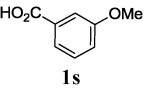
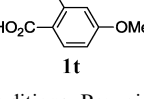
Entry	Acid	Product	Yield ^b (%)
1		2a	63
2		2b	75
3		2c	82
4		2c	81
5		2d	54 ^c
6		2d	61 ^c
7		2e	68 ^d
8		2f	64 ^d
9		2f	57 ^d
10		2g	67 ^d
11		2h	40 ^d
12		2i	52 ^d
13		2d	84
14		2j	43
15		2k	74 ^d
16		2l	75 ^d
17		2m	34 ^d

Table 2 (continued)

Entry	Acid	Product	Yield ^b (%)
18		2m	45 ^d
19		2n	58

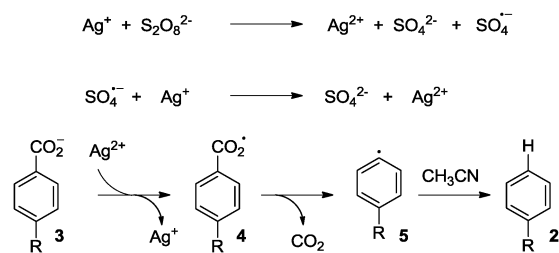
^a Reaction conditions: Benzoic acid **1** (0.3 mmol), AgOAc (0.06 mmol) and K₂S₂O₈ (1.5 mmol) in MeCN (3.0 mL) at 100 °C for 24 h. ^b Isolated yields. ^c 40 mol% AgOAc (0.12 mmol) was used. ^d Yield determined by ¹H NMR analysis using nitromethane as an internal standard.

acid itself, **1i**, underwent protodecarboxylation to benzene indicating that electron-withdrawing groups *per se* are not a requirement for the reaction. The parent acid has been conspicuous by its absence as a substrate in TM-catalysed decarboxylative transformations. The *ortho*-nitro compound **1n**, a classic decarboxylation substrate, was likewise effectively transformed into nitrobenzene **2d**. *m,p*-Disubstituted benzoic acids were also good substrates for the reaction (**1o–1q**).

Electron rich benzoic acids, by contrast, were less effective substrates for protodecarboxylation. *p*-Methoxybenzoic acid **1r** afforded only a low yield of anisole (34%, entry 17), with the deconjugated *m*-methoxybenzoic acid **1s** being slightly better, producing anisole in 45% yield. The deactivating effect of simple π -donors on loss of CO₂ from ArCO₂ is known, with *p*-MeOC₆H₄CO₂ undergoing decarboxylation six times slower than the parent benzoyloxy radical in CCl₄.¹¹ This deactivation could be partially ameliorated with electron withdrawing groups, with substrate **1t** (entry 20) undergoing protodecarboxylation to **2n** in 58% yield.

The mechanism of oxidative decarboxylation with K₂S₂O₈ and Ag(I) has been investigated by Koichi in seminal work on the alkanolic acid series.¹² Ag(I) is oxidised to Ag(II) *in situ* which oxidises the carboxylate in turn to the radical **4**. Loss of CO₂ would then afford the aryl radical **5**. Applications to aroic acids are rare,⁹ with the loss of CO₂ from **4** being slower than the alkyl case and requiring higher reaction temperatures.^{11,13} For the reaction at hand, however, we can effectively trap **5** through H-atom transfer from acetonitrile (Scheme 1).¹⁴

In conclusion, we have developed an oxidative radical process for the protodecarboxylation of benzoic acids. The reaction uses a cheap inorganic oxidant and catalytic amounts of silver under simple reaction conditions. The substrate scope is substantially expanded from existing methods for benzoic

**Scheme 1** Proposed mechanism for protodecarboxylation.

acid decarboxylation, and applications of this chemistry are underway in our group.

We thank Syngenta, the University of Manchester and the EPSRC for funding (Leadership fellowship to M. F. G.).

Notes and references

- Reviews: (a) W. I. Dzik, P. P. Lange and L. J. Goossen, *Chem. Sci.*, 2012, DOI: 10.1039/C2SC20312J, Advance article published 3 May 2012; (b) J. Cornella and I. Larrosa, *Synthesis*, 2012, **44**, 1670; (c) N. Rodriguez and L. J. Goossen, *Chem. Soc. Rev.*, 2011, **40**, 5030.
- (a) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074; (b) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094.
- (a) J. Cornella, M. Righi and I. Larrosa, *Angew. Chem., Int. Ed.*, 2011, **50**, 9429; (b) E. M. O'Brien, B. J. Morgan and M. C. Kozlowski, *Angew. Chem., Int. Ed.*, 2008, **47**, 6877.
- Ag catalysis: (a) L. J. Goossen, C. Linder, N. Rodriguez, P. P. Lange and A. Fromm, *Chem. Commun.*, 2009, 7173; (b) J. Cornella, C. Sanchez, D. Banawa and I. Larrosa, *Chem. Commun.*, 2009, 7176; (c) P. Lu, C. Sanchez, J. Cornella and I. Larrosa, *Org. Lett.*, 2009, **11**, 5710; (d) L. J. Goossen, N. Rodriguez, C. Linder, P. P. Lange and A. Fromm, *ChemCatChem*, 2010, **2**, 430.
- For Cu-catalysis at elevated temperatures, see: (a) L. J. Goossen, F. Manjolinho, A. B. Khan and N. Rodriguez, *J. Org. Chem.*, 2009, **74**, 2620; (b) L. J. Goossen, W. R. Thiel, N. Rodriguez, C. Linder and B. Melzer, *Adv. Synth. Catal.*, 2007, **349**, 2246; Pd-catalysis: J. S. Dickstein, C. A. Mulrooney, E. M. O'Brien, B. J. Morgan and M. Kozlowski, *Org. Lett.*, 2007, **9**, 2441.
- For protodecarboxylations using strong acid or stoichiometric metals, see: (a) R. W. Hay and M. J. Taylor, *Chem. Commun.*, 1966, 525; (b) T. Cohen and R. A. Schambach, *J. Am. Chem. Soc.*, 1970, **92**, 3189; (c) A. Cairncross, J. R. Roland, R. M. Henderson and W. A. Sheppard, *J. Am. Chem. Soc.*, 1970, **92**, 3187; (d) J. Chodowska-Palicka and M. Nilsson, *Acta Chem. Scand.*, 1970, **24**, 3353; (e) J. Chodowska-Palicka and M. Nilsson, *Acta Chem. Scand.*, 1971, **25**, 3451; (f) T. Cohen, R. W. Berninger and J. T. Wood, *J. Org. Chem.*, 1978, **43**, 837; (g) S. O. C. Mundle and R. Kluger, *J. Am. Chem. Soc.*, 2009, **131**, 11674.
- For a study on the activating role of *ortho*-substituents in protodecarboxylation, see: L. Xue, W. Su and Z. Lin, *Dalton Trans.*, 2011, **40**, 11926.
- (a) F. Zhang and M. F. Greaney, *Org. Lett.*, 2010, **12**, 4745; (b) F. Zhang and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2010, **49**, 2768.
- S. Seo, M. Slater and M. F. Greaney, *Org. Lett.*, 2012, **14**, 2650.
- Aryl iodides are known to undergo deiodination with peroxydisulfate. See: J. F. Bunnett and C. C. Wamser, *J. Am. Chem. Soc.*, 1967, **89**, 6712.
- J. Chateaufneuf, J. Luszytk and K. U. Ingold, *J. Am. Chem. Soc.*, 1988, **110**, 2886.
- J. M. Anderson and J. K. Kochi, *J. Am. Chem. Soc.*, 1970, **92**, 1651.
- (a) D. H. R. Barton, B. Lacher and S. Z. Zard, *Tetrahedron*, 1987, **43**, 4321; (b) M. P. Bertrand, H. Oumar-Mahamat and J. M. Surzur, *Tetrahedron Lett.*, 1985, **26**, 1209.
- Conducting the reaction of **1a** in *d*₃-MeCN gave a *ca.* 40% yield of the deuterated product *d*-**2a**.