ORGANIC LETTERS

2012
Vol. 14, No. 10
2650–2653

Decarboxylative C–H Arylation of Benzoic Acids under Radical Conditions

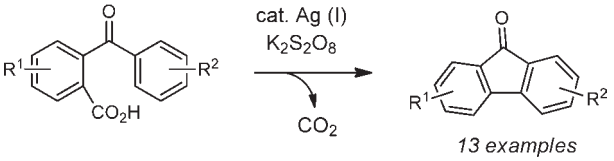
Sangwon Seo,[†] Mark Slater,[‡] and Michael F. Greaney*,[†]

School of Chemistry, University of Manchester, Oxford Rd, Manchester M13 9PL, U.K., and Syngenta, Jealott's Hill International Research Centre, Bracknell, RG42 6EY, U.K.

Michael.greaney@manchester.ac.uk

Received April 23, 2012

ABSTRACT

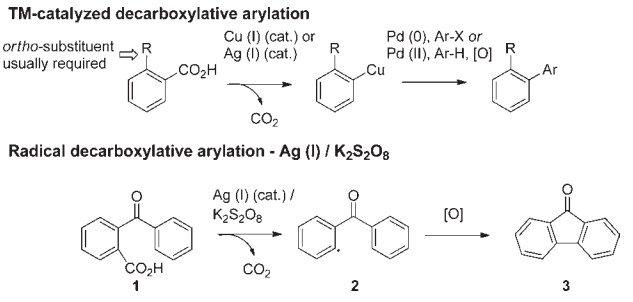


A decarboxylative radical cyclization reaction has been developed for the synthesis of fluorenones. The reaction uses Ag(I)/$K_2S_2O_8$ to oxidatively decarboxylate an aroylbenzoic acid to an aryl radical, which undergoes cyclization to afford fluorenone products in good yield.

Metal-catalyzed decarboxylation of benzoic acids is now established as a powerful method for C–H, C–C, and C–X bond formation.[1,2] The superb versatility and low cost of carboxylic acid starting materials makes the transformation appealing as a general method of functionalizing aromatic compounds. Substrate scope, however, has emerged as a major challenge in terms of the benzoic acids that will undergo efficient decarboxylation. An *ortho*-heteroatom substituent is a current requirement for aroic acid decarboxylative coupling below 150 °C,[3] making alternative decarboxylation methods necessary in order to fully exploit the potential of carboxylates in aromatic functionalization.

We were interested in examining oxidative decarboxylation in this context using radical-generating conditions of catalytic silver(I) salts and stoichiometric $K_2S_2O_8$.[4] These simple conditions have been widely exploited for the generation of alkyl radicals from alkanoic acids[5,6] but have not seen application for aryl radical generation.[7] Loss of CO_2 from an aroyloxy radical is slower than for the alkyl case,[8] and the resultant aryl radicals are more reactive and prone to unproductive side reactions. We reasoned,

Scheme 1. Metal-Catalyzed Decarboxylation



(1) Reviews: (a) Cornella, J.; Larrosa, I. *Synthesis* **2012**, *44*, 1670. (b) Rodriguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030. (c) Goossen, L. J.; Rodriguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100.

(2) Recent examples: (a) Hu, P.; Shang, Y.; Su, W. *Angew. Chem., Int. Ed.* **2012**, Early view, published online: 11th April 2012, DOI: 10.1002/anie.201200153. (b) Rudzki, M.; Alcalde-Aragones, A.; Dzik, W. I.; Rodriguez, N.; Goossen, L. J. *Synthesis* **2012**, *44*, 184. (c) Cornella, J.; Righi, M.; Larrosa, I. *Angew. Chem., Int. Ed.* **2011**, *50*, 9429. (d) Shang, R.; Huang, Z.; Chu, L.; Fu, Y.; Liu, L. *Org. Lett.* **2011**, *13*, 4240. (e) Cornella, J.; Rosillo-Lopez, M.; Larrosa, I. *Adv. Synth. Catal.* **2011**, *353*, 1359. (f) Collet, F.; Song, B.; Rudolphi, F.; Goossen, L. J. *Eur. J. Org. Chem.* **2011**, *2011*, 6486. (g) Xie, K.; Wang, S.; Yang, Z.; Liu, J.; Wang, A.; Li, X.; Tan, Z.; Guo, C.-G.; Deng, W. *Eur. J. Org. Chem.* **2011**, *2011*, 5711. (h) Zhao, H.; Wei, Y.; Xu, J.; Kan, J.; Su, W.; Hong, M. *J. Org. Chem.* **2011**, *76*, 882. (i) Dupuy, S.; Lazreg, F.; Slawin, A. M. Z.; Cazin, C. S. J.; Nolan, S. P. *Chem. Commun.* **2011**, *47*, 5455. (j) Zhang, F.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 4745.

(3) Examples of decarboxylative coupling with acids lacking an *ortho*-substituent: (a) Goossen, L. J.; Rodriguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248. (b) Goossen, L. J.; Linder, C.; Rodríguez, N.; Lange, P. P. *Chem.—Eur. J.* **2009**, *15*, 9336. (c) Goossen, L. J.; Lange, P. P.; Rodriguez, N.; Linder, C. *Chem.—Eur. J.* **2010**, *16*, 3906. (d) Goossen, L. J.; Rodriguez, N.; Lange, P. P.; Linder, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 1111.

(4) Anderson, J. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1970**, *92*, 1651.

(5) Minisci, F.; Citterio, A.; Giordano, C. *Acc. Chem. Res.* **1983**, *16*, 27.

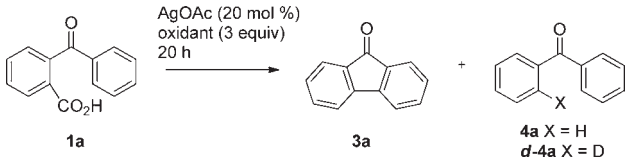
10.1021/ol3010694
Published on Web 05/09/2012

however, that an intramolecular coupling between a benzoic acid and a C−H component[9] in a substrate such as **1** might enable efficient C−C bond formation, being analogous to the classic Pschorr cyclization of a diazonium salt (Scheme 1).[10] Support for this idea came from work by Hey[11] and Thompson[12] in the 1960s, who showed that fluorenones **3** could be formed from benzoylbenzoic acids **1** in low (< 20%) yields through electrolysis and simple $K_2S_2O_8$ treatment, respectively. More recently, Baran and co-workers showed that boronic acids analogous to **1** are effective radical precursors under $K_2S_2O_8$/Ag(I) conditions, forming fluorenones **3** through a 'borono-Pschorr' process.[13]

We began our studies with the commercially available benzoylbenzoic acid **1a**. Importantly, this acid has been reported as a poor substrate for conventional Pd/Ag-mediated decarboxylation, cyclizing in 12% yield to fluorenone.[9b] We screened combinations of solvent, temperature, and oxidant in the presence of AgOAc (Table 1). Encouragingly, we observed a 29% yield of the desired fluorenone **3a** when the reaction was carried out in acetonitrile at 100 °C (Table 1), together with the protodecarboxylated product benzophenone (**4a**, 30%) as a byproduct (formed *via* decarboxylation to the aryl radical followed by hydrogen atom transfer from acetonitrile).

Varying temperature or oxidant was not effective in improving the yield of **3a** (entries 1−7), nor was adding transtion metals such as Pd (entry 9). A broad screen of solvents was then conducted with the aim of suppressing the unproductive hydrogen atom transfer pathway (entry 10). Unfortunately, the decarboxylation proved highly specific to acetonitrile, with little reaction taking place in any other solvent. The breakthrough result came with the use of deuterated acetonitrile, affording the desired fluorenone in good yield with only minor amounts of protodecarboxylation product (entry 11). It appears that the stronger C−D bond is slowing hydrogen atom abstraction from the solvent, enabling intramolecular C−C bond formation to take place. Isolation of *d*-**4a** as a side product confirmed that the solvent was acting as a hydrogen atom donor.

Table 1. Reaction Optimization[a]



entry	oxidant	solvent	temp (°C)	yield **3a**[b] (%)	ratio **3a:4a**[c]
1	$K_2S_2O_8$	MeCN	100	29	1:1.2
2[d]	$K_2S_2O_8$	MeCN	100	15	1:1.2
3	–	MeCN	100	n.d.	–
4	$K_2S_2O_8$	MeCN	80	<5[e]	–
5	$K_2S_2O_8$	MeCN	120	31	1:1.2
6	$Ce(SO_4)_2$	MeCN	100	n.d.	–
7	$PhI(OAc)_2$	MeCN	100	n.d.	–
8[f]	$K_2S_2O_8$	MeCN	100	6	1:1.2
9[g]	$K_2S_2O_8$	MeCN	100	27	1:1.2
10	$K_2S_2O_8$	solvent[h]	100	<5[e]	–
11	$K_2S_2O_8$	d_3-MeCN	100	69	9:1[i]
12	$K_2S_2O_8$	EtCN	100	14	1:3.3
13	$K_2S_2O_8$	^{i}PrCN	100	8	1:3.6
14[j]	$K_2S_2O_8$	d_3-MeCN	100	45	9:1[i]
15[j]	$K_2S_2O_8$	d_3-MeCN	130	76	9:1[i]

[a] Conditions: **1a** (0.3 mmol), AgOAc (0.06 mmol), oxidant (0.9 mmol), and solvent (2.0 mL) in a sealed microwave vial, 20 h, conventional heating. [b] Isolated yields; n.d. = not determined as no product was observed by LC/MS analysis. [c] Ratio determined by NMR integration. [d] Reaction under anhydrous conditions; 4 Å M.S., anhydrous MeCN and under N_2 (1 atm). [e] Yields estimated by LC/MS. [f] 10% AgOAc. [g] 10 mol % $Pd(OAc)_2$. [h] Solvent: $CHCl_3$, H_2O, EtOH, TFE, 1-chlorobutane, DCE, NMP, 1,2-dimethoxyethane, DMF, pyridine, THF, $MeNO_2$, xylene, benzene, chlorobenzene, $PhCF_3$, $PhCF_3/H_2O$ (1:1), DMSO, DMA, di(ethylene glycol), CCl_4, PhCN, toluene, acetone, NEt_3, cyclohexane, vinyl acetate, mesitylene, 1,4-dioxane, $(CF_3)_2$-CHOH, TFA. [i] Byproduct is deutero-decarboxylated product *d*-**4a**. [j] Microwave heating for 1 h.

Extension of this idea by substituting methyl groups onto the acetonitrile solvent was not successful (entries 12 and 13). We elected, therefore, to explore the deuteroacetonitrile conditions further and establish the substrate scope, using final optimized conditions of microwave irradiation at 130 °C (entry 15).

A range of aroylbenzoic acids were easily accessed in one step *via* ring opening of phthalic anhydride with an aryl lithium (Supporting Information). We were pleased to find that the cyclization was successful onto a series of *para*-substituted aromatics (Figure 1). *p*-Fluoro (**3b**), trifloromethyl (**3c**), and chloro (**3d**) all worked in good yields, whereas the more electron rich *p*-methoxy (**3e**) and *p*-methyl (**3f**) substituents afforded moderate yields of fluorenones. A *p*-phenyl group was well-tolerated (**3g**, 65%), whereas the 3,5-dimethyl substituted substrate cyclized in a similarly moderate yield (45%, **3h**) to the *p*-Me analog **3f**. There was little difference in yield when the subsituent was placed in the *ortho* position for fluoro (**3i**) and methyl (**3j**)

(6) Persulfate has been used with Pd-catalysis in the decarboxylative coupling of α-oxocarboxylic acids: (a) Li, M.; Wang, C.; Ge, H. *Org. Lett.* **2011**, *13*, 2062. (b) Fang, P.; Li, M.; Ge, H. *J. Am. Chem. Soc.* **2010**, *132*, 11898. (c) Li, M.; Ge, H. *Org. Lett.* **2010**, *12*, 3464.

(7) Minisci has studied phenyl radical addition to heteroaromatics, but yields are not reported: (a) Clerici, A.; Minisci, F.; Porta, O. *Gazz. Chim. Italia* **1973**, *103*, 171. (b) Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M.; Giordano, C. *J. Org. Chem.* **1986**, *51*, 4411.

(8) (a) Barton, D. H. R.; Lacher, B.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 4321. (b) Bertrand, M. P.; Oumar-Mahamat, H.; Surzur, J. M. *Tetrahedron Lett.* **1985**, *26*, 1209. (c) Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *110*, 2886.

(9) Decarboxylative C−H arylation: (a) Voutchkova, A.; Coplin, A.; Leadbeater, N.; Crabtree, R. H. *Chem. Commun.* **2008**, *47*, 6312. (b) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194. (c) Cornella, J.; Lu, P.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506. (d) Zhang, F.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 2768. (e) Wang, C.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 14006. (f) Hu, P.; Zhang, M.; Jie, X.; Su, W. *Angew. Chem., Int. Ed.* **2012**, *51*, 227.

(10) Galli, C. *Chem. Rev.* **1988**, *88*, 765.

(11) Bunyan, P. J.; Hey, D. H. *J. Chem. Soc.* **1962**, 2771. See also: Davies, D. I.; Waring, C. *J. Chem. Soc. C* **1968**, 2337.

(12) Russell, J.; Thomson, R. H. *J. Chem. Soc.* **1962**, 3379.

(13) Lockner, J. W.; Dixon, D. D.; Risgaard, R.; Baran, P. S. *Org. Lett.* **2011**, *13*, 5628.

relative to their *para*-congeners. We next examined *m*-substituted aromatics in the form of *m*-chloro and *m*-nitro-*p*-chloro substrates. The former proceeded in good yield with little regioselectivity between the two isomers **3k** and **3l**. This result is in line with typical Pschorr cyclizations of *m*-substituted arenes, which rarely show regioselectivity in the free radical aromatic substitution step.[14] The *m*-nitro-*p*-chloro compound, by contrast, was unusual in this regard, cycling successfully to a major regioisomer **3m**, with only minor amounts of the impure isomer arising from cyclization *para* to the nitro group being formed.

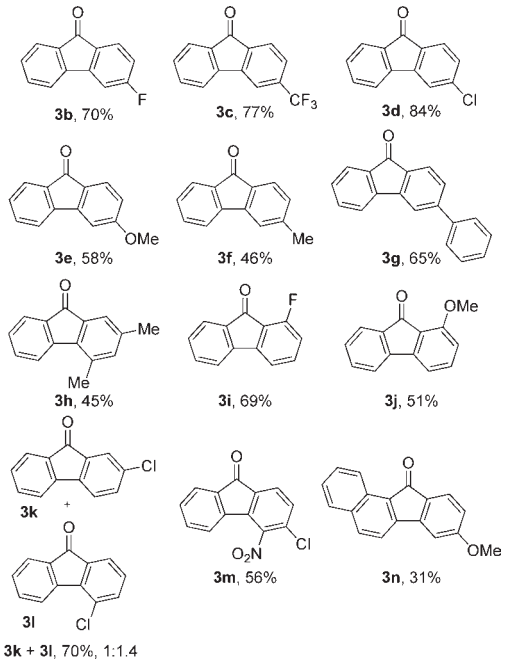
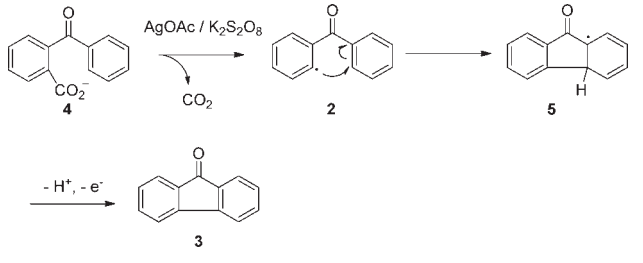


Figure 1. Decarboxylative fluorenone synthesis.

Scheme 2. Mechanism



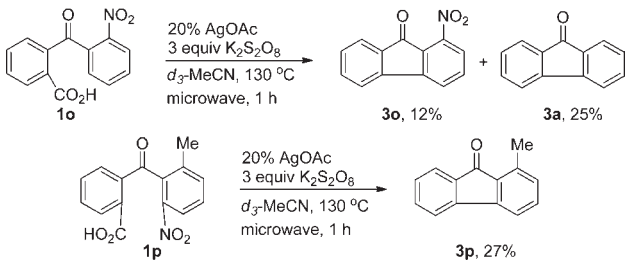
Finally, the benzofluorenone **3n** was formed in low yield with degradation evident in the reaction, possibly indicating that the strong oxidant $K_2S_2O_8$ was incompatible with the electron rich naphthyl system under the reaction conditions.

(14) Kyba, E. P.; Liu, S.-T.; Chockalingam, K.; Reddy, B. R. *J. Org. Chem.* **1988**, *53*, 351.

The reaction mechanism likely proceeds *via* aryl radical generation from oxidative decarboxylation with Ag(I)/$K_2S_2O_8$ and cyclization (Scheme 2). A second one-electron oxidation and proton loss from **5** are then required to give the aromatic fluorenone products **3**.[15] The reaction was tolerant of air but generally not of water, with the decarboxylation step proceeding poorly in water/d_3-MeCN mixtures.[16] Addition of TEMPO to the reaction as a radical probe blocked the decarboxylation step, with starting material being recovered.

An interesting side product was observed on exposure of *o*-nitro substrate **1o** to the reaction conditions, with small amounts of fluorenone **3a** being isolated in addition to the expected nitrofluorenone **3o** (Scheme 3). Given the stability of the nitro group to the reaction conditions (**3m** in Figure 1), and the lack of any deuterium incorporation in **3a**, it is unlikely that **3a** arises from denitration of **3o**. To investigate the reaction further we prepared the *o*-methyl-*o*-nitro substrate **1p** and observed cyclization to **3p** in low yield. This denitrative decarboxylative cross-coupling is unprecedented,[17] and likely proceeds *via* direct *ipso*-substitution of the nitro group[18] with loss of $NO_2^{\bullet}$.

Scheme 3. *o*-Nitro Substrates



In summary, we have developed a novel oxidative decarboxylation and cyclization reaction for carboxylic acids. By using catalytic silver to promote a radical pathway, we can access a class of aroic acids that are not productive in mixed Pd/Cu or Ag catalytic decarboxylative arylations. The reaction shows that aroic acids can be used as radical precursors for C–C bond formation, a transformation previously confined to alkanoic acids. The requirement of expensive d_3-MeCN as a reaction solvent is clearly a limitation in synthetic terms but demonstrates

(15) The order of these latter two steps, proton transfer (PT) *vs* electron transfer (ET), is not known at present. See the following for a discussion of PT *vs* ET in homolytic aromatic substitution: Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5018.

(16) Low yields of product **3a** were possible in water using slow addition of aq $K_2S_2O_8$; see Supporting Information.

(17) Denitrative cyclization has been reported for the diazonium analog of **1o** in a Pschorr cyclization: Hey, D. H.; Mulley, R. D. *J. Chem. Soc.* **1952**, 2276.

(18) For *ipso*-substitution of aromatic nitro groups with adamantyl radicals, see: Testaferri, L.; Tiecco, M.; Tingoli, M. *J. Chem. Soc., Perkin Trans. 2* **1979**, 469.

(19) For examples of product distribution control through deuteration of the substrate, see: Wood, M. E.; Bissiriou, S.; Lowe, C.; Norrish, A. M.; Senechal, K.; Windeatt, K. M.; Coles, S. J.; Hursthouse, M. B. *Org. Biomol. Chem.* **2010**, *8*, 4653 and references therein.

the interesting concept of controlling product distribution (as opposed to studying reaction rate and mechanism) through a solvent isotope effect.[19] Further investigations into this effect will be the subject of future work in our group.

Acknowledgment. Syngenta, the University of Manchester, and the EPSRC are thanked for funding (Leadership Fellowship to M.F.G.) along with the EPSRC mass spectrometry service at the University of Swansea. We also thank Professor W. B. Motherwell for helpful discussions.

Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.