ORGANIC
LETTERS

2000
Vol. 2, No. 17
2643–2646

Photostimulated Reactions of Phenylacetic Acid Dianions with Aryl Halides. Influence of the Metallic Cation on the Regiochemistry of Arylation

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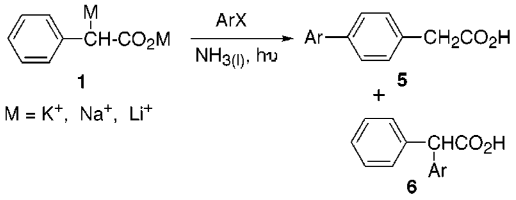
Received June 8, 2000

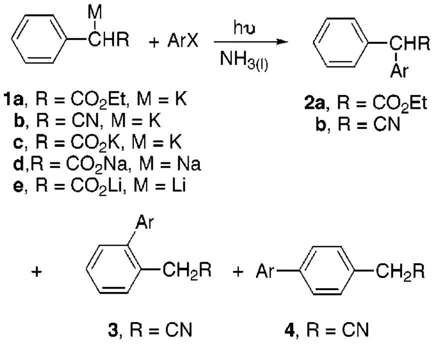
ABSTRACT



Phenylacetic acid dianions react via what appears to be an $S_{RN}1$ process with aryl halides under photostimulation to afford aryl substitution products 5 and 6. When the counterion is K^+, only 4-biphenylacetic acids 5 are obtained. Both α- and *para*-coupling occurs with Na^+ to give a mixture of 5 and 6, while exclusive formation of diphenylacetic acids 6 is observed with the dilithio salt of 1.

As part of a continuing study of radical-chain nucleophilic aromatic substitution reactions, we had discovered previously that photoinduced reactions of aryl and hetaryl halides with phenyl-stabilized carbanions such as the potassium enolate of ethyl phenylacetate (**1a**)[1,2] and potassiophenylacetonitrile (**1b**)[3–5] proceed by the radical-chain $S_{RN}1$[6] mechanism to form mainly products **2a,b**, derived from coupling of aryl radicals at the α-position (Scheme 1). However, while ester enolate **1a** reacted to give only α-substituted product **2a**, potassionitrile **1b** afforded small amounts (<10% total) of *ortho*- and *para*-substituted products **3** and **4**, respectively. These results, which represent rare examples of aryl-to-aryl

Scheme 1



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(1) Wong, J.-W.; Natalie, K. J.; Nwokogu, G. C.; Pisipati, J. S.; Flaherty, P. T.; Greenwood, T. D.; Wolfe, J. F. *J. Org. Chem.* **1997**, *62*, 6152–6159.

(2) Wong, J.-W. Ph.D. Dissertation, Virginia Polytechnic Institute and State University, 1981.

(3) Hermann, C. K. F.; Sachdeva, Y. P.; Wolfe, J. F. *J. Heterocycl. Chem.* **1984**, *24*, 1061–1065.

(4) Hermann, C. K. F. Ph.D. Dissertation, Virginia Polytechnic Institute and State University, 1984.

(5) Bunnett, J. F.; Gloor, B. F. *J. Org. Chem.* **1973**, *38*, 4156–4163.

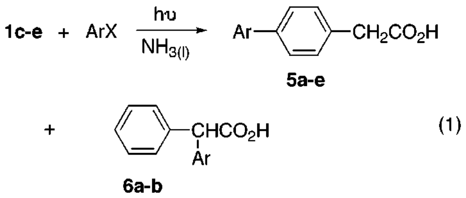
(6) For reviews, see: (a) Rossi, R. A.; de Rossi, R. H. *Aromatic Substitution by the $S_{RN}1$ Mechanism*; ACS Monograph 178; American Chemical Society: Washington, DC, 1983. (b) Norris, R. K. *Compr. Org. Synth.* **1991**, *4*, 451–482. (c) Rossi, R. A.; Pierini, A. B.; Santiago, A. N. *Org. React.* **1999**, *54*, 1–271.

10.1021/ol006177f CCC: $19.00

coupling in $S_{RN}1$ reactions involving phenyl-stabilized carbanions,[7−9] prompted us to investigate the possibility that other carbanions possessing a stabilizing phenyl substituent might exhibit analogous reactivity and regiochemistry.

In the present study, the dipotassio salt of phenylacetic acid dianion (**1c**) was chosen as the representative nucleophile to examine the characteristics of photoinduced arylations. The choice of **1c** was based on the fact that even though there appear to be no published examples of carboxylic acid dianions participating as nucleophiles in single electron transfer (SET)-initiated reactions of the $S_{RN}1$ type, the electrochemically induced oxidative α , *para*-dimerization of certain aryl carboxylic acid dianions has been demonstrated.[10] Furthermore, empirical calculations of electron density distributions in phenylacetic acid dianions using ^{13}C chemical shift data suggest that the *para*-position of potassio salt **1c** possesses ca. 40% as much negative charge as the α-position,[11] which could make the former a possible site for reaction with aryl radicals.

We now wish to report that photostimulated reactions of dianion **1c** with a variety of aryl halides results in regiospecific arylation to afford exclusively *para*-coupled products **5a−e**[12] in yields ranging from 31% to 73% (eq 1,Table 1).



For example, when a solution of dianion **1c**, generated by deprotonation of phenylacetic acid using 2 equiv of KNH_2 in liquid NH_3,[13] was treated with 4-bromotoluene under near-UV irradiation for 5 h,[14] 4-biphenylacetic acid **5d** was obtained in 49% isolated yield (entry 5).[15] The presence of *ortho*-substituents in the aryl halide resulted in either diminished product yields (entry 3) or no reaction at all, as in the case of bromomesitylene, 4-iodonitrobenzene, and 4-bromo-*N*,*N*-diethylaniline.

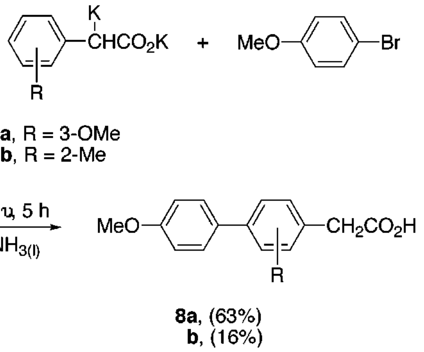
Table 1. Reactions of Aryl Halides with Dianions **1c−e**[a]

entry	aryl halide	dianion	product (yield, %)
1	PhI	**1c**	**5a** (73)
2	PhI	**1e**	**6a** (77)
3	2-MePhBr	**1c**	**5b** (31)
4	3-MePhBr	**1c**	**5c** (47)
5	4-MePhBr	**1c**	**5d** (49)
6	4-MeOPhBr	**1c**	**5e** (64)
7	4-MeOPhBr	**1d**	**5e** (25), **6b** (37)
8	4-MeOPhBr	**1e**	**6b** (61)

[a] All reactions were performed using 2−3 equiv of phenylacetic acid dianion relative to the aryl halide in liquid NH_3 solution and irradiation for 5 h with 350 nm lamps in a Rayonet RPR-240 photochemical reactor.

To assess the influence of phenyl substituents on the reactivity of dianion **1c**, photostimulated reactions of dipotassio salts **7a,b** were carried out in the presence of 4-bromoanisole. As shown in Scheme 2, the dipotassio salt of 3-methoxyphenylacetic acid (**7a**) reacted about as efficiently with 4-bromoanisole as the unsubstituted dianion **1c** (entry 6, Table 1), while the 2-methyl-substituted dianion **7b** afforded only a low yield of *para*-coupled product **8b**.

Scheme 2



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[7] The photoassisted α- and *para*-arylation of triphenylmethyl anion is reported to proceed by a combination of radical coupling and $S_{RN}1$ mechanisms; see: Tolbert, L. M.; Martone, D. P. *J. Org. Chem.* **1983**, *48*, 1185−1190.

[8] For examples of $S_{RN}1$ reactions involving *ortho* and *para* coupling of nitranions derived from aromatic amines, see: Kim, J. K.; Bunnett, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 7464−7466. (b) Pierini, A. B.; Baumgartner, M. T.; Rossi, R. A. *Tetrahedron Lett.* **1987**, *28*, 4653−4656.

[9] Numerous examples of *ortho*- and *para*-coupling reactions of phenoxides and naphthoxides proceeding by the $S_{RN}1$ mechanism have been reported; see: Rossi, R. A.; Pierini, A. B.; Santiago, A. N. *Org. React.* **1999**, *54*, 137−157.

[10] Renaud, P.; Fox, M. A. *J. Org. Chem.* **1988**, *53*, 3745−3752.

[11] Lambert, J. B.; Wharry, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 5857−5862.

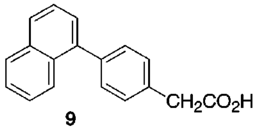
[12] The absence of the characteristic methine resonance for diarylacetic acids at ca. 5.0 δ in the ^1H NMR spectrum of reaction mixtures precluded arylation at the α-carbon of **1c**.

[13] (a) Hauser, C. R.; Chambers, W. J. *J. Am. Chem. Soc.* **1956**, *78*, 4942−4944. (b) Meyer, R. B.; Hauser, C. R. *J. Org. Chem.* **1961**, *26*, 3296−3698.

[14] Shorter reaction times resulted in lower product yields, e.g., after a 2 h reaction period only 22% of **5d** was obtained.

[15] **Representative Experimental Procedure**. To a solution of KNH_2 prepared from potassium (2.35 g, 60 mmol) in 300 mL of liquid ammonia was added slowly a solution of phenylacetic acid (4.08 g, 30 mmol) in 30 mL of anhydrous ether, and the resulting pale green solution was stirred for 30 min. The ammonia solution was then irradiated as 4-bromoanisole (1.87 g, 10 mmol) in 20 mL of ether was added dropwise via syringe. After the addition was complete, irradiation was continued for 5 h and the reaction mixture was poured slowly onto NH_4Cl (6.42 g, 120 mmol) contained in a 1-L beaker. The ammonia and ether were evaporated, 50 mL each of water and hexane were added to the solid residue, and the mixture was vigorously stirred. An insoluble solid that remained was filtered and dissolved in 100 mL of hot water, and the solution was acidified to pH = 1 with 2 M HCl. The resulting mixture was cooled to 0 °C, and the precipitated solid was filtered, washed with water, and air-dried to obtain 1.56 g (64%) of **5e**, mp 182−185 °C. Recrystallization from CH_2Cl_2/ether gave **5e** as colorless needles, mp 187−188 °C, lit. mp 188−188.5 °C, see Linnell, W. H.; Smith, H. J. *J. Chem. Soc.* **1959**, 557−559. ^1H NMR ($CDCl_3$) δ 3.68 (s, 2H), 3.84 (s, 3H), 6.96 (d, 2H), 7.32 (d, 2H), 7.50 (m, 4H). The aqueous layer from the original filtration was acidified with 2 M HCl, and the resulting oily mixture was extracted with 2 × 50 mL portions of ether. The ethereal solutions were combined, dried ($MgSO_4$), and concentrated to a pale yellow oil that solidified on standing; 2.47 g of essentially pure phenylacetic acid. Evaporation of the hexane solution under vacuum left 0.15 g of 4-bromoanisole.

The dianions of 2-methoxy- and 3-chlorophenylacetic acids did not undergo *para*-coupling with 4-bromoanisole, and the *para*-blocked compound, 4-bromophenylacetic acid, failed to yield any of the alternative α- or *ortho*-coupled products. 1-Bromo- and 1-iodonaphthalene underwent *para*-coupling reactions with dianion **1c** to give 4-(1-naphthyl)phenylacetic acid (**9**) in yields of 34% and 48%, respectively. Similarly, 2-bromonaphthalene afforded a 32% yield of 4-(2-naphthyl)-phenylacetic acid (**10**). All of the reactions that produced *para*-coupled products were characterized by essentially complete consumption of the respective aryl halides after 5 h of irradiation, and reductive dehalogenation of the substrate proved to be a significant side reaction in all cases.



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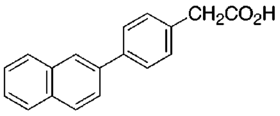

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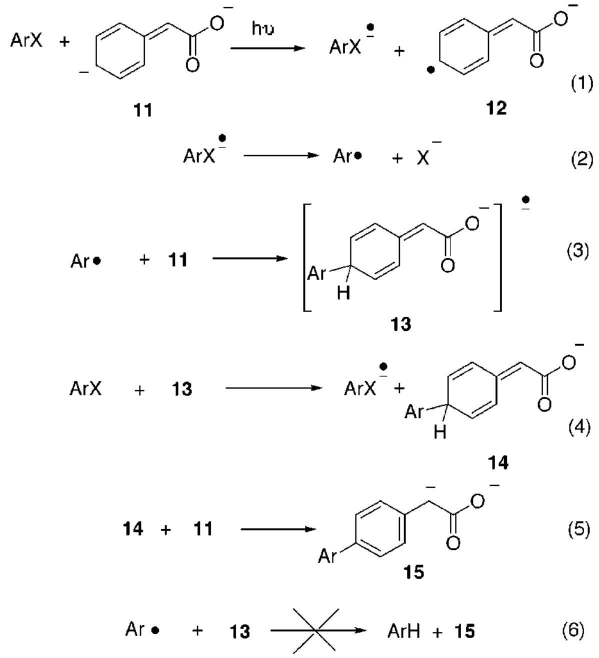
Varying the alkali metal counterion of phenylacetic acid dianion led to a marked influence on the regioselectivity of the photoinduced arylation reaction. Thus, while the dipotassio salt, **1c**, gave exclusively the *para*-coupled product **5e** with 4-bromoanisole (entry 6, Table 1), when the counterion was changed to Na$^+$, as in dianion **1d**, a 3:2 mixture of α : *para*-arylation products **6b** and **5e**, respectively, was obtained (entry 7, Table 1). With Li$^+$ as the counterion, substitution occurred exclusively at the α-position of dianion **1e** to give a 61% yield of diphenylacetic acid derivative **6b** (entry 8, Table 1). α-Coupling was also the only reaction observed between dilithio salt **1e** and iodobenzene (entry 2, Table 1). This surprising counterion effect may be rationalized in terms of differences in electron densities at the *para*-positions of dianions **1c** and **1e**. The large, soft K$^+$ ions of **1c** bond less tightly to the oxygens of the carboxylate group than the small, hard Li$^+$ ions of **1e**, resulting in a greater delocalization of charge to the *para*-position of the former. The disodium salt **1d** represents an intermediate case.

Some mechanistic aspects of the coupling process became evident with the finding that reaction of 4-bromotoluene with dianion **1c** failed to occur without near-UV irradiation. When an irradiated reaction involving these same reactants was carried out for 2 h in the presence of 20 mol % of the radical scavenger, di-*tert*-butyl nitroxide (DTBN),[16] the yield of *para*-coupled product **5d** was not diminished compared with that obtained in a similar uninhibited photoreaction.[14] The necessity for photostimulation strongly suggests the involvement of a SET mechanism in the arylation reaction. The relatively long reaction times required[17] and the lack of inhibition by a catalytic amount of DTBN[18] imply that the substitution process is an example of a rather inefficient $S_{RN}1$ reaction. The similar nature of the photoinduced α-arylations involving dilithio salt **1e** (5 h) including their resistance to inhibition by up to 20 mol % of DTBN, is consistent with operation of the same recalcitrant mechanism. The proposed mechanism for the *para*-coupling is illustrated in steps 1−5 of Scheme 3. The radical-chain reaction is initiated by SET from dianion **11** to ArX under the influence of near-UV irradiation (step 1). The resulting aryl radical anion dissociates to give Ar• (step 2), which then undergoes *para*-coupling reaction with dianion **11** affording product dianion radical **13** (step 3). Electron transfer from **13** to ArX (step 4) generates product anion **14** and the aryl radical anion, which continues the propagating cycle (steps 2−4). The substitution process then concludes with deprotonation−isomerization of **14** by excess dianion **11** to yield product dianion **15** (step 5). An alternative nonchain mechanism involving the coupling of substrate aryl radicals (Ar•) with radical anion **12**[19] seems unlikely in light of both the sluggishness of the arylation reaction and the observed metallic cation effect.

Scheme 3



As part of our mechanistic investigation, we considered possible termination steps involving dianion radical **13** that would be consistent with both the lethargic nature of the substitution reaction and reduction of the aryl halide. One such chain interrupting reaction might involve *para* hydrogen atom abstraction from **13** by Ar• to generate product dianion **15** and ArH (step 6). This possibility was subsequently discounted by the reaction of dipotassio 4-deuteriophenylacetate with 4-bromotoluene, which failed to yield any 4-deuteriotoluene. Another conceivable chain-breaking option

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[16] (a) Hoffman, A. K.; Feldman, A. M.; Geblum, E.; Hodgson, W. G. *J. Am. Chem. Soc.* **1964**, *86*, 639−646. (b) Nelsen, S. F.; Bartlett, P. D. *J. Am. Chem. Soc.* **1966**, *88*, 143−149. (c) Carver, D. R.; Hubbard, J. S.; Wolfe, J. F. *J. Org. Chem.* **1982**, *47*, 1036−1040.

[17] By comparison, monoanion **1a** reacts with iodobenzene under essentially identical conditions to give 90% of **2a** (Ar═Ph) after 1 h, see ref 2.

[18] Two molecular equivalents of DTBN (based on 4-bromotoluene) were required to completely quench the 2 h reaction.

[19] Galli, C. *Tetrahedron* **1988**, *44*, 5205−5208.

might be the reduction of Ar• by **13**. However, as in step 6, this entropically unfavorable encounter between two highly reactive intermediates present in low concentrations seems unlikely to play an important role in the arylation process. Another way in which the chain carrying Ar• might be taken out of the propagation cycle would involve reduction by dianion **11** to aryl anions, which then undergo protonation by liquid NH_3 to generate ArH. This pathway also seems improbable since no products expected from dimerization of radical anion **12**[10] were detected in any of the arylation reactions.

In conclusion, the reactions of dipotassio phenylacetic acid salts **1c** and **7a,b** with aryl halides described in this study represent unique examples of photostimulated arylation occurring at an aromatic carbon remote from the site of original carbanion generation. This regiochemistry contrasts with exclusive α-carbon substitution observed in typical two-electron S_N2-type displacement reactions of phenylacetic dianions.[13] Moreover, the metallic cation effect on the regioselectivity of substitution observed with dialkali salts **1c**−**e** appears to be unprecedented in photoinduced arylations of carbanionic species.[20] Finally, with further optimization, the *para*-coupling reactions described here could serve as a convenient, one-step synthesis of certain 4-biphenylacetic acids and their derivatives.

Acknowledgment. The authors are pleased to acknowledge the generous support of this work by the Harvey W. Peters Research Center for Parkinson’s Disease and Disorders of the Central Nervous System Foundation and by the National Science Foundation through grant CHE-8513216.

Supporting Information Available: ^1H NMR data, melting points, and literature references for known compounds **5a**, **5b**, **5d**, **5e**, **6a**, **6b**, **8a**, and **9b**. Additionally, elemental analyses or HRMS data for new compounds **5c**, **8b**, and **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) For a report of the influence of metallic cation on the stereoselectivity of $S_{RN}1$ arylation of imide α-enolates, see: Lotz, G. A.; Palacios, S. M.; Rossi, R. A. *Tetrahedron Lett.* **1994**, *35*, 7711−7714.