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Metal-Free Radical Aromatic Carbonylations Mediated by Weak Bases

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We report a new method of metal-free alkoxycarbonylation. This reaction involves the generation of aryl radicals from arenediazonium salts by a very weak base (HCO₂Na) under mild conditions. Subsequent radical trapping with carbon monoxide and alcohols gives alkyl benzoates. The conditions (metal-free, 1 equiv. base, MeCN, r.t., 3 h) tolerate various functional groups (I, Br, Cl, ¹⁰ CF₃, SF₅, NO₂, ester). Mechanistic studies indicate the operation of a radical aromatic substitution mechanism.

Introduction

ARTICLE TYPE

Benzoates are key structural motifs of numerous fine chemicals, agrochemicals, pharmaceuticals, materials, and 15 natural products.¹ The transition metal-catalyzed alkoxycarbonylation of aryl electrophiles with carbon monoxide and alcohols is the most versatile synthesis method for benzoates (Scheme 1a)² On the other hand, related metal-free carbonylations are rare.³ Lei and co-workers reported a radical 20 tert-butoxycarbonylation of aryl iodides mediated by KOtBu/phenanthroline (Scheme 1b).⁴ This reaction is most likely initated by single-electron transfer from extended heteroaromatic radical anions that form upon base-mediated thermal condensation. However, severe limitation arise from 25 the exclusive production of tert-butyl benzoates, the harsh conditions, and the little mechanistic insight.⁵ Our group and Xiao et al. simultaneously developed photoredox-catalyzed alkoxycarbonylations of arenediazonium salts with wide scope under mild conditions.⁶ We believed that a robust and 30 versatile method of alkoxycarbonylation would enable the reaction of easily accessible aryl electrophiles with various primary, secondary, and tertiary alcohols under mild conditions with the aid of a cheap initiator. Arenediazonium salts constitute an especially versatile class of aryl electro-35 philes that display distinct reactivity from aryl halides, can easily be prepared from anilines, and undergo ready degradation to aryl radicals in the presence of reductants and bases.⁷ The formation of aryl radicals from arenediazonium salts with very weak bases under ambient conditions was 40 demonstrated in the context of several radical aromatic

- ⁴⁰ demonstrated in the context of several radical atomatic substitution reactions.^{7b,8} The application of arenediazonium salts to radical alkoxycarbonylations were recently realized in photoredox-catalyzed processes (Scheme 1c).⁶ We surmised that the sequential combination of both reactivity concepts, *i*) ⁴⁵ the mild generation of aryl radicals from arenediazonium salts
- ⁴⁵ the mild generation of aryl radicals from archediazonium saits and very weak bases and *ii*) the facile trapping of aryl radicals with carbon monoxide and alcohols, would allow for an expedient method of alkoxycarbonylation of arenes and obviate the need for radical initiators, metal catalysts, inert
- ⁵⁰ conditions, or irradiation equipment (Scheme 1d).⁹



Scheme 1 Alkoxycarbonylation of aryl electrophiles.

Method development

Following earlier work on radical aromatic substitutions, 6a,10 55 we investigated the efficacy of weak carboxylates as initiators¹¹ of radical carbonylations. We aimed at the use of inorganic bases as they are cheap, environmentally benign, and can be easily removed from the organic products. The initial model reaction of the white crystalline 4-nitrobenzene-60 diazonium tetrafluoroborate (1) with CO and tert-butanol cleanly afforded the tert-butyl ester 2 (Table 1). It is important to note that transition metal-catalyzed alkoxycarbonylations mostly fail to deliver tert-butyl esters due to the steric bulk of the alcohol. Co-solvents were added to assist 65 the dissolution of the arenediazonium salt 1. A survey of inexpensive bases showed highest activity and selectivity with stoichiometric amounts of sodium formate which resulted in minimal hydrodediazonation toward 3.^{10b} No reaction was observed in the absence of base. Importantly, the reaction 70 displayed no sensitivity toward air and moisture. The optimized conditions involved equimolar sodium formate and 1 (~0.1 M) in a mixture of t-butanol/acetonitrile (10/1) under pressurized CO (50 bar) for 3 h at room temperature to give t-butyl 4-nitrobenzoate (2) in 80% yield (entry 1).

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 Table 2	Carbonylation	of arenedia	azonium	salts with	tert-butanol.

	1 equiv. H N ₂ BF ₄ 50 bar CO	HCO ₂ Na C , <u>t-BuOH</u>	L.K				
R H MeCN, 20 °C							
Aryl	Yield [%]	Aryl	Yield [%]				
$4-O_2N-C_6H_4$	75	4-MeO-C ₆ H ₄	44				
$4\text{-Br-}C_6\text{H}_4$	63	3-Br-C ₆ H ₄	52				
$4-Cl-C_6H_4$	66	3-Cl-C ₆ H ₄	60				
$4\text{-I-C}_6\text{H}_4$	42	$2-MeO-C_6H_4$	49				
$4-F_3C-C_6H_4$	50	2 - F_3C - C_6H_4	54				
4-Me-C ₆ H ₄	61	$2-O_2N-C_6H_4$	<5				
4-MeO ₂ C-C ₆ H ₄	56	$2-MeO_2C-C_6H_4$	<5				
$4-F_5S-C_6H_4$	51	1-naphthyl	54				

 a Conditions: are nediazonium tetrafluoroborate (0.9 mmol), HCO_2Na (0.9 $_{\rm 40}$ mmol), tBuOH (9 mL), MeCN (1.2 mL), CO (50 bar), r.t., 3 h.







Scheme 3 Alkoxycarbonylations with *sec*-alcohols.

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	N ₂ BF ₄	CO, <i>t</i> BuOH		
O₂N		base, solvent O	2N	" + _{O2} N
	1		2	3
Entry	Base	Solvent (mL)	Equiv. <i>t</i> BuOH	Yield 2/3 [%]
1	HCO ₂ Na	MeCN (0.4)	100	80 / 9
2	AcONa	MeCN (0.4)	100	71 / 19
3	BzONa	MeCN (0.4)	100	71 / 10
4	K ₂ CO ₃	MeCN (0.4)	100	71 / 8
5	HCO ₂ Na	MeCN (0.2)	100	76 / 9
6	HCO ₂ Na	MeCN (3)	1	8 / 3
7	NaH	MeCN (0.4)	100	24 / 15
8^b	HCO ₂ Na	MeCN (0.2)	66	61 / 17
9^b	nBuLi	MeCN (0.2)	66	22 / 18
10^{b}	H ₂ NNMe ₂	MeCN (0.2)	66	3 / 26
11^{b}	HCO ₂ Na	AcMe (0.2)	66	58 / 18
12^{b}	HCO ₂ Na	DMF (0.2)	66	26 / 25
13 ^b	HCO ₂ Na	H ₂ O (0.2)	66	18 / 20
14^b	HCO ₂ Na	MeCN (0)	66	40 / 18

^{*a*} Conditions: 4-Nitrobenzenediazonium tetrafluoroborate (0.3 mmol), base (0.3 mmol), r.t., CO (50 bar), 12 h, GC yields vs. internal 1-dodecanenitrile; ^{*b*}CO (30 bar).

⁵ The optimized conditions were applied to a set of diverse arenediazonium salts (Table 2). Halides, esters, CF₃, SF₅, and naphthyl substituents were tolerated. Especially the high chemoselectivity in the presence of aryl halide entities under the reaction conditions is a major advantage over metal-¹⁰ catalyzed protocols. With 2-nitro and 2-carboxymethyl substituents, only very little product formation was observed. Under similar conditions, methanol, ethanol, and *i*-propanol were reacted as simplest representatives of *n*- and *s*-alcohols (Scheme 2). Generally, alkoxycarbonylations of **4** afforded the ¹⁵ highest yields with MeOH, EtOH, and *i*PrOH while the more electrophilic **1** showed higher reactivity with *t*BuOH. Despite the good solubility of arenediazonium salts in these alcohols, the addition of acetonitrile as co-solvent was shown to lower

the rate of the hydrodediazonation pathway.^{10b} Generally, the ²⁰ yields of ethyl and *i*-propyl esters were slightly lower than those of the methyl esters which is a consequence of the higher propensity of the former to engage in hydrogen atom transfer reactions. Likewise, other *sec*-alcohols gave the benzoates in moderate yields and the corresponding ketones

- 25 from competing alcohol oxidation (Scheme 3). For short-chain alcohols, the resultant oxidized by-products are volatile and therefore require no laborious separation from the benzoates. In the case of tertiary alcohols, H atom transfer operated exclusively from the α -position of acetonitrile. Deuterium
- ³⁰ labelling in the methoxycarbonylation of 4-methoxybenzenediazonium tetrafluoroborate (4) with d_4 -methanol, sodium d_1 formate, and d_3 -acetonitrile, respectively, revealed the significant deuterium atom transfer from the solvent in methoxycarbonylations (Scheme 4). This trend was supported
- $_{35}$ by experiments with d_3 -MeCN, *t*-BuCN, and d_6 -acetone as cosolvents which enhanced the selectivity of the alkoxycarbonylation.

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Scheme 4 Competing hydrodediazonation by α-H atom transfer.

A methodological extension of the alkoxycarbonylation was realized with tethered alkenes and alkynes (Scheme 5). 5 Reactions of 2-allyloxybenzenediazonium tetrafluoroborate afforded 2,3-dihydrobenzofuran-3-yl acetates by a sequence of aryl radical formation, intramolecular 5-exo ring closure, and alkoxycarbonylation. The related propargyl derivative cleanly gave the benzofuran-3-yl acetate after acid-mediated 10 olefin isomerization during workup.^{6b} The latter reaction constitutes an inexpensive alternative to the palladiumcatalyzed Heck olefination of the same substrate.¹²



Scheme 5 Sequential cyclization-alkoxycarbonylation reactions.

¹⁵ Key mechanistic studies were performed that support the notion of a radical pathway involving intermediate aryl and acyl radicals (Scheme 6). The initiation of the arenediazonium ion degradation to reactive aryl radicals by very weak bases

was already reported earlier.7b,8 Nucleophilic attack of the 20 formate onto the diazonium terminus most likely generates a diazoformate adduct which decomposes to an aryl radical.⁸ Consistent with this ionic initiation step, the use of sodium trifluoroacetate instead of sodium formate gave identical reactivity with 1, whereas the much less electrophilic 4 was 25 unreactive with the less nucleophilic NaO₂CCF₃. With the radical trap 2,2,6,6-tetramethyl piperidinyloxyl (TEMPO), rapid formation of the aryl and aroyl adducts was observed under reaction conditions. We postulate that the employed base affects the acid-base equilibrium of the alcohol toward 30 the more nucleophilic alkoxide. However, acid-catalysis could enhance the electrophilicity of the aroyl radical. The direct attack of the alcohol/alkoxide onto the aroyl radical distinguishes this mechanism from carbonylations of organohalides (mostly iodides) which operate via the acyl halide ³⁵ intermediate.⁹ Both reactivity patterns can most effectively be provided by a buffered system comprising of a weak base. The potentially good reducing power of the intermediate aroyl radical and dioxa-substituted benzyl radical suggests the operation of a radical chain mechanism.¹³ Besides the initial 40 aryl radical formation, the base sodium formate could induce (minor) deprotonation to give the alcoholate R'O⁻ and/or the intermediate ketyl-type radical anion. The consumption of the base was indirectly proven by a steady decrease of the pH over the course of the reaction (to pH 4 upon completion).



Scheme 6 Postulated mechanism of the formate-mediated alkoxycarbonylation of arenediazonium salts.

Conclusion

We have developed a new alkoxycarbonylation protocol that ⁵⁰ affords alkyl benzoates from arenediazonium salts, carbon monoxide, and alcohols. This method provides a useful alternative to metal-catalyzed carbonylation reactions. The competition of hydrogen atom transfer can be reduced by the choice of alcohols and solvents. The radical reaction ⁵⁵ mechanism is most likely initiated by the ionic reaction between the aryl electrophile and sodium formate under mild conditions. The intermediacy of aryl and aroyl radicals was shown by radical trapping experiments. Further applications of the concept of weak base-initiated radical cascade ⁶⁰ processes to other substrates are actively being pursued in our laboratories.

General procedure for base-induced alkoxycarbonylation. A 20 mL vial was charged with a magnetic stir bar, the arenediazonium salt (0.9 mmol), sodium formate (0.9 mmol), 5 acetonitrile (1.2 mL for reactions with t-BuOH, 9 mL for other alcohols), the alcohol (9 mL of t-BuOH, 45 mmol of other alcohols) and capped with a snap-on lid. The lid was punctured with a needle and transferred to a high-pressure reactor (ParrTM). The reactor was sealed, placed on a magnetic stirring 10 plate, and slowly pressurized with CO up to 50 bar. After 3 h, the gas was slowly released and the vial retrieved. The reaction was quenched with water (5 mL) to give an emulsion which was extracted with ethyl acetate (3×5 mL), and the organic phases were washed with brine (5 mL) and dried 15 (MgSO₄). The solvents were evaporated in vacuo, and the residue was purified by flash column chromatography (SiO₂, pentane/ethyl acetate mixtures 100/0 to 100/20).

Acknowledgements

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25 Notes and references

^a Institute of Organic Chemistry, University of Regensburg, Germany. Fax: +49(0)941943-4617; Tel: -4802; E-mail: axel.jacobi@ur.de † Electronic Supplementary Information (ESI) available: [Experimental procedures, analytical data of all new compounds]. See DOI: .

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A radical aromatic substitution mechanism initiated by very weak bases effects the synthesis of benzoates under pressurized CO atmosphere.

