Conversion of N-Aromatic Amides to O-Aromatic Esters

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ABSTRACT

 $Ar \underbrace{N}_{H} R \xrightarrow{O}_{R} R \xrightarrow{2 \text{ eq. NaNO}_{2}}_{O \ C \ --> \ R. \ T.} Ar \underbrace{O}_{R} \xrightarrow{O}_{R}$ Ar = Aryl; R = Alkyl, Aryl 72 - 94%

N-Aromatic secondary amides can be transformed into O-aromatic esters in high yield via *N*-nitrosamide intermediates. The amides can be generated in situ from the corresponding aromatic amines or nitro compounds, and phenols can easily be made from the esters. The reaction can be modified by addition of methyl methacrylate or toluene at 0 °C to give polymerization or deamination, respectively. The rearrangement mechanism may involve radical formation and recombination.

The oxygenation of aromatic rings is a useful synthetic transformation, but direct methods to accomplish this in a controlled fashion are rare. A common strategy is nitration of an aromatic ring, followed by reduction of the nitro group, diazotization of the resulting amino group, and finally decomposition of the diazo group in the presence of water to give the desired phenol. While the nitration, reduction, and diazotization steps are generally straightforward, even a brief survey of the literature shows that the decomposition of diazonium salts in water gives highly variable yields of phenols ranging from excellent to none, depending on the other functional groups present, and a variety of techniques have been developed in an effort to improve yields.^{1,2} Therefore, development of alternative general methods to replace N-aromatic nitrogen with O-aromatic oxygen is desirable.

Several decades ago, White and co-workers showed that N-aliphatic secondary amides could be converted to N-nitrosamides, which would thermally rearrange to acyloxy-azoaliphatics and decompose in inert solvents to give O-aliphatic esters and nitrogen (Scheme 1).^{3–9} Mechanistic

studies were carried out on this unusual reaction, and it was postulated that decomposition occurred by loss of nitrogen to give a carbocation and acyloxy anion, which quickly recombine to give the ester. While interesting,¹⁰ this specific transformation is of limited synthetic utility as O-aliphatic esters and their corresponding aliphatic alcohols are readily available through other synthetic methods. In contrast, the analogous reaction of N-aromatic secondary amides to give O-aromatic esters would be a useful alternative to the decomposition of aromatic diazonium salts to give phenols because the O-aromatic esters can generally be quantitatively converted to phenols, if desired, by base-catalyzed transesterification or saponification/protonation.¹¹ However, White reported that attempts to convert N-aromatic secondary amides to O-aromatic esters by thermal decomposition of the corresponding N-nitrosamides were unsuccessful,⁵ pre-



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⁽²⁾ Cohen, T.; Dietz, A. G., Jr.; Miser, J. R. J. Org. Chem. 1977, 42, 2053.

⁽³⁾ White, E. H. J. Am. Chem. Soc. 1954, 76, 4497.
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example	R	R′	ester yield, % ^a	mp, °C	lit. mp, °C ^b	purity, % ^a
1	<i>p</i> -nitrophenyl	methyl	93	81-82	81-82	
2	<i>p</i> -methoxyphenyl	methyl	80			98
3	<i>p</i> -bromophenyl	methyl	92	21-23	21.5	
4	<i>p</i> -cyanophenyl	methyl	88	63 - 65	63	
5	<i>p</i> -phenylphenyl	methyl	94	87-88	88-89	
6	<i>p</i> -methylphenyl	methyl	82			97
7	<i>m</i> -methylphenyl	methyl	83			91
8	o-tert-butylphenyl	methyl	94	24 - 26	24.3	
9	phenyl	phenyl	91	68-70	68-70	
10	<i>p</i> -cyanophenyl	<i>p</i> -methoxyphenyl	91	60	60 ¹⁹	
11	1-naphthyl	methyl	91	47 - 49	47-49	
12	8-acetamido-1-naphthyl	methyl	83	146 - 148	147 - 148	
13	<i>p</i> -phenylphenyl	trifluoromethyl	94	34 - 36	$34 - 36^{18}$	
14	2-pyridyl	methyl	72			8521
15	4-[2.2]paracyclophanyl	methyl	76	134 - 135	$132.5 - 134^{11}$	

^a Yield refers to isolated, purified product in the case of solids; for liquid esters yield refers to total isolated yield corrected for purity. ^b All mp's were taken from ref 16 unless otherwise noted. ^c Purities of liquid esters were determined by semiquantitative GC-MS; mass spectra matched literature values taken from ref 17 unless otherwise as noted.

sumably as a result of the difficulty of forming the intermediate phenyl carbocation.

Literature descriptions of the conversion of 4-amino-[2.2]paracyclophane to 4-hydroxy[2.2]paracyclophane by the diazotiation/decomposition routes reported relatively low vields.^{11–13} and repetition in our laboratory gave uniformly unacceptable results (<10% yield). Therefore, treatment of N-acetyl-4-amino[2.2]paracyclophane14 with excess sodium nitrite in 2:1 acetic anhydride/acetic acid at 0 °C (to generate ⁺NO in situ), followed by warming to room temperature, was carried out to form the corresponding N-nitrosamide,⁴ which was to be isolated, transferred to an inert solvent, and thermolyzed in an attempt to generate 4-acetoxy[2.2]paracyclophane (Scheme 2). However, the isolated product



was shown not to be the N-nitrosamide but rather the desired 4-acetoxy[2.2]paracyclophane^{11,13} in 76% yield (Table 1, example 15).¹⁵ The 4-acetoxy[2.2]paracyclophane was guan-

(8) White, E. H. Organic Syntheses; Wiley: New York, 1973; Collect. Vol. V, p 336. (9) White, E. H.; Dzadzic, P. M. J. Am. Chem. Soc. **1976**, 98, 4020.

(10) For other recent research concerning N-nitrosamide rearrangements, see: Darbeau, R. W.; Perez, E. V.; Sobieski, J. I.; Rose, W. A.; Yates, M. C.; Boese, B. J.; Darbeau, N. R. J. Org. Chem. 2001, 66, 5679 and references therein.

titatively converted to 4-hydroxy[2.2]paracyclophane by hydroxide-catalyzed transesterification in methanol.^{11,13} This surprising result provided the impetus to investigate the scope and synthetic utility of this transformation.

The results of conversion of a variety of N-aromatic secondary amides to O-aromatic esters are shown in Table 1.15 Solid products were characterized by melting points¹⁶ and liquid esters by GC-MS.¹⁷ Yields were uniformly very good to excellent, and the technique is clearly tolerant of a wide range of functional groups and their position on the aromatic rings, most notably the excellent yield (94%) for

(12) Cram, D. J.; Allinger, N. L. J. Am. Chem. Soc. 1955, 77, 6289.

(13) Cipiciani, A.; Fringuelli, F.; Mancini, V.; Piermatti, O.; Pizzo, F.; Ruzziconi, R. J. Org. Chem. 1997, 62, 3744.

(14) Falk, H.; Reich-Rohrwig, P.; Schlögl, K. Tetrahedron 1970, 26, 511.

(15) The desired acetamide (1-3 mmol) is placed in a flask and dissolved in 15 mL of a 2:1 mixture of acetic anhydride and acetic acid. The flask is cooled to 0 °C in an ice bath. While the mixture is being slowly stirred magnetically, solid sodium nitrite (2 equiv, 1.6 equiv if the molecule has a nitrile group) is added to the mixture, and the vessel is lightly capped. Evolution of a brown gas occurs, the solution may change color, and sometimes a solid comes out of solution. The flask is kept in the ice bath for 2 h and allowed to warm to room temperature, where it is typically kept for 24 h, although the reaction may be complete much sooner. The solution may darken on standing. The mixture is poured into ice/water, and for solid samples, the resulting solid that forms is collected by suction filtration. Prolonged stirring is sometimes needed to sufficiently hydrolyze acetic anhydride, which can contribute to oil formation. Traces of acetic acid/anhydride can often be removed from the solid by dissolving in ethanol. pouring into ice/water, and collecting the resulting solid by suction filtration. The samples can be recrystallized from appropriate solvents as needed. For liquid or low melting point esters, the aqueous mixture from quenching the reaction is extracted with methylene chloride (3 \times 50 mL). The combined methylene chloride extracts are washed with saturated sodium bicarbonate solution (3 \times 50 mL) and dried using anhydrous magnesium sulfate. Methylene chloride is removed under reduced pressure to give the desired crude ester.

(16) Literature mp's were taken from The Dictionary of Organic Compounds, 6th ed.; Chapman and Hall: New York, 1996 unless otherwise noted.

⁽⁵⁾ White, E. H. J. Am. Chem. Soc. 1955, 77, 6011.

⁽⁶⁾ White, E. H. J. Am. Chem. Soc. 1955, 77, 6014.

⁽⁷⁾ White, E. H.; Elliger, C. A. J. Am. Chem. Soc. 1967, 89, 165.

⁽¹¹⁾ Norcross, B. E.; Becker, D.; Cukier, R. I.; Schultz, R. M. J. Org. Chem. 1967, 32, 220.

⁽¹⁷⁾ Unless otherwise noted, mass spectra were correlated with standard spectra available on the SDBS website, http://www.aist.go.jp/RIODB/SDBS/ (20Dec2001).

the sterically hindered o-tert-butylphenyl acetate (Table 1, example 8). The carboxyl moiety (R' in Table 1) can also be varied to yield O-aromatic benzoate or trifluoroacetate esters (Table 1, examples 9, 10, and 13¹⁸), showing that ester formation occurs by recombination of fragments rather than by reaction of the aromatic fragment with solvent. Two other specific examples of the synthetic utility of this reaction are the formation of *p*-cyanophenyl *p*-methoxybenzoate (Table 1, example 10), a liquid crystalline compound,¹⁹ and 1,8bisacetoxynaphthalene (Table 1, example 12), a convenient precursor to 1,8-dihydroxynaphthalenes, which are of interest as unusual ligands²⁰ but are otherwise difficult to access synthetically. Heterocycles can also be used as substrates as shown for the synthesis of 2-acetoxypyridine²¹ (Table 1, example 14), which is essentially 2-hydroxypyridine that is protected from tautomerization to 2(1H)-pyridone. Such molecules can be difficult to access by conventional routes.

The synthetic utility of this reaction can be expanded. Aromatic amines may be converted to O-aromatic acetates in a one-pot reaction by in situ generation of the amides, simply by dissolving the amine in acetic anhydride and heating briefly, followed by cooling and addition of appropriate amounts of acetic acid and sodium nitrite.²² Further, aromatic amines are often generated by catalytic hydrogenation (Pd/C) of aromatic nitro compounds. By carrying out the hydrogenation in acetic anhydride, the amide can be generated in situ after reduction.²³ The catalyst can be removed by filtration, the solution cooled, appropriate amounts of acetic acid and sodium nitrite added, and after reaction and warming to room temperature, the O-aromatic acetate may be generated. This latter reaction sequence constitutes a two-step, essentially one-pot conversion of aromatic nitro compounds to aromatic acetates.²⁴ The yield advantage of carrying out this reaction sequence versus stepwise synthesis was demonstrated for the synthesis of 4-acetoxybiphenyl from 4-nitrobiphenyl (Scheme 3). Isolating both 4-aminobiphenyl and 4-acetamidobiphenyl in the reaction sequence before conversion to 4-acetoxybiphenyl gave an overall yield of 79%. Isolating the 4-aminobiphenyl but generating the 4-acetamidobiphenyl in situ before

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(20) Poirier, M.; Simard, M.; Wuest, J. D. Organometallics 1996, 15, 1296.

(23) Rylander, P. N. *Hydrogenation Methods*; Academic Press: Orlando, 1985; p 105.

(24) 4-Nitrobiphenyl (0.307 g, 1.54 mmol) was placed in a hydrogenation flask and dissolved in 20 mL of acetic anhydride and 10 mL of acetic acid. Palladium (10% on C, 30 mg) was added, and the bottle was attached to a Parr hydrogenation apparatus. Hydrogenation was carried out with shaking for 3 h at 25 psi H₂. The catalyst was removed by filtration through filteraid, and the solution was cooled in an ice bath for 30 min. Reaction with sodium nitrite (0.212 g, 3.08 mmol) and workup was carried out as described above¹⁵ to give 0.317 g (97%) of 4-biphenylacetate, mp 87–89 °C (lit. mp 88-89 °C).¹⁶



^{*a*} (a) H₂, Pd/C, ethanol; (b) Ac₂O, heat; (c)¹⁵ 2:1 Ac₂O/AcOH, NaNO₂, 0 °C \rightarrow rt; (d)²² (1) Ac₂O, heat, (2) AcOH, NaNO₂, 0 °C \rightarrow rt; (e)²⁴ (1) H₂, Pd/C, 2:1 Ac₂O/AcOH, (2) filter, (3) NaNO₂, 0 °C \rightarrow rt.

conversion to 4-acetoxybiphenyl gave an overall yield of 87%. However, carrying out the reaction sequence without isolating any of the intermediate compounds gave 4-acetoxy-biphenyl in 97% yield.

White postulated that decomposition of aliphatic nitrosamides generated carbocation/anion pairs. However, yields for the conversion of N-aromatic amides to O-aromatic esters were uniformly high regardless of the electron-donating/withdrawing character of the substituents (Table 1), casting doubt on a carbocation/anion pair mechanism and suggesting decomposition via either a radical or cyclic, concerted mechanism (Scheme 4). Indeed, a homolytic radical cleavage



mechanism has been postulated for the decomposition of N-aromatic nitrosamides in aromatic solvents for the synthesis of biaryls.²⁵ White usually generated nitrosamides using N_2O_4 and isolated them before allowing them to rearrange. The reaction conditions presented here allow for in situ generation of nitrosamides, and the solvent must provide a nonreactive environment that facilitates the rearrangement. Disruption of the inert solvent environment by reactive moieties would allow trapping of reactive intermediates.

Evidence for the role of solvent came from two experiments. In the first experiment, the N-nitrosamide of *N*-(4nitrophenyl)acetamide, isolated at low temperature, was used as an initiator for methyl methacrylate (MMA) polymeriza-

⁽¹⁸⁾ Ayres, D. C.; Levy, D. P. Tetrahedron 1986, 42, 4259.

⁽²¹⁾ Cohen, T.; Deets, G. L. J. Org. Chem. 1972, 37, 55.

^{(22) 4-}Aminobiphenyl (2.56 g, 15.1 mmol) was placed in a 250-mL round-bottom flask and dissolved in 60 mL of acetic anhydride. The flask was fitted with a condenser, and the solvent was heated to reflux for 30 min and allowed to cool to room temperature. Acetic acid (30 mL) was added, and the flask was cooled to 0 °C in an ice bath. Reaction with sodium nitrite (2.04 g, 30.0 mmol) and workup was carried out as described above¹⁵ to give 3.06 g (96%) of 4-biphenylacetate, mp 87–88 °C (lit. mp 88–89 °C).¹⁶

⁽²⁵⁾ Bachman, W. E.; Hoffman, R. A. Org. React. 1944, 2, 224-261.

tion,²⁶ which will occur radically but not cationically. UV– visible spectroscopy showed that *p*-nitrophenyl moieties were present in the polymer. Generation of the N-nitrosamide in situ at low temperature and use of the solution as an initiator also gave polymer, while a blank containing all of the reaction components except N-(4-nitrophenyl)acetamide failed.

In a second experiment, the N-nitrosamide of 4-acetamidobiphenyl was generated as usual at 0 °C. Before allowing the reaction mixture to warm, a large excess of toluene was added.²⁷ After reaction, the two major isolated products were biphenyl and bibenzyl, with only traces of 4-acetoxybiphenyl. Such a result could be explained by the generation of biphenyl radicals, followed by benzylic hydrogen abstraction from the toluene to form biphenyl and benzyl radicals. The benzyl radicals would combine to form bibenzyl. A cationic reactive intermediate would be expected to generate mainly benzyltoluenes, which were not observed. This reaction may be a useful alternative to reduction of diazonium salts for the deamination of aromatic primary amines.²⁸

In summary, the method for conversion of N-aromatic secondary amides to O-aromatic esters presented here is inexpensive and convenient, carried out in low environmental impact solvents, using minimal equipment, and not requiring isolation of intermediate N-nitrosamides or diazonium salts. We have scaled-up the reaction without difficulty to effect multigram conversions. Yields are uniformly high (although conditions were not optimized), and the reaction can be carried out with a variety of functional groups present in the substrate. The method can be simply modified to be carried out directly on aromatic amines and in some cases can be extended to be carried out on aromatic nitro compounds. Phenols can easily be generated from the resulting esters, and workup procedures could be easily developed to obtain the phenol without isolating the ester. While the results presented here are suggestive of radical intermediates, further studies will needed to elucidate the exact nature of the mechanisms of these reactions.

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(28) Kornblum, N. Org. React. 1944, 2, 262.

⁽²⁶⁾ *N-p*-Nitrophenylacetamide (0.138 g, 0.765 mmol) was treated as described for the synthesis of esters, 15 except that the reaction was quenched before warming by pouring into ice/water and kept at 0 °C with stirring until a solid formed. The solid was collected quickly by suction filtration to give 0.135 g of the corresponding crude N-nitrosamide. This Nnitrosamide was added to 30 mL of distilled methyl methacrylate in a large test tube. The tube was capped, covered with foil, and allowed to stand at room temperature for 48 h. The resulting viscous sample was dissolved in chloroform and added dropwise to methanol to precipitate polymer. The polymer was purified by reprecipitating twice from chloroform into methanol, collection by suction filtration, and air-drying to a constant weight of 1.251 g. In a separate set of experiments, N-p-nitrophenylacetamide (0.093 g, 0.52 mmol) was dissolved in 2 mL of acetic anhydride and 1 mL of acetic acid, chilled in ice bath for 30 min, and 0.071 g NaNO₂ (1.3 mmol) and allowed to remain at 0 °C for 2 h. A blank was prepared using the same amounts of acetic anhydride, acetic acid, and NaNO2 under identical conditions. Each solution was added separately to test tubes containing 30 mL of methyl methacrylate (which had been filtered through neutral alumina to remove inhibitors and was shown not to contain polymer) each. Reaction and purification was carried out as above to give 0.227 g of polymer from the initiator containing the acetamide. Polymer was not obtained from the blank.

^{(27) 4-}Acetamidobiphenyl (0.217 g, 1.02 mmol) was placed in a 125mL Erlenmeyer flask and dissolved in 10 mL of acetic anhydride and 5 mL of acetic acid. The flask was cooled to 0 °C in an ice bath. While the mixture was being slowly stirred magnetically, solid sodium nitrite (0.142 g, 2.05 mmol) was added to this mixture, and the vessel was lightly capped. Evolution of a brown gas occurred, and the solution turned lime green. The flask was kept in the ice bath for 2 h. Toluene (70 mL) was added, and the flask was kept in the ice bath for 10 min. The flask was allowed to warm to room temperature and was kept there for 24 h. Water (50 mL) was added, and the toluene layer was separated, washed 3× with sat. NaHCO₃, once with water, and dried over MgSO4. Filtration and removal of solvent under reduced pressure gave 0.181 g of product (mp 60–83 °C). Semiquantitative GC-MS¹⁶ showed that the sample contained 64% bibenzyl, 34% biphenyl, and 1% 4-biphenylacetate.