A New, Regioselective, Tandem Amidation Reaction of Electron-Rich Arenes

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Introduction

Amides can be prepared by several well-established procedures including acylation of amines, hydration of nitriles, and rearrangement reactions such as the Schmidt and Beckmann procedures. These methods were reviewed by Beckwith.[1]

A direct arylamidation procedure has been reported, in which an arene can condense with a hydroxamic acid,[2] but this has limited scope.[3] Apart from a recent report by Nahmed and Jenner, who carried out reductive amidation of nitroarenes,[4] there appear to be few, if any, other literature methods for obtaining in a single step *N*-arylamides from aromatic compounds which do not possess an amino function. Three steps are often required: typically nitration of the arene, followed by reduction of the introduced nitro functionality to form an amine, and finally, acylation of the amine to give the amide.

We now report a convenient one-step tandem amidation reaction which can be conducted on electron-rich arenes, regioselectively, under mild conditions. The reaction can also be carried out as a two-step sequence in one pot.[5]

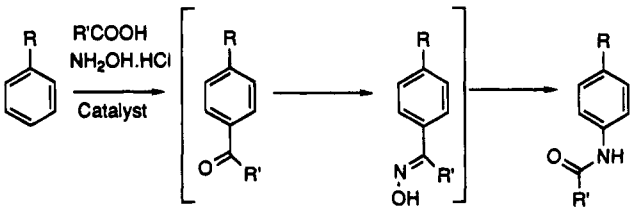
Results and Discussion

The tandem reaction starts with *para*-selective *C*-acylation of an electron-rich aryl nucleus in the presence of a Lewis acid. This is followed by oxime formation and Beckmann rearrangement *in situ*. The reaction is carried out by stirring at moderate temperature, a mixture of the Lewis acid, the aromatic starting material, the acylating agent (a carboxylic acid or anhydride), and a salt of hydroxylamine (see Scheme 1).

A catalyst of sufficient flexibility is required to effect efficient and regioselective *C*-acylation of the aryl species and then to allow oximation to proceed to give the *anti*-oxime with respect to the aryl group. This stereochemistry is required such that the arene would be the moiety to migrate in the next step.[6] To complete the reaction, Beckmann rearrangement must further proceed under the influence of the catalyst to afford the desired *N*-arylamide.

It is noteworthy that the sequence of reactions discussed above and depicted in Scheme 1 recently was developed into a commercial process for the manufacture of the analgesic *N*-(4-hydroxyphenyl)acetamide.[7] In that

Scheme 1



patented process, however,[8,9] the three reactions were each carried out under different conditions, which necessitated isolation before further elaboration. It would appear therefore, that if all steps could be conducted in tandem, the process would become more attractive.

Several potentially useful catalysts or reagents were investigated for this purpose,[10] including polyphosphoric acid (PPA),[11,12] P_2O_5, H_2SO_4, ion exchange resins in the sulfonic acid[13] and phosphonic acid forms,[14] zeolites, and P_2O_5 in $MeSO_3H$. This last mentioned reagent has been developed by Eaton's group as a convenient alternative to PPA.[15] Some of the catalysts or reagents were employed in the presence of solvents to azeotropically distill the water formed in the reaction, but this approach failed. The reaction was performed successfully with PPA and with P_2O_5 in $MeSO_3H$. PPA was clearly the more effective, probably owing to the combination of its solvent properties, mild acid characteristics, and versatility in facilitating Friedel–Crafts reactions, Fries rearrangements, and Beckmann rearrangements.[11,12]

Table 1 presents examples which demonstrate the scope of the reaction when conducted in PPA. All of the reactions proceeded at temperatures between 70 and 115 °C, and with two exceptions could be worked up within 4 h. Acetamidations of a range of monosubstituted benzene derivatives including PhOMe, PhOEt, PhEt, PhOH, and PhOAc were successful. With PhOH as the starting arene, excess acylating agent was used so that the product would be predominantly the readily crystallizable *N*-(4-acetoxyphenyl)acetamide, rather than a mixture of this compound and *N*-(4-hydroxyphenyl)-acetamide. In order to obtain *N*-(4-hydroxyphenyl)-acetamide directly from either PhOH or PhOAc, at the completion of the amidation the diluted reaction mixtures were allowed to stand at room temperature for a few hours or were warmed for a lesser period to allow hydrolysis of the ester to occur. The product could then be collected by extraction into EtOAc.

Entries 7 and 8 in Table 1 show that the aromatic ring in the starting material may be disubstituted, and entry 4 indicates that, if desired, two phenyl groups in the one molecule may be amidated simultaneously. The reaction also proceeded with polyaromatic compounds such as 1- and 2-methoxynaphthalenes (entries 10 and 11) as starting arenes, the latter giving rise to regioselective amidation at the 6-position. Entry 9 showed that the reaction also worked with *C*-acylating agents which

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Table 1. Example Amidation Reactions and Conditions

entry no.	starting arene[a]	reagent (equiv)	T (°C)	time (h)	product	yield (%)
1	PhOMe	A:[b] 2.0 B: 1.1	70	2	*N*-(4-methoxyphenyl)acetamide	89[c]
2	PhOAc	A: 2.0 B: 1.1	80	1	*N*-(4-acetoxyphenyl)acetamide	63[c]
3	PhEt	A: 2.0 B: 1.1	110	14	*N*-(4-ethylphenyl)acetamide	80[d]
4	$(PhOCH_2CH_2)_2O$	A: 2.5 B: 2.2	80	3	*N,N'*-[oxybis[2,1-(ethanediyloxy)-4,1-phenylene]]bisacetamide	95[c]
5	PhOH	C: 2.0 B: 1.1	80	3	*N*-(4-acetoxyphenyl)acetamide	71[c]
6	PhOEt	A: 2.5 B: 1.1	80	2.5	*N*-(4-ethoxyphenyl)acetamide	75[c]
7	1,2-dimethoxybenzene	A: 1.1 B: 1.1	70	8	*N*-(3,4-dimethoxyphenyl)acetamide	92[c]
8	2-methoxyphenol	A: 2.5 B: 1.1	80	2.5	*N*-(4-acetoxy-3-methoxyphenyl)acetamide (four parts) *N*-(3-acetoxy-4-methoxyphenyl)acetamide (one part)	67[c]
9	PhOH	D: 2.0 B: 1.1	80	4	4-[(1-oxobutyl)amino]phenylbutanoate	45[c]
10	1-methoxynaphthalene	A: 2.0 B: 1.1	115	2	*N*-(4-methoxy-1-naphthyl)acetamide	59[d]
11	2-methoxynaphthalene	A: 2.0 B: 1.5	80	3	*N*-(6-methoxy-2-naphthyl)acetamide	72[d]

[a] All reactions used 10 g of PPA per g of starting material. [b] A = HOAc; B = $NH_2OH.HCl$; C = Ac_2O; *n*-PrCOOH. [c] Isolated yield. [d] Conversion as determined by GC.

contained more than two carbons in the chain. The reaction failed, however, when aniline was used as starting arene, the major product being acetanilide. Alternative acylating agents which have two potentially reactive functional groups, such as lactic acid, glycine, and oxalic acid, gave products other than amides.

The pathway of the tandem reaction was studied by isolation of the intermediates and byproducts which were obtained from a range of reactions in which PhOH was the starting arene (entry 5). Along with *N*-(4-acetoxyphenyl)acetamide (**11**), which was isolated in 71% yield, and the next most abundant product, *N*-(4-hydroxyphenyl)acetamide (**10**), the occurrence of all of the minor products identified could be rationalized in terms of a reaction sequence involving ketone formation, followed by oximation and Beckmann rearrangement, as illustrated by Scheme 2. Since Fries rearrangements have been reported to occur in PPA under comparable thermal conditions,[12] some of the steps depicted in Scheme 2 may be reversible, although for simplicity, they have not been shown as such. The minor products formed from the reaction of PhOH (**1**) included PhOAc (**2**), 2'-hydroxyacetophenone (**3**), 4'-hydroxyacetophenone (**4**), 4'-acetoxyacetophenone (**5**), *N*-(2-hydroxyphenyl)acetamide (**6**), 2-methylbenzoxazole (**7**), *N*-(2-acetoxyphenyl)acetamide (**8**), and 4'-hydroxy-*N*-methylbenzamide (**9**). Although the proportion of byproducts varied with the conditions, oximes were difficult to detect in reaction mixtures with PPA. Ketones **4** and **5** could be intermediates resulting from *para*-selective *C*-acylation of the starting PhOH (**1**), and PhOAc (**2**) could be formed by a retro-Fries rearrangement of 2'- or 4'-hydroxyacetophenone (**3** or **4**) and/or by esterification. 2'-Hydroxyacetophenone (**3**), *N*-(2-hydroxyphenyl)acetamide (**6**), 2-methylbenzoxazole (**7**), and *N*-(2-acetoxyphenyl)acetamide (**8**) could all be produced as a result of initial *C*-acylation of PhOH (**1**) at the *ortho*-position instead of at the more favored *para*-position[16] or, to a lesser extent, by Fries rearrangement of PhOAc.[12] Finally, 4'-hydroxy-*N*-methylbenzamide (**9**) could arise from Beckmann rearrangement of the minor *syn*-oxime of 4'-hydroxyacetophenone.

To further explore the reaction pathway, an experiment was carried out by using an alkyl aryl ketone as starting material, thereby obviating the need for a *C*-acylation step. Hydroxylamine sulfate was added to a stirred mixture of ketone **4** in PPA and the temperature held at 80 °C for 2.5 h. After this time, the ketone had been converted to *N*-arylacetamide **10** (83%) and *N*-methylbenzamide (**9**) (15%). Included among the trace residual components were the starting ketone **4**, PhOAc (**2**), ketone **3**, and the oxime of 4'-hydroxyacetophenone. The product distribution indicated that oximation and Beckmann rearrangement of the ketone proceeded readily in the presence of PPA. On the other hand, less than 2% of this could be accounted for in terms of the potentially competing retro-Fries rearrangement. The trace amounts of oximes detectable during the reaction were consistent with the earlier findings of Pearson and Stone[17] that Beckmann rearrangements of acetophenone oximes proceed rapidly in PPA. That work[17] precluded any need here to subject the oxime of 4'-hydroxyacetophenone to Beckmann rearrangement in the presence of PPA.

Ganboa and Palomo[18] have previously developed a one-pot method for directly converting ketones to amides by using hydroxylamine hydrochloride and a catalytic amount of triflic acid in formic acid. Yields ranged from 60 to 96% for the examples reported. In the present work, the conversion of ketone **4** to *N*-arylacetamide **10** using PPA as both reagent and solvent suggests that this methodology represents a useful and convenient alternative to the procedure of Ganboa and Palomo and has the advantage of avoiding any requirement for strong acid.

The tandem process was next performed stepwise in a single pot, with regular monitoring of the progress of each step. In this series of experiments PhOMe (1 mol) was selected as starting arene and HOAc (1.3 mol) as acylating agent. A mixture of the two compounds was heated at 80 °C in PPA, and samples were withdrawn for analysis at intervals of 5 min. After 15 min, the conversion of PhOMe to 4'-methoxyacetophenone was 95%. This

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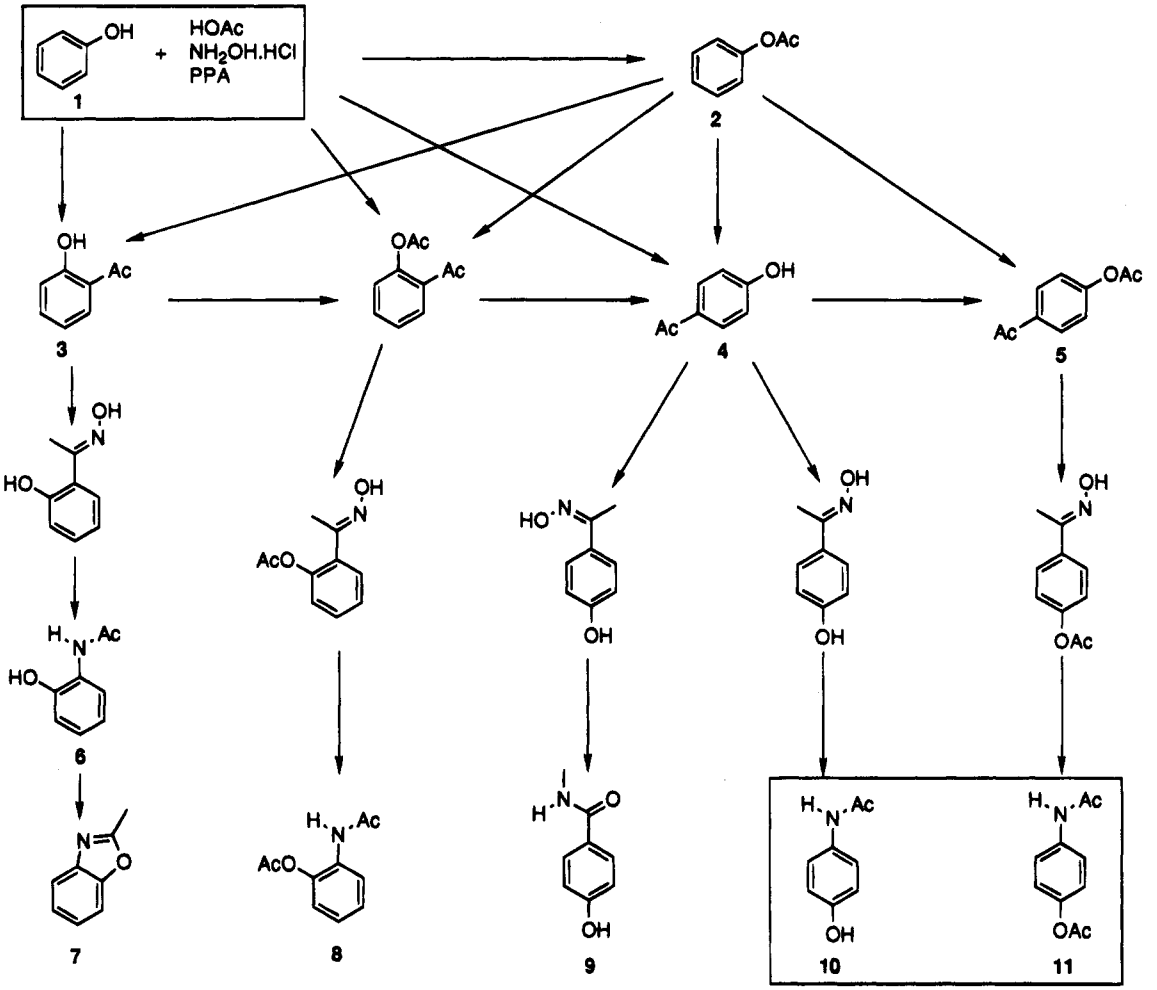
Scheme 2



reaction was repeated without sampling, and after 15 min, hydroxylamine sulfate (1 equiv relative to PhOMe) was added in one batch. The heating was continued, and aliquots were withdrawn for analysis at intervals of 1 min over a 10-min period. After 5 min, the conversion to *N*-(4-methoxyphenyl)acetamide was 95%, and after 8 min it was quantitative. These results showed that for this reaction sequence, the combined oximation and Beckmann rearrangement steps had proceeded more rapidly than the *C*-acylation, which therefore was rate-determining. Finally, in an experiment where no samples were withdrawn during the reaction sequence, HOAc and PhOMe were heated for 15 min at 80 °C in PPA. The hydroxylamine salt was added and the mixture heated for a further 5 min and worked up to give *N*-(4-methoxyphenyl)acetamide in 85% yield.

The nature of the intermediates and byproducts identified in the tandem reaction and the findings that the reaction can be completed when the intermediates are used as starting materials indicate that the tandem reaction proceeds essentially by the pathway shown in Scheme 1. The product distribution of the tandem reaction thus will be determined mainly by the *C*-acylation step, which appears to be rate-limiting and can be temperature dependent, and to a lesser extent by the ratio of the transient *anti*- and *syn*-oximes produced. Higher temperatures tend to give rise to *ortho*-attack in the *C*-acylation step or can lead to rearrangements of *para*-substituted derivatives, so moderate temperatures should be used. Since the oximation and Beckmann rearrangements usually proceed readily under the conditions, the efficiency of the *C*-acylation step can have a critical influence on the final yield of amide.

This work has shown that the tandem reaction can be operated as a one-step reaction, wherein the arene, hydroxylamine salt, and the acylating agent are introduced simultaneously, or as a two-step sequence in which the ketone is allowed to accumulate before being converted to the amide. If the latter procedure is followed, an excess of the arene should not be used, so as to avoid PPA-catalyzed coupling reactions, which can produce 1,1-diarylalkanols and 1,1,1-triarylalkanes from intermediate alkyl aryl ketones.

To our knowledge the tandem reaction is the first report of *C*-acylation, oximation, and Beckmann rearrangement being conducted sequentially in one pot. In view of its simplicity and the mild and uniform thermal conditions under which the individual steps can proceed, the reaction has already been found to be a versatile and convenient route to *N*-arylamides in the laboratory and could find industrial applications.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR were recorded at 200 and 50 MHz, respectively, and chemical shifts are in ppm relative to TMS. EIMS were obtained at 70 eV, scanning from *m/z* 450 to 40 each second, with sample introduction by GC. The GC was performed with a QS BP5 capillary column 25 m in length. Helium was used as carrier gas at a flow rate of 2.0 mL/min. The oven was maintained at 50 °C for 2 min and then

programmed at 10 °C/min to 280 °C and held at this final temperature for 10 min. Mp were recorded using a Kofler block and were uncorrected. Physical data for products listed in Table 1 or synthesized as reference compounds agreed with literature values.

Reference Compounds. With the exception of $(PhOCH_2CH_2)_2O$, which was prepared by a literature method,[19] the starting arenes in Table 1, 2-methylbenzoxazole, 4′-hydroxyacetophenone, 2′-hydroxyacetophenone, and *N*-(4-hydroxyphenyl)acetamide, were all purchased. *N*-(2-Hydroxyphenyl)acetamide was prepared by acetylation of 2-aminophenol. The oximes of 2′- and 4′-hydroxyacetophenone were prepared by the method of Ranganathan et al.[20] 4-Hydroxy-*N*-methylbenzamide was synthesized by stirring 4-hydroxybenzoyl chloride[21] with aqueous methylamine at room temperature for 3 h. 4′-Acetoxyacetophenone, *N*-(2-acetoxyphenyl)acetamide, 4-acetoxy-*N*-methylbenzamide, and *N*-(4-acetoxyphenyl)acetamide were all prepared from their phenolic precursors, with acetyl chloride.

Example Preparations. The conditions used have been summarized in Table 1, and for purposes of clarification, full directions for two example preparations are presented below.

N-(4-Methoxyphenyl)acetamide. A mixture of PhOMe (3.0 g, 0.03 mol), glacial HOAc (3.3 g, 0.06 mol), and $NH_2OH.HCl$ (2.1 g, 0.03 mol) was heated in 30 g of PPA (116% H_3PO_4) with stirring at 80 °C for 2 h and then allowed to cool over 30 min. Cold water (110 mL) was added. *N*-(4-Methoxyphenyl)acetamide (4.4 g) deposited as an off-white crystalline solid, mp 126–7 °C (*cf.* lit.[22] mp 130–2 °C), in 96% purity and was collected by filtration. EIMS [*m/z* (rel int)]: 165 (M^+, 44), 123 (66), 108 (100), 80 (18), 53 (11), 52 (18), 43 (42). ^{13}C NMR (d_6-Me_2CO, 50 MHz): δ 168.8, 156.7, 133.6, 121.7, 114.6, 55.7, 24.1.

N-(4-Ethoxyphenyl)acetamide (Phenacetin). A mixture of PhOEt (3.0 g, 0.02 mol), glacial HOAc (3.0 g, 0.05 mol), and $NH_2OH.HCl$ (1.9 g, 0.03 mol) was added to PPA (30 g; 112–116% H_3PO_4) with stirring at 80 °C. After 2.5 h the mixture was cooled for 15 min, ice–water (100 mL) was added, and within a few min the product began to crystallize. It was filtered off and recrystallized from water to give *N*-(4-ethoxyphenyl)acetamide as colorless flakes (2.7 g; 61% yield after recrystallization), mp 132–133 °C (*cf.* lit[22] mp 134–5 °C). EtOAc extraction of aqueous residues afforded additional material, making the overall yield 75%. EIMS [*m/z* (rel int)]: 179 (M^+, 72), 137 (47), 109 (93), 108 (100), 81 (17), 80 (19), 53 (16), 52 (13), 43 (41). ^{13}C NMR (d_6-Me_2CO, 50 MHz): δ 168.5, 156.4, 133.3, 121.6, 115.2, 64.1, 24.1, 15.2.

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