Formation of 3-Aryl-5-nitroisocoumarins from 5-Nitroisocoumarins and Aromatic Acyl Chlorides under Friedel−Crafts Conditions

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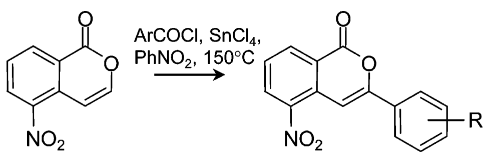

Treatment of 5-nitroisocoumarin with aromatic acyl chlorides under Friedel−Crafts conditions gives 3-aryl-5-nitroisocoumarins, rather than the expected 4-acyl-5-nitroisocoumarins. This procedure was optimized for reaction temperature (150 °C), solvent (nitrobenzene), and Lewis acid ($SnCl_4$). Reaction of 5-nitroisocoumarin with [^{13}C]-carbonyl benzoyl chloride under the optimum conditions gave 5-nitro-3-phenylisocoumarin in which the ^{13}C is located at the 3-C of the heterocycle, indicating that the benzoyl carbon framework is incorporated intact.

As part of our continuing research on the design and synthesis of heterocyclic compounds as enzyme inhibitors and potential drugs,[1−3] we required a series of 4-acyl-5-nitroisocoumarins, which we planned to synthesize by Friedel−Crafts acylation of 5-nitroisocoumarin **1** (Scheme 1). We have previously described[4,5] efficient synthetic routes to 3-substituted 5-nitroisocoumarins and isoquinolin-1-ones, but none of these could be readily adapted to synthesis of the new targets. The carbocyclic ring of **1** is deactivated by the presence of the nitro group, and we rationalized that the 4-position should be the most nucleophilic site of the heterocycle because this is formally an enol ester. However, this position may be subject to some steric obstruction by the *peri* nitro group. There is one brief previous report of acetylation of 5-unsubstituted 3-arylisocoumarins at this position.[6] The few other 4-acylisocoumarins that

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TABLE 1. Outcomes of Reactions of Acyl Chlorides with 1 under Various Friedel−Crafts Conditions[a]

entry	acyl chloride	Lewis acid	solvent	temp (°C)	product	yield (%)
A[b]	PhCOCl	$SnCl_4$	$PhNO_2$	100	**3a**	21
B	PhCOCl	$SnCl_4$	$PhNO_2$	150	**3a**	42
C	PhCOCl	$SnCl_4$	$PhNO_2$	180	**3a**	27
D	PhCOCl	$AlCl_3$	$PhNO_2$	150	**3a**	38
E	PhCOCl	$Sn(OTf)_2$	$PhNO_2$	150	**3a**	19
F	PhCOCl	$ZnCl_2$	$PhNO_2$	150	SM[c]	0
G	PhCOCl	$Zn(OTf)_2$	$PhNO_2$	150	SM[c]	0
H	PhCOCl	$SnCl_4$	$MeNO_2$	100	**3a**	17
I	PhCOCl	$SnCl_4$	C_2HCl_5	150	**3a**	13
J	$Ph^{13}COCl$	$SnCl_4$	$PhNO_2$	150	**3g**	39
K	$4\text{-}O_2NC_6H_4COCl$	$SnCl_4$	$PhNO_2$	150	**3b**	12
L	$4\text{-}F_3CC_6H_4COCl$	$SnCl_4$	$PhNO_2$	150	**3d**	11
M	$4\text{-}EtOC_6H_4COCl$	$SnCl_4$	$PhNO_2$	150	SM[c]	0
N	$4\text{-}ClC_6H_4COCl$	$SnCl_4$	$PhNO_2$	150	**3c**	29
O	$4\text{-}MeC_6H_4COCl$	$SnCl_4$	$PhNO_2$	150	**3e**	23
P	$3\text{-}MeC_6H_4COCl$	$SnCl_4$	$PhNO_2$	150	**3f**	21
Q	$4\text{-}FC_6H_4CH_2COCl$	$SnCl_4$	$PhNO_2$	150	[d]	0
R	$Me(CH_2)_4COCl$	$SnCl_4$	$PhNO_2$	150	[d]	0

[a] Reaction time 3 days. [b] Reaction time 7 days. [c] Only **1** recovered. [d] Mixture of unidentifiable decomposition products.

have been prepared were synthesized by Stille coupling of 4-iodo-3-phenylisocoumarin with 1-ethoxy-1-tributylstannylethene, followed by hydrolysis of the enol ether;[7] by reaction of isocoumarin-4-carbonyl chlorides with malonate-derived anions, followed by hydrolysis and decarboxylation;[8] and by Friedel−Crafts reaction in the reverse sense, i.e., reaction of 3-methylisocoumarin-4-carbonyl chloride with bromobenzene and $AlCl_3$.[9] We therefore instigated a short study on the Friedel−Crafts acylation of 5-nitroisocoumarin **1** (Scheme 1) with aromatic and aliphatic acyl chlorides.

5-Nitroisocoumarin **1** was prepared by condensation of methyl 2-methyl-3-nitrobenzoate with dimethylformamide dimethyl acetal, followed by treatment with damp silica, as previously reported by us.[3] Treatment with benzoyl chloride in nitrobenzene, using tin(IV) chloride as the Lewis acid, proceeded very slowly at 100 °C (Table 1, entry A). TLC analysis indicated the formation of only one product, with no long-lived intermediates being evident. ^{1}H NMR analysis of the product isolated after 7 days showed the presence of a phenyl group and the expected signals for the 6-H, 7-H, and 8-H of the isocoumarin. However, the IR spectrum showed only one carbonyl absorption at 1739 cm^{-1}, and the ^{13}C NMR spectrum confirmed that the product was not the simple acylated isocoumarin **2**, as only one carbonyl carbon was present, at δ 160.3, corresponding to an enol ester. Comparison of the NMR and IR spectra and mp with an authentic sample, together with coelution on TLC, confirmed that it was 5-nitro-3-phenylisocoumarin **3a**. We have previously synthesized this compound by four other independent routes,

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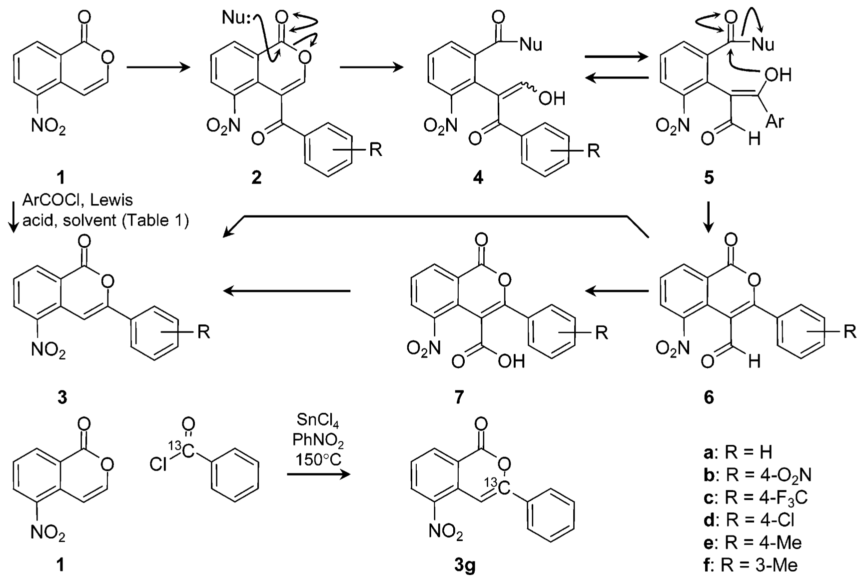
SCHEME 1. Formation of 3-Aryl-5-nitroisocoumarins 3 from 1 and Aroyl Chlorides under Friedel−Crafts Conditions



Hg^{2+}-catalyzed cyclization of methyl 3-nitro-2-phenylethynylbenzoate,[4] from 2-iodo-3-nitrobenzoic acid and phenylethyne by tandem Castro−Stevens reaction/6-*endo*-dig cyclization,[4] Hurtley coupling/acyl cleavage/cyclization of 2-bromo-3-nitrobenzoic acid with 1,3-diphenylpropane-1,3-dione,[10] and reductive dehalogenation of 4-iodo-5-nitro-3-phenylisocoumarin.[4]

Seeking to investigate this unexpected outcome, a series of experiments were designed to test the effects of temperature, nature of the Lewis acid, nature of the solvent, and nature of the acyl chloride on the course of the reaction. Entries A, B, and C test the effect of temperature (100 °C, 150 °C, and 180 °C, respectively). Increasing the temperature to 150 °C significantly increased the rate of reaction, and a 42% yield of **3a** was obtained after 3 days; increasing the reaction time at this temperature did not increase the yield. By contrast, the yield of **3a** was lower at 180 °C, probably owing to thermal degradation of substrates, intermediates, or product. Thus the optimum temperature was set at 150 °C for most of the remaining experiments.

Entries B, D, E, F, and G compare the effects of different Lewis acids, while holding other parameters constant. Whereas the strong Lewis acid $AlCl_3$ gave results similar to $SnCl_4$ (entry D), a lower yield was obtained with tin(II) triflate (entry E). No reaction was observed with the weaker Lewis acids zinc chloride and zinc triflate (entries F and G, respectively), even at prolonged reaction times. These data give a first insight into the mechanism by which **3a** is formed, in that strong Lewis acidity and forcing conditions are required, suggesting that the initial step may be the desired Friedel−Crafts acylation of the 4-position of **1**.

The effect of the nature of the solvent was tested in entries A, B, H, and I. Replacement of nitrobenzene with nitromethane had little effect on the reaction; these comparative studies were carried out at 100 °C (entry A vs entry H), owing to the lower boiling point of nitromethane. The nonoxidizing solvent pentachloroethane gave a lower but significant yield of **3a** at 150 °C (entry I), when compared with nitrobenzene at the same temperature (entry B).

The reaction of [^{13}C]-carbonyl benzoyl chloride with **1** under the optimum conditions ($SnCl_4$, $PhNO_2$, 150 °C) gave important information on the course of the reaction. Two reaction paths were conceivable: one in which the phenyl becomes detached from the carbonyl of the benzoyl chloride and adds to 3-C of the isocoumarin and one in which 3-C of the product 3-aryl-isocoumarin is derived from the carbonyl of the benzoyl chloride and the 3-carbon atom of the starting isocoumarin **1** is lost. In the former route, the ^{13}C would not be incorporated into the product, whereas the latter route would give material with the ^{13}C located at 3-C. Entry J (Table 1) gave material which was shown by low-resolution MS to contain one ^{13}C atom. Its location within the product **3g** was determined by NMR. Firstly, the ^{1}H NMR spectrum of **3g** revealed the signal for the 4-H as a slightly broadened doublet with $J = 5.5$ Hz. The corresponding signal for the unlabeled **3a** is a singlet which is broadened by long-range extended-**W** coupling to 8-H.[4] This coupling constant is consistent with both $^{2}J_{C-H}$ and $^{3}J_{C-H}$, which shows that the ^{13}C could be located at position 3, 4a, 5, or 8a of the isocoumarin or position 1′ of the phenyl; it could not be at position 4 of the isocoumarin, as the corresponding $^{1}J_{C-H}$ would be >100 Hz for this arrangement. The precise location of the ^{13}C was confirmed by the ^{13}C NMR spectrum. Firstly, the intensity of the peak at δ 156.8, which had previously been confirmed by HMQC and HMBC assignment as being due to the 3-C in the unlabeled material **3a**, was greatly enhanced in the spectrum of **3g**. Secondly, one-bond couplings were observed to the adjacent carbons, with $^{1}J_{C-C} = 75$ Hz between 3-C and 4-C and $^{1}J_{C-C} = 68$ Hz between 3-C and 1′-C of the phenyl (Figure 1). These couplings were manifest both as doublets for the 4-C and 1′-C signals and as satellite doublets to the 3-C signal. Longer-range couplings, with 1 Hz < J < 5 Hz, were observed between the 3-C and 1-C, 5-C, 8a-C, 2′,6′-C_2, and 3′,5′-C_2. As expected, the three-bond $^{3}J_{C-C}$ couplings (3.8−5 Hz) were larger than the two-bond $^{2}J_{C-C}$ coupling constants (0−3.1 Hz), with the two-bond coupling to 4a-C being ca. 0 Hz. The *trans*-like $^{3}J_{C-C}$ coupling to 5-C (5 Hz) was greater than the analogous *cis*-like $^{3}J_{C-C}$ coupling to 8a-C (3.8 Hz) (Figure 1). These observations confirm that the ^{13}C derived from the Ph^{13}COCl

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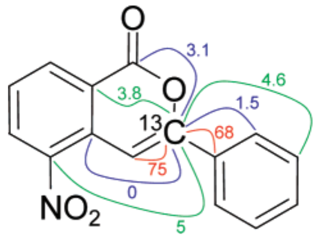

FIGURE 1. Structure of ^{13}C-labeled product **3g**, showing $^{1}J_{C-C}$ NMR couplings (red), $^{2}J_{C-C}$ couplings (blue), and $^{3}J_{C-C}$ couplings (green).

is located at the 3-position of the product **3a**, thus the benzoyl carbon framework is incorporated intact.

The incorporation of the intact benzoyl group into the product 5-nitro-3-phenylisocoumarin **3g**, together with the need for a strong Lewis acid, allows a mechanism to be postulated (Scheme 1). It is proposed that the first step is the expected Friedel−Crafts acylation of position-4, generating **2**. 5-Nitroisocoumarins are readily ring-opened by nucleophiles, and attack of chloride or, possibly, triflate at the carbonyl of **2** would afford enol **4**. This is in tautomeric equilibrium with enol **5**. Cyclization then affords the 4-formyl-3-phenylisocoumarin **6**. Transformation of **6** into the observed product **3a** then requires either a direct decarbonylation of the aldehyde or oxidation to the carboxylic acid **7** and decarboxylation. Decarboxylations of isocoumarin-4-carboxylic acids have been reported to occur under forcing conditions and have been used synthetically to access substituted and fused isocoumarins from homophthalic acid and its esters.[11−13] In contrast, Kim et al.[8] noted that 6,8-dihydroxy-4-formyl-3-methylisocoumarin, prepared by analogous isomerization of 3-acetyl-6,8-dihydroxyisocoumarin in hot aqueous formic acid, is stable under the conditions of this rearrangement. These reports suggest that it is likely that direct decarbonylation is unlikely but that oxidation to a carboxylic acid is required before loss of the one-carbon unit, a proposal which is consistent with the lower yield obtained when a nonoxidizing solvent, pentachloroethane, was used (Table 1, entry I vs entry B). The rate-limiting step in the overall process appears to be the initial Friedel−Crafts acylation, with subsequent rapid rearrangement, oxidation, and decarboxylation, because no intermediates were observed by TLC or by NMR spectroscopy on crude reaction mixtures.

The generality of this new reaction was explored by the use of a range of benzoyl chlorides, carrying electron-withdrawing, electron-neutral, and electron-donating substituents. Reaction of 4-nitrobenzoyl chloride (with a −M substituent) and of 4-trifluoromethylbenzoyl chloride (carrying a −I group) with **1** under the standard conditions gave the 3-aryl-5-nitroisocoumarins **3b** and **3c**, respectively, albeit in lower yields (entries K and L). The reaction did not proceed with the electron-rich 4-ethoxybenzoyl chloride (entry M), but satisfactory yields of **3d−f** were obtained from the corresponding chloro- and methylbenzoyl chlorides carrying substituents with no great electronic effect (entries N, O, and P). Attempts to extend the reaction to aliphatic acyl chlorides failed, in that 4-fluorophenylacetyl chloride and hexanoyl chloride only gave mixtures of decomposition products (Entries Q and R, respectively).

In this Note, we have reported a new reaction of an isocoumarin under forcing Friedel−Crafts conditions to give 3-arylisocoumarins. The new reaction has been optimized for reaction temperature (150 °C), solvent (nitrobenzene), and Lewis acid ($SnCl_4$). The scope of this reaction has been shown to be limited to aroyl chlorides carrying electron-withdrawing and electron-neutral substituents. Reaction of 5-nitroisocoumarin **1** with [^{13}C]-carbonyl benzoyl chloride under the optimum conditions gave 5-nitro-3-phenylisocoumarin in which the ^{13}C is located at the 3-C of the heterocycle, indicating that the benzoyl carbon framework is incorporated intact. Although the yields are modest, limiting its synthetic utility, this tandem acylation/rearrangement/decarboxylation demonstrates that simple Friedel−Crafts acylation of isocoumarins at the 4-position is likely not to be feasible.

Experimental Section

5-Nitro-3-phenylisocoumarin (3a) (Table 1, entry B). $SnCl_4$ (148.5 mg, 0.57 mmol) was added to 5-nitroisocoumarin **1** (100 mg, 0.52 mmol) in $PhNO_2$ (1.0 mL). After 30 min, PhCOCl (140.5 mg, 1.04 mmol) was added, and the mixture was stirred at 150 °C under Ar for 3 days. The cooled mixture was quenched with ice−water (2.0 mL) and extracted with EtOAc (2 × 20 mL). The combined extracts were washed (NaOH, brine) and dried ($MgSO_4$). Evaporation under reduced pressure and chromatography (hexane/EtOAc 15:1) gave **3a** (40 mg, 42%) as a pale yellow solid: mp 145−146 °C (lit.[4] mp 142−143 °C); IR ν_{max} 1739, 1626, 1525, 1341 cm^{-1}; ^{1}H NMR δ 7.48−7.51 (3 H, m), 7.59 (1 H, t, J = 7.8 Hz), 7.85 (1 H, br s), 7.92 (2 H, m), 8.48 (1 H, dd, J = 8.2, 1.2 Hz), 8.61 (1 H, ddd, J = 8.2, 1.2, 0.8 Hz); ^{13}C NMR δ 96.3, 122.3, 125.9, 127.1, 129.0, 131.1, 131.2, 131.6, 131.9, 135.8, 144.2, 156.8, 160.3.

5-Nitro-3-(4-nitrophenyl)isocoumarin (3b) (Table 1, entry K). Compound **1** was treated with 4-nitrobenzoyl chloride, as for entry B, to give **3b** (12%) as a yellow solid: mp 211−214 °C; IR ν_{max} 1724, 1626, 1537, 1344 cm^{-1}; ^{1}H NMR δ 7.70 (1 H, d, J = 8.0 Hz), 8.03 (1 H, br s), 8.11 (2 H, d, J = 7.2 Hz), 8.36 (2 H, d, J = 7.2 Hz), 8.54 (1 H, dd, J = 8.3, 1.1 Hz), 8.67 (1 H, br d, J = 8.2 Hz); ^{13}C NMR δ 99.2, 122.8, 124.3, 126.7, 128.5, 131.0, 131.2, 131.8, 135.9, 137.0, 149.0, 154.0, 159.0; MS m/z 335.0288 (M + Na) ($C_{15}H_8NaN_2O_6$ requires 335.0280). Anal. Calcd for $C_{15}H_8N_2O_6$: C, 57.70; H, 2.58; N, 8.97. Found: C, 57.64; H, 2.51; N, 8.79.

5-Nitro-3-(4-trifluoromethylphenyl)isocoumarin (3c) (Table 1, entry L). Compound **1** was treated with 4-trifluoromethylbenzoyl chloride, as for entry B, to give **3c** (11%) as a pale yellow solid: mp 163−164 °C (lit.[10] mp 163−164 °C); ^{1}H NMR δ 7.67 (1 H, t, J = 8.2 Hz), 7.75 (2 H, d, J = 8.2 Hz), 7.93 (1 H, d, J = 0.8 Hz), 8.03 (2 H, d, J = 8.2 Hz), 8.51 (1 H, dd, J = 8.2, 1.6 Hz), 8.57 (1 H, ddd, J = 8.2, 1.6, 0.8 Hz); ^{19}F NMR δ −63.54 (3 F, s).

3-(4-Chlorophenyl)-5-nitroisocoumarin (3d) (Table 1, entry N). Compound **1** was treated with 4-chlorobenzoyl chloride, as for entry B, except that chromatography was omitted, to give **3d** (29%) as a pale yellow solid: mp 204−205 °C (lit.[10] mp 204−205 °C); ^{1}H NMR δ 7.47 (2 H, d, J = 6.6 Hz), 7.62 (1 H, t, J = 8.0 Hz), 7.87 (2 H, d, J = 6.9 Hz), 7.88 (1 H, br s), 8.50 (1 H, dd, J = 8.3, 1.9 Hz), 8.63 (1 H, br d, J = 8.0 Hz).

5-Nitro-3-(4-methylphenyl)isocoumarin (3e) (Table 1, entry O). Compound **1** was treated with 4-methylbenzoyl chloride, as for entry B, to give **3e** (23%) as a pale yellow solid: mp 181−182 °C (lit.[4,14] mp 175−176 °C); ^{1}H NMR δ 2.42 (3 H, s), 7.29 (2

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H, d, J = 8.6 Hz), 7.57 (1 H, t, J = 8.2 Hz), 7.82 (1 H, s), 7.83 (2 H, d, J = 8.4 Hz), 8.48 (1 H, br d, J = 8.2 Hz), 8.61 (1 H, br d, J = 8.5 Hz).

5-Nitro-3-(3-methylphenyl)isocoumarin (3f) (Table 1, entry P). Compound **1** was treated with 3-methylbenzoyl chloride, as for entry B, to give **3f** (21%) as a pale yellow solid: mp 152−154 °C; IR ν_{max} 1731, 1621, 1518, 1337 cm^{-1}; ^{1}H NMR δ 7.30 (1 H, d, J = 7.4 Hz), 7.40 (1 H, t, J = 7.7 Hz), 7.58 (1 H, t, J = 8.0 Hz), 7.71 (1 H, d, J = 7.7 Hz), 7.73 (1 H, s), 7.83 (1 H, s), 8.47 (1 H, d, J = 8.2 Hz), 8.61 (1 H, d, J = 7.7 Hz); MS m/z 282.0761 (M + H) ($C_{16}H_{12}NO_4$ requires 282.0766). Anal. Calcd for $C_{16}H_{11}NO_4$: C, 68.32; H, 3.94; N, 4.98. Found: C, 68.58; H, 4.07; N, 4.79.

5-Nitro-3-phenyl-3-[^{13}C]-isocoumarin (3g) (Table 1, entry J). Compound **1** was treated with Ph^{13}COCl, as for entry B, to give **3g** (39%) as a pale yellow solid: mp 145−146 °C (lit.[4] mp 142−143 °C for unlabeled compound); ^{1}H NMR δ 7.49−7.51 (3 H, m), 7.60 (1 H, t, J = 8.2 Hz), 7.87 (1 H, br d, J = 5.5 Hz), 7.94 (2 H, m), 8.49 (1 H, dd, J = 8.2, 1.2 Hz), 8.61 (1 H, ddd, J = 7.8, 1.2, 0.8 Hz); ^{13}C NMR δ 96.3 (d, J = 75.1 Hz), 122.3 (d, J = 3.8 Hz), 125.9 (d, J = 1.5 Hz), 127.1 (CH, s), 129.0 (CH, d), 131.1 (d, J = 68.2 Hz), 131.2 (s), 131.6 (s), 131.9 (s), 135.8 (s), 144.3 (d, J = 5 Hz), 156.8 (s), 156.8 (d, J = 75.9 Hz), 156.8 (d, J = 67.5 Hz), 160.3 (d, J = 3.1 Hz); MS m/z 559.1052 (2M + Na) ($^{13}C_2{}^{12}C_{28}H_{18}-N_2-Na_1O_8$ requires 559.1028), 537 (2M + H), 291.0476 (M + Na) ($^{13}C_1{}^{12}C_{14}H_9N_1Na_1O_4$ requires 291.0463), 269 (M + H).

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Supporting Information Available: General experimental details and copies of the ^{1}H NMR spectra for **3b**,**f**,**g** and of the ^{13}C NMR spectrum of **3g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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