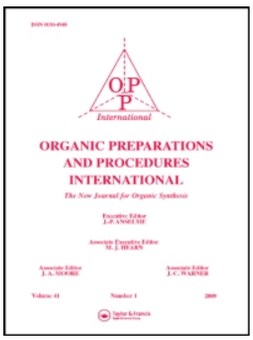

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Organic Preparations and Procedures International

The New Journal for Organic Synthesis

ISSN: 0030-4948 (Print) 1945-5453 (Online) Journal homepage: https://www.tandfonline.com/loi/uopp20

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To cite this article: Nikolaos Kontonikas, Panagiota Kotsampasakou, Nikolaos Sakalis & Vassilis J. Demopoulos (2019) A Study of the Electrophilic Aroylation of 1-Aryl-1*H*-pyrroles: An Improved Preparation of an Active and Selective Aldose Reductase Inhibitor, Organic Preparations and Procedures International, 51:2, 147-152, DOI: 10.1080/00304948.2019.1577109

To link to this article: https://doi.org/10.1080/00304948.2019.1577109

Organic Preparations and Procedures International, 51:147–152, 2019

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A Study of the Electrophilic Aroylation of 1-Aryl-1*H*-pyrroles: An Improved Preparation of an Active and Selective Aldose Reductase Inhibitor

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The aroyl-1-aryl-1*H*-pyrrole moiety is an important scaffold present in a number of biologically active compounds.[1–5] Based on such precedent, we were prompted to study the electrophilic benzoylation of 1-phenyl-1*H*-pyrrole **(1)**. We sought to develop an appropriate methodology for the selective preparation of 1-aryl-1*H*-pyrrolyl derivatives with aroyl substituents at the underexplored pyrrolyl C-α position. The new methodology described herein was applied to prepare the known active and selective aldose reductase inhibitor (ARI) ([1,1'-biphenyl]-4-yl)[1-(3,5-difluoro-4-hydroxyphenyl)-1*H*-pyrrol-2-yl]methanone **(2)**.[2] We have previously prepared compound **2**, however in low yield and not selectively.[2] Thus, in the present work we improve our own methodology.

Initially, the $AlCl_3$ catalyzed reaction of **1** with benzoyl chloride was investigated by varying the ratio of reactants[2,5] and by adding nitromethane[6] (*Table 1*, entries 1–3). In all cases, the main product was the C-*β* substituted pyrrolyl derivative **3**. We noted, however, that the addition of nitromethane resulted in the formation of small amounts of the C-α isomer **4**. Subsequently, the $AlCl_3$ was replaced with the weaker Lewis acids Et_2AlCl[7] or $BF_3{\cdot}OEt_2$[1,8] (*Table 1*, entries 4 and 5). In the first case, the reaction was clean and both isomers were formed in good yields, with the higher yield that of the C-*β* isomer **3**. On the other hand, $BF_3{\cdot}OEt_2$ proved to be an ineffective catalyst; only traces of products were formed, and a substantial amount of the pyrrolyl starting material remained unreacted even after seven days. Finally, the reaction of **1** with benzoyl chloride was studied in the presence of DBN,[9] Zn,[10] or I^-,[11] without any added Lewis acid catalyst. With the first two methods, no reaction was observed; but the use of I^- resulted in the selective formation of the C-α isomer **4**. We found out that the best yield was obtained with the combination of CH_3CN as the solvent and KI as the catalyst (*Table 1*, entry 6). All compounds were isolated by flash column chromatography, and the solids were further recrystallized. Structural identification was based on spectroscopic methods (IR, NMR and HRMS).

The data show that the most selective procedure for C-α substitution is the one with CH_3CN and KI. Thus, we went on to investigate selective preparation of the

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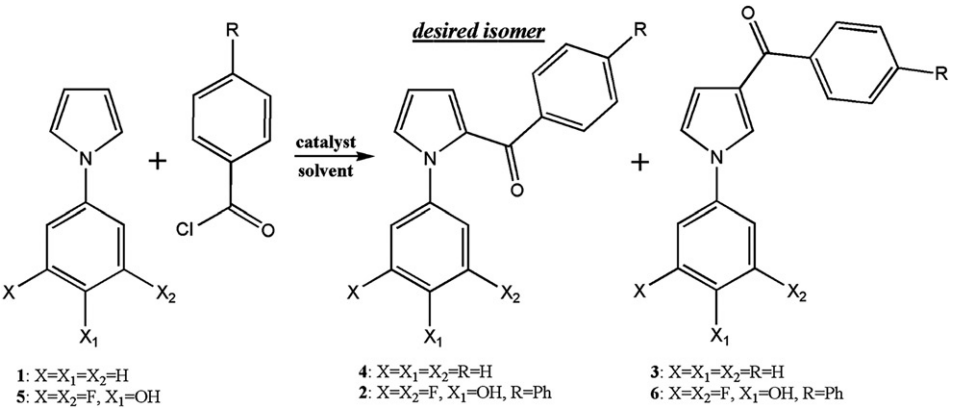
Table 1
Conditions and Yields for the Electrophilic Aroylation Reactions

Entry	1-Aryl-1*H*-pyrrole (1 mmol)	Aroyl chloride (equivalents)	Catalyst(s) (equivalents), solvent (mL)	Time(h), conditions	Product[a] (yield%)
1	**1**	R = H (2.24)	$AlCl_3$ (2.4), $ClCH_2CH_2Cl$ (29.5)	48, room temp.	**4** (0) **3** (39)
2	**1**	R = H (2.24)	$AlCl_3$ (1.2), $ClCH_2CH_2Cl$ (14.5)	24, room temp.	**4** (0) **3** (72)
3	**1**	R = H (2.24)	$AlCl_3$ (1.2) and CH_3NO_2 (1.2), $ClCH_2CH_2Cl$ (14.5)	24, room temp.	**4** (10.5) **3** (72)
4	**1**	R = H (2)	Et_2AlCl (1.4), $ClCH_2CH_2Cl$ (4)	2, ice bath	**4** (41) **3** (57)
5	**1**	R = H (3)	$BF_3.Et_2O$ (3), $ClCH_2CH_2Cl$ (10.5)	168, room temp.	**4** (5) **3** (3) [**1** (25)]
6	**1**	R = H (1.2)	KI (0.6), CH_3CN (1)	24, reflux	**4** (40) **3** (16)
7	**5**	R = Ph (2.4)	KI (1.2) CH_3CN (2)	24, reflux	**2** (61) **6** (24)

[a]Yields are for isolated products.



Scheme 1

ARI **2**. Under the above conditions **2** could be synthesized in good yield (61%, *Table 1*, entry 7), much higher than that reported previously (34%).[2] In that preparation, the electrophilic aroylation of **5** was catalyzed by $AlCl_3$. It is hoped that the ready availability of **2** will stimulate further research.

To summarize, we have developed an effective synthetic procedure for preparing potentially bioactive 2-aroyl-1-aryl-1*H*-pyrrole derivatives.

Experimental Section

All reagents were purchased from Sigma–Aldrich and used without further purification. Melting points are uncorrected and were determined in open glass capillaries using a Mel-Temp II apparatus. IR spectra were taken with a Perkin-Elmer FT-IR System Spectrum BX. NMR spectra were recorded on an Agilent 500/54 (DD2) spectrometer (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR) using tetramethylsilane (TMS) as the internal standard. Mass spectra were obtained on a hybrid LTQ Orbitrap Discovery mass spectrometer (Thermo Scientific, Bremen, Germany), which was equipped with an electrospray ionization (ESI) MAX2 source. Flash column chromatography was carried out with Merck silica gel 60 (230–400 Mesh ASTM). TLC was run with Merck Silica gel/TLC-cards. All solvents used for column chromatography were routinely distilled prior to use. Petroleum ether refers to the fraction with bp 40–60 °C.

General Procedure for the Electrophilic Benzoylation of 1 in the Presence of a Lewis Acid Catalyst (Table 1, entries 1–5)

To a stirred cold (ice bath) solution of benzoyl chloride in 1,2-dichloroethane under a nitrogen atmosphere, the catalyst was added and stirring was continued at the same temperature for 10 min. After this period, **1** was added and stirring was continued for the specified time and temperature conditions. The reaction mixture was then poured into ice/water (150 mL), stirred overnight, the two phases were separated and the aqueous fraction extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were washed with 5% aqueous $NaHCO_3$ solution (1x100 mL), brine (1x100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash chromatography with a mixture of petroleum ether/ethyl acetate 18:1 as the eluent.

*General Procedure for the Electrophilic Aroylation of 1-Aryl-1*H*-pyrrole 1 or 5 in the Presence of KI (Table 1, entries 6 and 7)*

To a stirred mixture of 1-aryl-1*H*-pyrrole **1** or **5** and KI in anhydrous CH_3CN (3Å molecular sieves) under a nitrogen atmosphere, the appropriate aroyl chloride was added and the resulted mixture was heated at 82 °C for the specified time. The reaction mixture was then poured, with the aid of 5 mL CH_3CN, into a 1% aqueous $Na_2S_2O_3$ solution (100 mL). The resulting mixture was stirred overnight at room temperature under a nitrogen atmosphere.

Entry 6: The mixture was then extracted with CH_2Cl_2 (3x50 mL), the combined extracts were washed with 5% aqueous $NaHCO_3$ solution (1x50 mL), brine (1x50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash chromatography with a mixture of petroleum ether/ethyl acetate 18:1 as the eluent.

Entry 7: The mixture was then acidified, to pH∼2, with 5% aqueous HCl solution and extracted with 9:1 $CHCl_3$/EtOH (3x50 mL). The acidification step was necessary in order to free any present phenolic salts before the extraction. The combined extracts were evaporated under reduced pressure, the residue was dissolved in 1,4-dioxane (27 mL), treated with 5% aqueous NaOH solution (27 mL) and the resulting mixture was stirred overnight at room temperature under a nitrogen atmosphere. The reaction

mixture was then concentrated to half of its volume under reduced pressure, H_2O (50 mL) was added, cooled (ice bath), acidified with concentrated aqueous HCl solution, extracted with CH_2Cl_2 (3x50 mL) while cold, and the organic extracts were concentrated under reduced pressure. The residue was dissolved in a mixture of ethyl acetate (70 mL) and petroleum ether (70 mL), and this was washed consecutively with a phosphate buffer (Na_2HPO_4-KH_2PO_4) pH 8 (6x50 mL), 5% aqueous HCl solution (1x50 mL), brine (1x50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash chromatography with a mixture of petroleum ether/ethyl acetate 18:1 as the eluent.

Phenyl(1-phenyl-1H-pyrrol-2-yl)methanone (4). An analytical sample was prepared by recrystallization from 95% aqueous ethanol; R_f=0.65, petroleum ether/ethyl acetate 8:2; mp 68-69 °C; *lit.*[12] 116 °C; *lit.*[13,14] 95-96; *lit.*[15] brown oil; IR (KBr): 1628 (C = O) cm^{-1}, consistent with the reported[13] IR data; ^{1}H NMR ($CDCl_3$): δ 6.34 (dd, J = 2.7, 3.9 Hz, 1H, pyrrolyl 4-*H*), 6.89 (dd, J = 1.6, 3.9 Hz, 1H, pyrrolyl 3-*H*), 7.12 (dd, J = 1.8, 2.4 Hz, 1H, pyrrolyl 5-*H*), 7.31–7.35 (m, 2H, phenyl 3-*H* and 5-*H*), 7.35–7.39 (m, 1H, phenyl 4-*H*), 7.40-7.48 (m, 4H, phenyl 2-*H* & 6-*H* and benzoyl 3-*H* and 5-*H*), 7.55 (t, J = 7.4 Hz, 1H, benzoyl 4-*H*), 7.87–7.91 (m, 2H, benzoyl 2-H & 6-H), consistent with the reported[13–15] ^{1}H NMR data; ^{13}C NMR ($CDCl_3$): δ 109.5, 123,5, 125.5, 127.5, 128.1, 128.9, 129.5, 131.0, 131.1, 131.9, 139.0, 140.6, 184.8, consistent with the reported[13–15] ^{13}C NMR data; HRMS *m/z* calc. for $C_{17}H_{13}NO$: 247.0997(248.1075 for $M + H)^+$; Found: 248.1085 (ESI+).

Phenyl(1-phenyl-1H-pyrrol-3-yl)methanone (3). Viscous oil; R_f=0.49, petroleum ether/ethyl acetate 8:2; IR (neat): 1633 (C = O) cm^{-1}, consistent with the reported[4] IR data; ^{1}H NMR ($CDCl_3$): δ 6.88 (s, 1H, pyrrolyl 4-*H*), 7.11 (d, J = 2.1 Hz, 1H, pyrrolyl 5-*H*), 7.34 (t, *J* = 7.2 Hz, 1H, phenyl 4-*H*), 7.42 (d, *J* = 7.5 Hz, 2H, phenyl 3-*H* and 5-*H*), 7.46 (d, *J* = 7.2 Hz, 2H, phenyl 2-*H* & 6-*H*), 7.49 (d, *J* = 7.4 Hz, 2H, benzoyl 3-*H* and 5-*H*), 7.55 (t, *J* = 7.4 Hz, 1H, benzoyl 4-*H*), 7.61 (s, 1H, pyrrolyl 2-*H*), 7.88 (d, *J* = 7.7 Hz, 2H, benzoyl 2-*H* and 6-*H*), consistent with the reported[3,4] ^{1}H NMR data; ^{13}C NMR ($CDCl_3$): δ 112.4. 121.1, 121.2, 126.1, 126.2, 127.1, 128.2, 128.9, 129.8, 131.5, 139.7, 139.8, 190.7, consistent with the reported[3] ^{13}C NMR data; HRMS *m/z* calc. for $C_{17}H_{13}NO$: 247.0997(248.1075 for $M + H)^+$; Found: 248.1082 (ESI+).

([1,1'-Biphenyl]-4-yl)[1-(3,5-difluoro-4-hydroxyphenyl)-1H-pyrrol-2-yl]methanone (2). An analytical sample was prepared by recrystallization from CH_2Cl_2/petroleum ether; R_f=0.33, petroleum ether/ethyl acetate 8:2; mp 210-213 °C; *lit.*[2] 214–216 °C; IR (nujol): 3137 (OH), 1592 (C = O) cm^{-1}, consistent with the reported[2] IR data; ^{1}H NMR ($CDCl_3$ + DMSO-d_6, the addition of DMSO-d_6 was necessary in order to dissolve the compound): δ 6.03 (br s, 1H, O-*H*), 6.25 (dd, *J* = 2.8, 3.8 Hz, 1H, pyrrolyl 4-*H*), 6.74-6.86 (m, 3H, pyrrolyl 3-*H* and phenyl 2-*H* and 6-*H*), 6.96-6.99 (m, 1H, pyrrolyl 5-*H*), 7.31 (t, *J* = 7.4 Hz, 1H, biphenyl 4'-*H*), 7.39 (t, *J* = 7.6 Hz, 2H, biphenyl 3'-*H* and 5'-*H*), 7.56 (d, *J* = 7.3 Hz, 2H, biphenyl 2'-*H* and 6'-*H*), 7.60 (d, *J* = 8.3 Hz, 2H, biphenyl 3-*H* and 5-*H*), 7.86 (d, *J* = 8.3 Hz, 2H, biphenyl 2-*H* and 6-H), consistent with the reported[2] ^{1}H NMR data; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, the addition of DMSO-d_6 was necessary in order to dissolve the compound): δ 109.7(dd, J = 7.5, 17.4 Hz), 123.2, 126.7, 126.8, 127.1, 127.2, 128.0, 128.9, 129.9, 130.0, 131.1 (t, J = 10.0 Hz), 133.9 (t, J = 15.8 Hz), 137.5, 139.9, 144.7, 152.0 (dd, J = 8.1, 243.7 Hz), 184.1; HRMS *m/z* calc. for $C_{23}H_{15}F_2NO_2$: 375.1071 (374.0993 for $M\text{-}H)^-$; Found: 374.0997 (ESI^-).

([1,1'-Biphenyl]-4-yl)[1-(3,5-difluoro-4-hydroxyphenyl)-1H-pyrrol-3-yl]methanone (6). An analytical sample was prepared by recrystallization from CH_2Cl_2/petroleum ether; R_f=0.18, petroleum ether/ethyl acetate 8:2; mp 202–204 °C; *lit.*[2] 205–207 °C; IR (nujol): 3154 (OH), 1617 (C = O) cm^{-1}, consistent with the reported[2] IR data; ^{1}H NMR ($CDCl_3$ + DMSO-d_6, the addition of DMSO-d_6 was necessary in order to dissolve the compound): δ 6.12 (br s, 1H, O-*H*), 6.73 (dd, J = 1.6, 2.8 Hz, 1H, pyrrolyl 4-*H*), 6.86-6.92 6.92 (m, 3H, pyrrolyl 5-*H* and phenyl 2-*H* and 6-*H*), 7.27 (t, J = 6.9 Hz, 1H, biphenyl 4'-*H*), 7.36 (t, J = 7.6 Hz, 2H, biphenyl 3'-*H* and 5'-*H*), 7.42 (t, J = 1.7 Hz, 1H, pyrrolyl 5-*H*), 7.51-7.54 (m, 2H, biphenyl 2'-*H* and 6'-*H*), 7.59 (d, J = 8.1 Hz, 2H, biphenyl 3-*H* and 5-*H*), 7.82 (d, J = 8.2 Hz, 2H, biphenyl 2-*H* and 6-*H*), consistent with the reported[2] ^{1}H NMR data; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, the addition of DMSO-d_6 was necessary in order to dissolve the compound): δ 105.3 (dd, J = 8.3, 17.8 Hz), 112.3, 125.8, 125.85, 126.1, 126.9, 127.1, 127.9, 128.8, 129.5, 130.5 (t, J = 11.0 Hz), 133.5 (t, J = 16.1 Hz), 138.2, 140.0, 144.5, 152.7 (dd, J = 8.4, 244.9 Hz), 189.9; HRMS *m/z* calc. for $C_{23}H_{15}F_2NO_2$: 375.1071 (374.0993 for M-H)$^-$; Found: 374.0999 (ESI$^-$).

Acknowledgments

Many thanks to Dr. Evagelos Gikas (Department of Pharmaceutical Chemistry, Faculty of Pharmacy, National and Kapodistrian University of Athens) for the mass spectral data.

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