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PREPARATION OF 8-ALKYL 7-(2-IMIDAZOLINYLAMINO)QUINOLINES VIA PALLADIUM MEDIATED ALKYLATIONS

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ABSTRACT

A convenient preparation of 8-alkyl substituted 7-(2-imidazolinylamino)quinolines from the corresponding 8-trifluoromethanesulfonates, utilizing palladium cross-coupling reactions is described.

During the course of our efforts to design and synthesize α_2 adrenergic agonists, 8-ethyl-7-(2-imidazolinylamino)quinoline, **1**, was identified as a potent and selective compound. As illustrated in Scheme 1, the initial synthetic route to the desired quinoline progressed through classical construction of the quinoline ring system via a modified Doebner–Miller reaction.[1] Starting with commercially available 4-ethylbenzoic acid (**2**),

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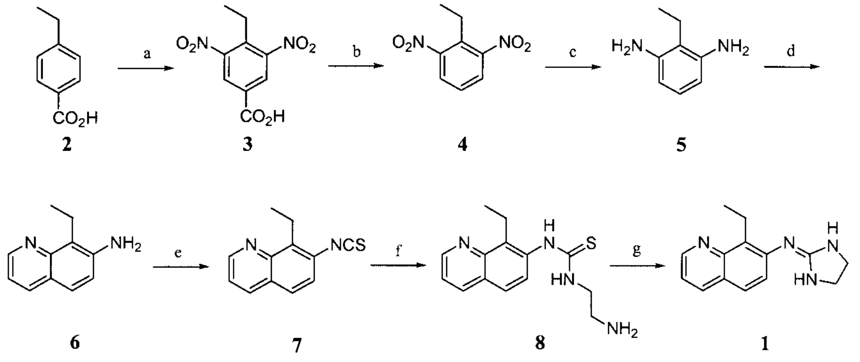
dinitration in the presence of fuming nitric acid and sulfuric acid gave rise to dinitrobenzoic acid **3** in high yield (96%). Treatment of **3** with copper bronze in refluxing quinoline provided the decarboxylated 2,6-dinitroethylbenzene (**4**) in poor yield (24%). Attempts to optimize the decarboxylation failed to produce higher isolated yields of the desired ethylbenzene **4**. Catalytic reduction to diamine **5**, followed by treatment with 1,1,3-trimethoxypropane in the presence of $FeCl_3$, $ZnCl_2$, and 1N HCl in absolute ethanol afforded quinoline **6** in low yield (36%). Attempts to optimize this step consistently provided isolated yields in the 32–38% range. Construction of the aminoimidazoline proceeded through formation of the isothiocyanate **7** by treatment with di-2-pyridylthionocarbonate (98% yield), conversion to thiourea **8** with ethylenediamine and finally cyclization to the imidazoline by treatment with mercuric acetate to provide 8-ethyl-7-(2-imidazolinylamino)-quinoline (**1**) as the acetate salt in good overall yield from the isothiocyanate (81%). Kilolab scale-up feasibility studies of this process identified it as much too costly, owing largely to the poor chemical yields and the failure to optimize both the decarboxylation and quinoline ring formation steps. Clearly, a new process needed to be identified.

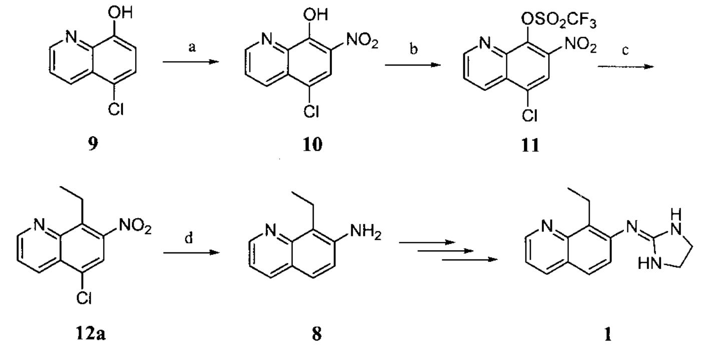


a: HNO_3, H_2SO_4; b: Cu-bronze, quinoline; c: Pd-C/H_2, MeOH; d: 1,1,3-trimethoxypropane, $FeCl_3$, $ZnCl_2$, HCl, ethanol; e: DPT, 4-DMAP, CH_2Cl_2; f: ethylenediamine, CH_2Cl_2; g: $Hg(OAc)_2$, MeOH

Scheme 1.

Although the literature is rich with methods aimed towards preparing 8-alkyl substituted quinolines via ring forming reactions,[2] these methods all offer limitations in their scope, essentially making them undesirable for scale-up. In determining a suitable starting material for the new process, a cornerstone of thought included having the quinoline ring system in place at the start, thus avoiding the need for ring formation. Stille reported the coupling of aryltrialkylstannanes to 8-quinolyl trifluoromethanesulfonate[3] and Crisp and Papadopoulos described the coupling of trialkylaluminum reagents to 2-quinolyl trifluoromethanesulfonate,[4] both *via* palladium mediated cross-couplings. However, in both cases, no additional substitution on the quinoline ring system was examined. With this precedent in mind, we viewed commercially available 5-chloro-8-hydroxyquinoline (**9**) as a suitable starting material. As illustrated in Scheme 2, nitration of **9** with 1.1 equivalents of KNO_3 in concentrated H_2SO_4 at 5–10°C gave rise to 5-chloro-8-hydroxy-7-nitroquinoline (**10**) in good yield (86%), which was then treated with 1.0 equivalents of triflic anhydride in the presence of triethylamine in CH_2Cl_2 to provide triflate **11** (90%). Reaction of triflate **11** with tetraethyltin (1.04 equiv) in the presence of $PdCl_2(PPh_3)_2$ (0.02 equiv) and LiCl (3.0 equiv) in DMF at 80°C gave rise to the desired 8-ethyl substituted quinoline **12** in good yield (75%). Contrary to the reports of Crisp and Papadopoulos,[4] alkyl transfer from organostannanes did occur, with this transfer most likely being attributed to the activating effect of the nitro group *ortho* to the trifluoromethanesulfonate. In fact, when triethylaluminum was used as the alkyl source (1.5 equiv Et_3Al, 0.05 equiv $PdCl_2(PPh_3)_2$, 1.3 equiv LiCl, DMF), the reaction proceeded at room temperature, providing **12** in good yield (74%). Finally, catalytic reduction of the nitro group, along with concomitant reduction of the chloro moiety furnish 7-amino-8-ethylquinoline (**8**, 68%), which was then carried on to the desired 7-(2-imidazolinyl)quinoline as previously described.

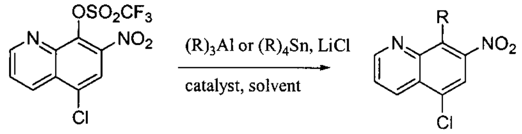
Pursuant to an ongoing study requiring access to a series of 8-alkyl substituted 7-(2-imidazolinylamino)quinolines, the palladium



a: KNO_3, H_2SO_4, 5-10 °C; b: triflic anhydride, Et_3N, CH_2Cl_2, 0 °C; c: Et_4Sn, $PdCl_2(PPh_3)_2$, LiCl, DMF, 80 °C; d: 10% Pd-C, H_2 (1 atm), MeOH, EtOAc (5:1 v:v), NaOH.

Scheme 2.

Table 1. Palladium Mediated Alkylations of Compound 11



11 **12a-c**

Entry	R_3Al/R_4Sn	Catalyst	Solvent	Temperature (°C)	Product	% Yield
1	Et_4Sn	$PdCl_2(PPh_3)_2$	DMF	80	12a, R=Et	75
2	Et_3Al	$PdCl_2(PPh_3)_2$	DMF	rt	12a, R=Et	74
3	Et_3Al	$Pd(PPh_3)_4$	DMF	rt	12a, R=Et	28
4	*n*-Pr_3Al	$PdCl_2(PPh_3)_2$	DMF	rt	12b, R=*n*-Pr	65
5	*n*-Bu_4Sn	$Pd(PPh_3)_4$	Dioxane	100	12c, R=*n*-Bu	no reaction
6	*n*-Bu_4Sn	$PdCl_2(PPh_3)_2$	DMF	100	12c, R=*n*-Bu	60

cross-coupling reaction described above was considered as a quick and facile method to expand the structure-activity relationships of this class of α_2 agonists. As illustrated in Table 1, quick access to the *n*-propyl (Entry 4) and *n*-butyl (Entry 6) analogs was now possible. A brief survey of the scope of this coupling indicated that triethylaluminum coupled more efficiently in the presence of $PdCl_2(PPh_3)_2$ (Entry 2) than in the presence of $Pd(PPh_3)_4$ (Entry 3). Moreover, coupling proceeded at room temperature when using the alkylaluminum reagents, (Entries 2–4) whereas elevated temperatures were required when utilizing alkylstannanes (Entries 1, 5, 6). The overall improvement of the new synthetic route was directly measured by the enhancement of overall isolated yield of **1** (4%, Doebner–Miller strategy vs. 44%, Pd mediated coupling strategy). Although the palladium mediated coupling described above seemed plausible for the kilolab campaign, further development of quinoline **1** was halted, thus no attempt was made to examine this process on the kilogram scale.

EXPERIMENTAL SECTION

General Methods

Proton NMR spectra were taken on a GE QE-300 (300 MHz) spectrometer or a Bruker AC-300 (300 MHz) quad-nuclei probe system.

All chemical shifts were reported in δ scale as parts per million downfield from $(CH_3)_4Si$. Spectra taken in $CDCl_3$ were referenced either to $(CH_3)_4Si$ or to residual $CHCl_3$ (7.24 ppm). Spectra taken in D_2O were referenced to HOD (4.80 ppm), those in $(CD_3)_2CO$ were referenced to residual $(CH_3)_2CO$ (2.04 ppm), those in CD_3OD were referenced to residual CH_3OH (3.30 ppm), and those in $(CD_3)_2SO$ were referenced to residual $(CH_3)_2SO$ (2.49 ppm). Carbon-13 spectra were taken on a GE QE-300 (75 MHz) spectrometer or a Bruker AC-300 (75 MHz) quad-nuclei probe system. Spectra taken in $CDCl_3$ were referenced to solvent (78 ppm), those in CD_3OD were referenced to solvent (49 ppm), those in $(CD_3)_2SO$ were referenced to solvent (39.7 ppm), and those in $(CD_3)_2CO$ were referenced to solvent (206.5, 29.8 ppm). Mass spectra were determined on a Fision's Trio 2000 equipped with a robotic probe. Chemical ionization spectra were obtained using methane and/or ammonia as a reagent gas. Thin layer chromatography was performed on silica gel 60 F-254 precoated plates. Flash chromatography was performed using silica gel 60 (Merck, 230–400 mesh). Melting points were obtained with an Electrothermal IA9200 and are uncorrected. Elemental analysis were obtained from Oneida Research Services, Whiteboro, NY. Unless otherwise stated, all commercially available reagents were used without further purification. All reactions were normally run under an inert atmosphere (argon or nitrogen). Brine referred to saturated aqueous sodium chloride. Residual solvent was removed under vacuum (ca. 0.03 mm Hg) at rt.

5-Chloro-8-hydroxy-7-nitroquinoline 10: To a 250 mL round bottom flask was added 5-chloro-8-hydroxyquinoline **9** (7.07 g, 0.039 mol) and H_2SO_4 (70 mL). This mixture was cooled to 5–10°C and solid KNO_3 (4.14 g, 0.041 mol) was slowly added over a period of one hour. Upon completion of addition, the reaction mixture was poured over 1 liter of ice/water and an orange precipitate formed. The solid was filtered and dried in a vacuum oven to give rise to 5-chloro-8-hydroxy-7-nitroquinoline **10** (7.5 g, 86%). m.p. 198.5–199.4°C; ^{1}H-NMR (DMSO-d_6): 9.08–9.03 (1H, dd, $J = 4.1$, 1.0 Hz), 8.57–8.51 (1H, dd, $J = 8.5$, 0.9 Hz), 8.12 (1H, s), 7.91–7.86 (1H, dd, $J = 8.5$–4.3 Hz); ^{13}C-NMR (DMSO): 150.82, 150.45, 140.35, 133.93, 132.67, 128.91, 126.28, 122.27, 118.38.

5-Chloro-7-nitro-8-trifluoromethanesulfonylquinoline 11: To a 500 mL round bottom flask was added 5-chloro-8-hydroxy-7-nitroquinoline **10** (5.0 g, 0.02 mol) and methylene chloride (200 mL). This heterogeneous mixture was cooled to 0°C and neat triethylamine (3.1 mL, 0.02 mol) was added *via* syringe. The resulting mixture was stirred at 0°C for approximately 30 min (or until all solids have dissolved). Neat triflic anhydride was slowly added over a period of ten minutes and the resulting mixture was stirred at 0°C for ten minutes. The reaction mixture was filtered through a plug of SiO_2 (eluted with 300 mL 60 : 40 hexane : ethyl acetate) and the resulting organic fraction was concentrated in vacuo to give rise to 5-chloro-7-nitro-8-trifluoromethanesulfonylquinoline **11** (6.98 g, 90%). m.p. 111.0–112.5°C; ^{1}H-NMR ($CDCl_3$): 9.23–9.21 (1H, dd, $J = 4.0$, 1.5 Hz), 8.69–8.66 (1H, dd, $J = 8.5$, 1.5 Hz), 8.22 (1H, s), 7.85–7.80 (1H, dd, $J = 8.5$, 4.0 Hz); ^{13}C-NMR ($CDCl_3$): 153.39, 141.24, 140.20, 138.10, 133.18, 132.08, 129.70, 125.50, 121.09, 120.73, 116.48.

5-Chloro-8-ethyl-7-nitroquinoline 12a: To a 25 mL round bottom flask under N_2 was added 5-chloro-7-nitro-8-trifluoromethanesulfonylquinoline **11** (500 mg, 1.4 mmol), DMF (7 mL), Et_4Sn (0.29 mL, 1.45 mmol), LiCl (178 mg, 4.2 mmol), and $Pd(Cl)_2(PPh_3)_2$ (20 mg, 0.028 mmol). The mixture was heated to 80°C for 18 h. The resulting reaction mixtures was then cooled to room temperature and diluted with diethyl ether (100 mL), washed with sat'd KF (3 × 75 mL), H_2O (2 × 75 mL), and brine (1 × 75 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated to give rise to a yellow residue. The residue was chromatographed (90 : 10 hexane : ethyl acetate) to give rise to 5-chloro-8-ethyl-7-nitroquinoline **12a** (249 mg, 75%). m.p. 88.3–89°C; ^{1}H-NMR ($CDCl_3$): 9.1 (1H, dd), 8.6 (1H, dd), 8.0 (1H, s), 7.65 (1H, dd), 3.45 (2H, q), 1.4 (3H, t); ^{13}C-NMR ($CDCl_3$): 151.54, 138.04, 133.15, 128.10, 123.66, 121.07, 20.78, 15.00. Anal. Calcd for $C_{11}H_9ClN_2O_2$: C, 55.83; H, 3.83; N, 11.84. Found: C, 55.96; H, 3.94; N, 11.99.

5-Chloro-7-nitro-8-*n*-propylquinoline 12b: To a 100 mL round bottom flask under N_2 was added 5-chloro-7-nitro-8-trifluoromethanesulfonylquinoline **11** (1.0 g, 2.8 mmol), DMF (20 mL), LiCl (154 mg, 3.6 mmol), $Pd(Cl)_2(PPh_3)_2$ (98 mg, 0.01 mmol), and (n-propyl)$_3$Al (660 mg, 4.2 mmol). The mixture was stirred at rt for 48 h. The resulting reaction mixture was poured into 150 mL ice/H_2O and then partitioned between H_2O and diethyl ether (100 mL). The aqueous phase was washed with diethyl ether (3 × 100 mL). The combined organic fractions were washed with brine (1 × 100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give rise to an orange solid. The residue was chromatographed (90 : 10 hexane : ethyl acetate) to give rise to 5-chloro-7-nitro-8-*n*-propylquinoline **12b** as an off-white solid (460 mg, 65%). ^{1}H-NMR ($CDCl_3$): 9.10–9.08 (1H, dd, $J = 4.2$, 1.8 Hz), 8.61–8.58 (1H, dd, $J = 8.5$, 1.8 Hz), 7.97 (1H, s), 7.66–7.61 (1H, dd, $J = 8.5$, 4.3 Hz), 3.45–3.42 (2H, dd, $J = 9.2$, 7.7 Hz), 1.81–1.73 (2H, m), 1.08 (3H, t, $J = 7.4$ Hz); ^{13}C-NMR ($CDCl_3$): 151.46, 148.58, 147.16, 137.08, 132.99, 129.98, 128.00, 123.60, 121.07, 28.97, 24.12, 14.46. CIMS (NH_3, CH_4) m/e 253 (M + 3), 251 (M+1), 221 (M-NO); Anal. Calcd for $C_{12}H_{11}ClN_2O_2$: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.52; H, 4.81; N, 11.48.

5-Chloro-8-*n*-butyl-7-nitroquinoline 12c: To a 100 mL round bottom flask under N_2 was added 5-chloro-7-nitro-8-trifluoromethanesulfonylquinoline **11** (1.0 g, 0.0028 mol), DMF (20 mL), (n-Bu)$_4$Sn (1.01 g, 0.0029 mol), LiCl (0.356 g, 0.0084 mol), and $Pd(Cl)_2(PPh_3)_2$ (39 mg, 0.39 mmol). The mixture was heated to 100°C for 22 h. The resulting reaction mixture was then cooled to room temperature and diluted with diethyl ether (100 mL) then washed with sat'd KF (3 × 75 mL), H_2O (2 × 75 mL), and brine (1 × 75 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated to give rise to a yellow residue. The residue was chromatographed (95 : 5 hexane : ethyl acetate) to give rise to 5-chloro-8-*n*-butyl-7-nitroquinoline **12c** as a white solid (462 mg, 57%). ^{1}H-NMR ($CDCl_3$): 9.10–9.08 (1H, dd, $J = 4.2$, 1.8 Hz), 8.61–8.58 (1H, dd, $J = 8.5$, 1.8 Hz), 7.97 (1H, s), 7.66–7.61 (1H, dd, $J = 8.5$, 4.3 Hz), 3.48–3.43 (2H, dd, $J = 9.2$, 7.7 Hz), 1.73–1.66 (2H, m), 1.54–1.47 (2H, m), 0.97 (3H, t, $J = 7.4$ Hz); ^{13}C-NMR ($CDCl_3$): 151.46, 148.58, 147.16, 137.08, 132.99, 129.98, 128.00, 123.60, 121.07, 32.84, 26.82, 23.15, 13.74. Anal. Calcd for $C_{13}H_{13}ClN_2O_2$: C, 58.99; H, 4.95; N, 10.58. Found: C, 59.02; H, 4.99; N, 10.74.

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