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Synthesis of Substituted Quinolines Using the Dianion Addition of *N*-Boc-anilines and α-Tolylsulfonyl-α,*β*-unsaturated Ketones

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A short and versatile synthesis of substituted quinolines is provided. Alkylation of sodium tolylsulfinate with bromomethyl- or chloromethyl ketones generates *β*-keto sulfones. Knoevenagel condensation of the *β*-keto sulfones with an aldehyde provides α-tolylsulfonyl-α,*β*-unsaturated ketones. Michael addition of the dianion of *N*-Boc-anilines in the presence of CuCN and LiCl with the unsaturated ketone generates a 1,4-adduct, which after deprotection of the Boc group and thermal elimination of the tolyl sulfone provides the quinoline.

Introduction

The quinoline ring system is found in natural products. Compounds containing the quinoline ring have diverse biological activity[1] and have been developed for the treatment of malaria,[2] antibacterial infections,[3] and HIV disease.[4] Substituted quinolines have also been reported to have biological activity as antagonists of endothelin,[5] $5HT_3$,[6] and NK-3 receptors.[7] They also function as inhibitors of gastric (H^+/K^+)-ATPase[8] and dihydroorotate dehydrogenase.[9]

Current methods for quinoline synthesis[10] often do not allow for adequate diversity and substitution on the quinoline ring system, mainly due to the limited availability of the starting material (especially isatin derivatives). Recently, there have been reports of improved Doebner reaction conditions for preparing diverse quinolines via solid-phase synthesis.[11] There has also been several reports of novel or improved methods for synthesizing functionalized quinolines.[12] In this paper, we disclose an efficient and regiocontrolled synthesis of 2,4,6-trisubstituted quinolines from commercially available bromomethyl or chloromethyl ketones, aldehydes and anilines. The chemistry exploits the dual nature of the tolyl sulfone group both as an electron-withdrawing group and later as a leaving group. The chemistry is versatile. Both aliphatic and aromatic ketones or aldehydes as well as anilines with electron-withdrawing or -donating groups can be employed. In contrast to the existing synthetic approaches for the quinoline ring system, modification of position 6 of the quinoline can be made in the last step of the synthesis.

Results and Discussion

The feasibility of this methodology for preparing 2,4,6-trisubstituted quinolines was demonstrated by using three different chloromethyl or bromomethyl ketones, four different aldehydes, and three different *N*-Boc-anilines. Alkylation of sodium tolylsulfinate with bromomethyl or chloromethyl ketones **1a**−**c** under reflux for 2 h in ethanol gave *β*-keto sulfones **2a**−**c** in 62−90% yields after crystallization. The Knoevenagel condensation conditions employed an aldehyde, 0.2 equiv of piperidine, and 0.4 equiv of acetic acid in toluene under dehydrating conditions (Scheme 1).[13] Conditions for the formation of

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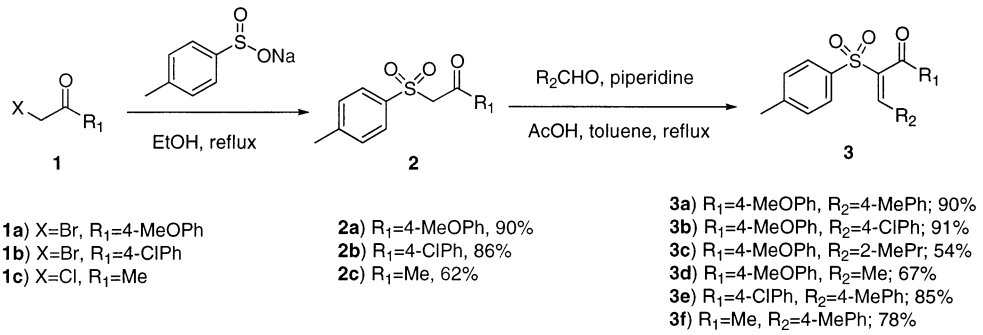
SCHEME 1



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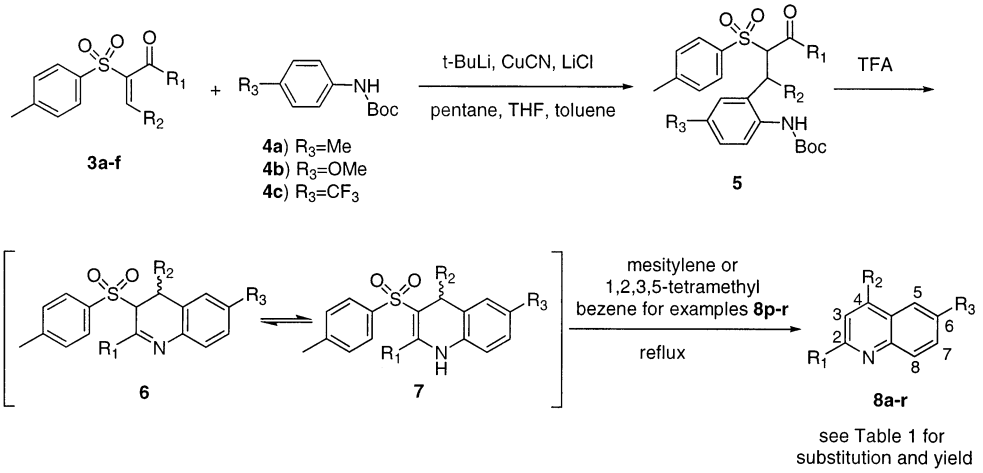

3d employed acetic anhydride as the dehydrating agent in a sealed reaction vessel, due to the volatility of the reagents.[14] The stereochemistry of the *E*-olefin was confirmed by 2D NOE experiments for compounds **3a** and **3c**. It is assumed that this is the thermodynamic product, since piperidine elimination and addition to the α,*β*-unsaturated double bond is reversible. Compound **3c** was not stable at room temperature for extended periods of time, due to isomerization of the double bond.

Three possibilities for dianion formation were explored. We found that dianion from *N*-2-(4-biphenyl)isopropyloxycarbonyl (Bpoc) protected anilines, used successfully by Ellman in his benzodiazepine synthesis,[15] failed to give good results in this system. Dianion from trifluoroacetate-*o*-bromoaniline[16] allowed formation of the quinolines after deprotection of the trifluoroacetate and thermolysis of the tolyl sulfone. However, this approach is limited by the availability of *o*-bromoanilines. The preferred method for the dianion formation was finally introduced by using *N*-Boc-anilines with 2.5 equiv of *t*-BuLi.[17] These *N*-Boc-anilines **4a**−**c** were prepared from the anilines and di-*tert*-butyl dicarbonate with NaOH in THF (**4a**, R_3 = methyl, 87%; **4b**, R_3 = methoxy, 89%; **4c**, R_3 = trifluoromethyl, 88%). Our initial attempts at the dianion addition to the α-tolylsulfonyl-α,*β*-unsaturated ketones **3** afforded 1,4- as well as 1,2-addition adducts (both adducts could be taken on to different substituted quinolines). This is in contrast to several recent reports that alkyllithium and Grignard reagents give 1,4-addtion adduct selectively in the absence of CuI or CuCN when the double bond is doubly activated with two electron-withdrawing groups on the α-carbon.[18] In our examples, selectivity for 1,4-addition was obtained by addition of 0.5 equiv of CuCN and 0.5 equiv of LiCl after the dianion was formed. Toluene was found to accelerate the reaction.[19] Typically, the last steps of our quinoline synthesis were performed as a dianion addition, an aqueous workup and filtration through silica gel to remove the residual *N*-Boc-aniline, addition of TFA for 3 h to remove the Boc group, concentration, addition of mesitylene or 1,2,3,5-tetramethylbenzene, and heating overnight (Scheme 2). The initial addition of the *N*-Boc-aniline dianion generates diasteriomers **5**, which produce a single quinoline product after deprotection of the Boc group and thermal elimination of the tolyl sulfone. Since concerted thermal elimination of tolyl sulfone is syn to the hydrogen, it is suggested that the trans isomer is equilibrated to the cis isomer via an imine−enamine equilibration. It is also possible that the tolyl sulfone eliminates and then proton loss occurs. Either mechanism is consistent with the results.

Table 1 lists the yields for the quinolines formed by the dianion addition to α-tolylsulfonyl-α,*β*-unsaturated

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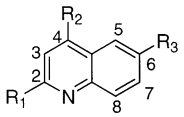
TABLE 1. Yields of Products 8 from α-Tolylsulfonyl-α,β-unsaturated Ketones 3



8a-r

compd	R_1	R_2	R_3	yield (%)
8a	4-MeOPh	4-MePh	Me	54
8b	4-MeOPh	4-MePh	OMe	60
8c	4-MeOPh	4-MePh	CF_3	55
8d	4-MeOPh	4-ClPh	Me	56
8e	4-MeOPh	4-ClPh	OMe	61
8f	4-MeOPh	4-ClPh	CF_3	60
8g	4-MeOPh	2-MePr	Me	52
8h	4-MeOPh	2-MePr	OMe	58
8i	4-MeOPh	2-MePr	CF_3	50
8j	4-MeOPh	Me	Me	51
8k	4-MeOPh	Me	OMe	58
8l	4-MeOPh	Me	CF_3	59
8m	4-ClPh	4-MePh	Me	51
8n	4-ClPh	4-MePh	OMe	55
8o	4-ClPh	4-MePh	CF_3	50
8p	Me	4-MePh	Me	48
8q	Me	4-MePh	OMe	51
8r	Me	4-MePh	CF_3	60

ketones **3**. Compounds **8p**−**r** required more elevated temperatures for elimination of the tolyl sulfone group. The four-step synthesis of trisubstituted quinolines, from readily available bromomethyl or chloromethyl ketones, aldehydes, and *N*-Boc-anilines, proceeds in overall yields of 23−50%. Methyl or substituted phenyls are introduced at positions 2 and 4 of the quinoline ring system. Position 6 is substituted with methyl, trifluoromethyl, or methoxy groups.

Conclusion

An efficient, flexible, and regiocontrolled synthesis of 2,4,6-trisubstituted quinolines from readily available bromomethyl ketones, aldehydes, and anilines is demonstrated. A tolyl sulfone group has been used to direct the chemistry, from 1,4-addition of *N*-Boc-aniline dianion to the electron-deficient olefin to the elimination of the tolyl sulfone to form the quinoline. The chemistry allows both aliphatic and aromatic ketones or aldehydes as well as anilines with electron-withdrawing or -donating groups to be employed. The overall yields in four-step synthesis are from 23 to 50%. Some differences were observed in the ease of elimination of the tolyl sulfone based on the structure of the aniline or aldehyde. Electron-rich anilines or aromatic aldehydes facilitated elimination. In contrast to traditional methods of quinoline synthesis, this reaction sequence sets position 2, then position 4, and last adds the 6 position from a 4-substituted aniline. Compound **5** or **6** provides for the possibility of alkylation prior to sulfone elimination to functionalize the 3-position of the quinoline. The known regioselectivity of dianion formation in other substituted *N*-Boc-anilines or *N*-Boc-aminoheterocycles[20] suggests the ease with which these substituted quinolines and heterocyclic pyridines could also be formed. These studies are currently in progress.

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Experimental Section

General. All reactions were performed under nitrogen. ^{1}H NMR and ^{13}C NMR spectra were recorded in ppm (δ) on a 300 MHz instrument using TMS as internal standard. Elemental analyses were performed by Robertson Micolit Laboratories. Anhydrous THF, toluene, and *tert*-butyllithium in pentane (1.7 M) were purchased. Flash chromatography was performed with silica gel 60 (230−400 mesh). Melting points were determined and are uncorrected.

2-(*p*-Toluenesulfonyl)-4′-methoxyacetophenone (2a). A mixture of 2-bromo-4′-methoxyacetophenone (45.8 g, 200 mmol) and *p*-toluenesulfinic acid sodium hydrate (35.6 g, 200 mmol) in ethanol (1 L) was heated at reflux for 1.5 h. The mixture was stirred and cooled to room temperature, and the resulting solid was collected, washed with ethanol (2 × 50 mL), dried to give 54.6 g (90%) of pure **2a**: mp 126.0−127.0 °C; IR 2951, 2906, 1676, 1599, 1572 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.45 (s, 3H), 3.90 (s, 3H), 4.67 (s, 2H), 6.95 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H), 7.95 (d, J = 8.8 Hz, 2H); ^{13}C NMR 20.9, 55.1, 62.5, 113.4 (2C), 127.7 (2C), 128.3, 129.1 (2C), 131.1 (2C), 135.8, 144.3, 163.7, 186.0. Anal. Calcd for $C_{16}H_{16}O_4S$: C, 63.14; H 5.30; S, 10.54. Found: C, 63.49; H, 5.35; S, 10.33.

1-(4′-Methoxyphenyl)-3-(4′-methylphenyl)-2-(*p*-toluenesulfonyl)-2-(*E*)-propen-1-one (3a). A mixture of **2a** (4.6 g, 15 mmol), *p*-tolualdehyde (2.0 g, 16.5 mmol), piperidine (0.18 g, 2 mmol), and acetic acid (0.42 g, 7 mmol) in toluene (40 mL) was heated at reflux for 2 h with azeotropic removal of water using a Dean−Stark trap.[13] The mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc/toluene 3:1:1) to give 5.5 g (90%) of pure **3a** as a solid: mp 141.0−142.0 °C; IR 2939, 1650, 1597, 1572 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.26 (s, 3H), 2.43 (s, 3H), 3.82 (s, 3H), 6.84 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.8 Hz, 2H), 7.93 (s, 1H); ^{13}C NMR 21.3, 21.5, 55.4, 114.0 (2C), 128.4 (2C), 128.7, 128.8, 129.5 (2C), 129.6 (2C), 130.2 (2C), 132.2 (2C), 136.9, 138.7, 140.3, 141.5, 144.4, 164.5, 190.4. The *E*-conformation was assigned by a 2D NOE experiment. Anal. Calcd for $C_{24}H_{22}O_4S$: C, 70.91; H, 5.46; S, 7.89. Found: C, 70.52; H, 5.62; S, 7.69.

1-(4′-Methoxyphenyl)-2-(*p*-toluenesulfonyl)-2(*E*)-buten-1-one (3d). A mixture of **2a** (6.08 g, 20 mmol), acetaldehyde (2.5 mL, 45 mmol), and acetic anhydride (3.0 mL, 32 mmol) in toluene (8 mL) was heated at 100 °C in a sealed reaction vessel for 3 days.[14] The mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc/toluene 3:1:1) to give 4.4 g (67%) of pure **3d** as a solid: mp 118.0−119.9 °C; IR 3072, 1654, 1608, 1584 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.72 (d, J = 7.0 Hz, 3H), 2.42 (s, 3H), 3.89 (s, 3H), 6.94 (d, J = 8.8 Hz, 2H), 7.25 (m, 1H), 7.29 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 8.1 Hz, 2H), 7.89 (d, J = 8.8 Hz, 2H); ^{13}C NMR 15.5, 21.5, 55.5, 114.1 (2C), 128.3 (2C), 129.3, 129.5 (2C), 132.2 (2C), 136.8, 140.6, 143.2, 144.4, 164.6, 189.1. Anal. Calcd for $C_{18}H_{18}O_4S$: C, 65.43; H, 5.49; S, 9.71. Found: C, 64.84; H, 5.68; S, 9.56.

***N*-(*tert*-Butoxycarbonyl)-*p*-toluidine (4a).** To a solution of *p*-toluidine (6.5 g, 60 mmol) in THF (30 mL) and 2 N NaOH (30 mL) was added di-*tert*-butyl dicarbonate (65 mL, 1.0 M in THF) slowly at room temperature. The mixture was stirred at room temperature overnight and concentrated in vacuo. The residue was diluted with EtOAc (150 mL), and the organic phase was washed with water (2 × 70 mL) and brine (50 mL) and dried ($MgSO_4$). The solution was then concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 6:1) to give 10.8 g (87%) of pure **4a** as a solid: mp 92.5−93.5 °C; IR 3355, 3336, 3000, 1697, 1597, 1529 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.55 (s, 9H), 2.30 (s, 3H), 6.32 (br s, 1H), 7.07 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H); ^{13}C NMR 20.6, 28.3 (3C), 80.2, 118.7 (2C), 129.4 (2C), 132.4, 135.7, 152.9.

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H 8.27; N, 6.67. Found: C, 69.52; H, 8.26; N, 6.67.

2-(4′-Methoxyphenyl)-4-(4′-methylphenyl)-6-methylquinoline (8a). To **4a** (518 mg, 2.5 mmol) in THF (10 mL) at −30 °C was added *t*-BuLi (3.7 mL, 6.25 mmol, 1.7 M in pentane) dropwise. The mixture was stirred at −20 °C for 2.5 h and then cooled to −50 °C. A solution of CuCN (112 mg, 1.25 mmol) and LiCl (53 mg, 1.25 mmol) in THF (1.5 mL) was added to the above mixture. After 10 min, **3a** (406 mg, 1 mmol) in THF (4 mL) was added, followed by toluene (10 mL). The mixture was stirred from −50 to −10 °C for 1 h and quenched with saturated aqueous ammonium chloride (5 mL). The reaction mixture was warmed to room temperature and diluted with EtOAc (20 mL). The organic phase was separated, washed with water (10 mL) and brine (2 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. Filtration through silica gel (hexane/EtOAc 3:1, then 1:3) was performed to remove **4a**, and the intermediate **5a** was collected. To the intermediate **5a** was added TFA (5 mL), and the mixture was stirred at room temperature for 3 h. After removal of TFA, mesitylene (10 mL) was added to the residue. The mixture was heated at reflux overnight and then concentrated in vacuo. The resulting residue was purified by flash chromatography (hexane/EtOAc 6:1) to give 183 mg (54%) of pure **8a** as a solid. mp 135.0−137.0 °C; IR 2918, 1605, 1589, 1545, 1514, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) 2.43 (s, 3H), 2.45 (s, 3H), 3.83 (s, 3H), 7.00 (d, J = 8.9 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.50 (dd, J = 1.5, 8.5 Hz, 1H), 7.63 (br s, 1H), 7.69 (s, 1H), 8.09 (d, J = 8.5 Hz, 1H), 8.12 (d, J = 8.9 Hz, 2H); ^{13}C NMR 21.2, 21.7, 55.3, 114.1 (2C), 118.8, 124.4, 125.5, 128.7 (2C), 129.2 (2C), 129.4 (2C), 129.5, 131.5, 132.3, 135.6, 135.7, 138.0, 147.3, 148.3, 155.5, 160.6; MS (APCI) $(M + H)^+$ 340. Anal. Calcd for $C_{24}H_{21}NO$: C, 84.92; H, 6.24; N, 4.13. Found: C, 84.70; H, 6.42; N, 4.04.

Supporting Information Available: Characterization data and proton and carbon NMR data for compounds **2b,c**, **3b,c,e,f**, **4b,c**, and **8b**−**r**. This material is available free of charge via the Internet at http://pubs.acs.org.

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