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Expeditious preparation of 2-substituted quinolines

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Abstract—A library of 2-substituted quinolines was synthesized in solution from mixtures of Grignard reagents and a quinolinium salt. Grignard reagents were prepared in one pot, taking advantage of the entrainment method for their preparation from unreactive alkyl halides. Then mixtures of 2-alkylquinolines were readily accessible for biological tests or separated by centrifugal-partition chromatography (CPC) prior to the biological screening.

A fast access to a large number of biologically active compounds is one of the most challenging targets for the medicinal chemist today. Combinatorial chemistry on solid support for the preparation of non-peptidic libraries has been developed by many groups.[1] However, organic reactions of large scope performed in solution remain an attractive tool for the preparation of a large variety of compounds. The ideal process would be thus to synthesize in solution a large number of compounds in one pot, then either to perform the biological tests on the mixture or to separate all substituents for individual screenings. In this letter, we wish to report some preliminary results on the one pot preparation of several 2-alkylquinolines which have been easily separated by centrifugal-partition chromatography (CPC)[2] for biological evaluations.

Several 2-alkyl- and 2-alkenylquinolines, the chimanines, have been isolated from *Galipea longiflora*[3] and have shown very promising activity against several leishmania strains,[4] and in vivo tests have demonstrated their oral leismanicide property.[5] Some activity against *Plasmodium vinckei petteri* was also expressed by some of them.[6] Therefore, we were interested in establishing some structure–activity relationships, based on the nature of the alkyl chain branched at the 2-position of quinoline. Several methods were reported for the preparation of 2-alkylpyridines;[7] however, few reports appeared in the literature concerning the synthesis of 2-substituted quinolines.[8] Webb reported that phenylmagnesium bromide added on *N*-oxycarbonylisobutyloxyquinolinium chloride at low temperature in good yield and good regioselectivity, since the desired 2-phenylquinoline was obtained without any positional isomers.[9] We thus thought that this reaction might be generalized to the preparation of 2-substituted quinolines (Fig. 1). First we performed the addition of propylmagnesium bromide onto different *N*-oxycarbonylalkyloxyquinolinium chlorides under various reaction conditions in order to find the best procedure. TLC and crude ^{1}H NMR spectra showed complete and clean formation of the desired product, when the reactions were run at low temperature.

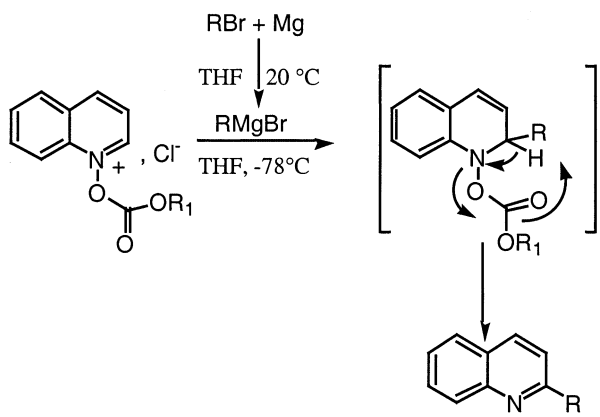

Figure 1.

Keywords: quinolines; Grignard reagents; multi-components reaction.

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Finally 2-propylquinoline was best obtained when isobutyl chloroformate was added at room temperature to quinoline *N*-oxide, followed by addition at −78°C of 1.2 equiv. of a 1 M solution of propylmagnesium bromide and, after 2.5 h of stirring, the reaction was quenched at −78°C with $NaHCO_3$. After usual workup and purification by flash chromatography through evaporation of the solvents under a slight vacuum (>30 mm Hg), the desired 2-propylquinoline was obtained in 67% yield (Table 1, entry 1). We then prepared separately several 2-substituted quinolines under the same reaction conditions as described above, in typical chemical yields ranging from 32 to 82% (Table 1). It is worth noting that primary alkyl Grignard reagents gave good yields (entries 1, 4 and 7), whereas secondary Grignard reagent such as *i*-PrMgBr gave lower yields (Table 1, entry 6). Alkenyl or alkynylmagnesium halides gave the desired products with good to excellent yields (Table 1: entries 2, 3, 5 and 8).

Then, we decided to prepare several 2-alkylquinolines, possessing very long aliphatic chains, in one pot by first preparing mixtures with odd number aliphatic chain and even number aliphatic chain Grignard reagents, mixtures **A** and **B**, respectively. Indeed, it is known that entrainment methods for the preparation of reluctant alkyl halides involve the use of active alkyl halides (e.g. ethyl bromide) in conjunction with unreactive halide to initiate the reaction by activation of the metal surface.[10] Indeed, in our case, the presence of either propyl bromide or butyl bromide with tridecanyl bromide or hexadecyl bromide, respectively, allowed us to prepare in THF the desired alkylmagnesium bromides in good yields, and therefore molar solution of several Grignard reagents. We thus prepared two different mixtures of Grignard reagents: mixture **A** containing *n*-propyl-, *n*-pentyl-, *n*-heptyl-, *n*-nonyl-, *n*-undecanyl and *n*-tridecanylmagnesium bromides and mixture **B** containing *n*-ethyl-, *n*-butyl-, *n*-hexyl-, *n*-octyl-, *n*-decyl-, *n*-dodecyl-, *n*-tetradecyl-, and *n*-hexadecylmagnesium bromides. GC analyses of hydrolyzed aliquots from these mixtures led us to conclude that all organometallic reagents were formed in similar yields (around 80% for mixtures **A** and **B**), and usual Grignard titrations[11] showed molarities ranging from 0.8 to 1 M, depending on the experiment. Then we separately added these two mixtures of Grignard reagents to a cooled solution (−78°C) containing *N*-oxycarbonylisobutyloxyquinolinium chloride, and followed the procedure described above. After work-up, the crude mixtures were first analyzed by GC, showing that the expected alkylquinolines were present equally in the mixtures. TLC of the crude mixtures showed in both cases broad spots, hardly separable by flash chromatography. Preparative HPLC analyses of these mixtures would have required large quantities of solvents, as well as the desired columns and equipment. Therefore we turned our attention to the separation by CPC (solvent[12]: heptane/CH_3CN/MeOH), which combined an inexpensive procedure (few solvent without expensive columns[13]) and a very efficient separation process.[2] Thus, all expected 2-alkylquinolines were obtained as pure materials in yields ranging from 30 to 50% (Fig. 2). Purities were checked by GC and showed to be greater to 96%. Lower yields of 2-alkylquinolines so prepared, compared to those obtained in the single reaction experiments, may be rationalized by involving two factors. The first one is due to the split of the mobile phase where 10% was flushed through the evaporating light-scattering detector[14], used as an universal detector, thus 10% of the mixture was consumed. Finally discrepancies in the observed yields is explained by the volatility of the smaller molecules compared to those of larger

Table 1.

Entry	R (of RMgBr)	Yield (%)
1	*n*-Pr	67
2	Vinyl	82
3	$Me_3SiC{\equiv}C$	53
4	But-3-en-1-yl	73
5	Prop-1-en-1-yl	68
6	*i*-Pr	32
7	*n*-Decyl	79
8	Methyl-2-prop-1-en-1-yl	63

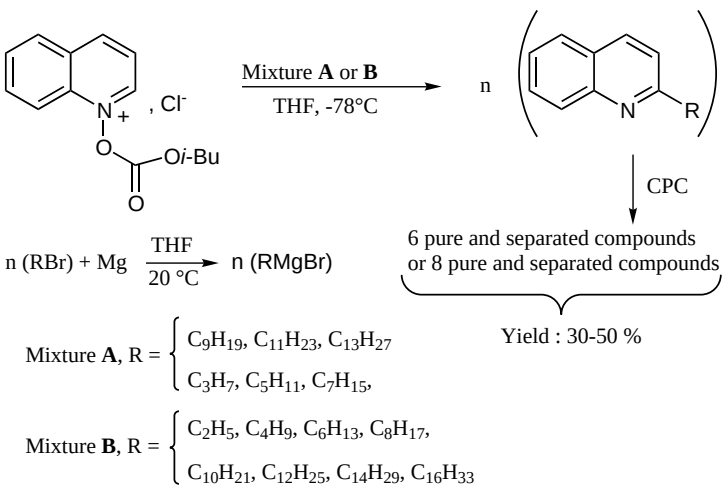

Figure 2.

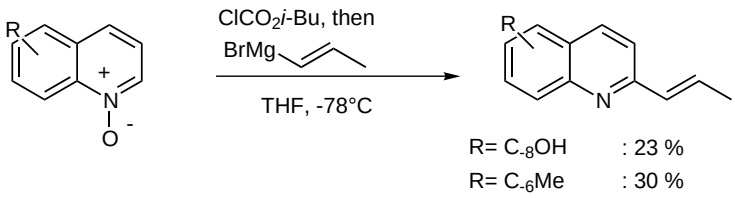

Figure 3.

molecules (as already observed for the separate preparations of 2-propylquinoline and 2-decylquinoline, see Table 1).

It is worth noting that crude mixtures could then be tested, as well as the separated quinolines so obtained, in several biological screenings (results not shown[15]).

In order to increase the structural diversity, we are now investigating both introduction of functions on the Grignard reagent and on the quinoline nucleus. For instance, 2-propenyl-8-hydroxyquinoline and 2-propenyl-6-methylquinoline have been prepared, albeit in moderate 23 and 30% yields, respectively, by applying the reaction conditions described above (Fig. 3). Optimization and generalization of this procedure is now under study.

In conclusion, this study shows for the first time that long aliphatic chain Grignard reagents can be prepared in a very efficient manner as mixtures of alkylmagnesium bromides (GC analyses as well as titration's showed no detectable cross-coupling reactions between Grignard reagents). These mixtures are synthetically useful reagents and can react, for instance, with *N*-oxycarbonylisobutyloxyquinolinium chloride at low temperature to afford the desired 2-alkylquinolines in good yields.[16] CPC allowed us to obtain the pure isolated compounds which were then submitted to different biological tests. The use of mixtures of several functionalized quinolines as starting material, in conjunction with mixtures of Grignard reagents would improve the structural diversity of the desired 2-alkylquinolines, and this is now under way in our laboratory. Indeed, the CPC technique, combined with multi-Grignard component reactions (MGCR), seems a very attractive tool for a quick access to structurally related compounds of biological interests.

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12. Stationary phase: saturated heptane with CH_3CN (200 mL); mobile phase: heptane/CH_3CN/CH_3OH (22/16/62 v/v); rotation: 1000 rpm; detector ELSD (2.1 bar at 30°C); injector: 4 g in 15 mL; MP total: 990 mL.
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15. Results of the structure–activity relationships in this series will be shortly reported elsewhere.
16. Spectroscopic data (^1H and ^{13}C NMR in $CDCl_3$ at 200 and 50 MHz, respectively, CI-MS (NH_4^+), IR) are in accord with the proposed structures. Some representative data are given: **1-(2-quinolyl)propane**: ^1H NMR (δ ppm): 1.03 (t, $J=7.3$ Hz, 3H), 1.86 (sext., $J=7.6$ Hz, 2H), 2.96 (t, $J=7.8$ Hz, 2H), 7.30 (d, $J=8.5$ Hz, 1H), 7.48 (dd, $J=7.5$, 7.3 Hz, 1H), 7.68 (dd, $J=7.4$, 7.3 Hz, 1H), 7.78 (d, $J=8.0$ Hz, 1H), 8.04 (d, $J=8.4$ Hz, 1H), 8.08 (d, $J=8.2$ Hz, 1H); ^{13}C NMR (δ ppm): 13.57, 22.77, 40.79, 120.90, 125.15, 126.30, 127.02, 128.42, 128.80, 135.61, 147.51, 162.30; CI-MS (m/z) 172 (MH^+, 100), 143 (12);

1-(2-quinolyl)ethylene: ^{1}H NMR (δ ppm): 5.66 (d, $J=10.9$ Hz, 1H), 6.26 (d, $J=17.7$ Hz, 1H), 7.04 (dd, $J=17.7$, 10.9 Hz, 1H), 7.49 (dd, $J=7.2$, 6.9 Hz, 1H), 7.60 (d, $J=8.7$ Hz, 1H), 7.69 (ddd, $J=7.0$, 8.3, 0.6 Hz, 1H), 7.77 (d, $J=7.9$ Hz, 1H), 8.06 (d, $J=9.9$ Hz, 1H), 8.08 (d, $J=8.8$ Hz, 1H); ^{13}C NMR (δ ppm): 118.26, 119.68, 126.17, 126.90, 127.34, 129.22, 129.46, 136.17, 137.87, 147.93, 155.96; CI MS (m/z) 156 (MH^+, 100); **2-(2-quinolyl)trimethylsilylethyne**: ^{1}H NMR (δ ppm): 0.30 (s, 9H), 7.52 (m, 2H), 7.69 (dd, $J=7.5$, 7.5 Hz, 1H), 7.75 (d, $J=8.4$ Hz, 1H) 8.08 (d, $J=8.4$ Hz, 1H), 8.10 (d, $J=8.3$ Hz, 1H); ^{13}C NMR (δ ppm): –0.35, 95.50, 104.19, 124.24, 126.99, 127.30, 127.40, 129.26, 129.84, 135.90, 143.09, 147.94; CI-MS (m/z) 225 (M^+, 100); **4-(2-quinolyl)butene**: ^{1}H NMR (δ ppm): 2.48 (dt, $J=7.6$, 7.0 Hz, 2H), 2.99 (t, $J=7.4$ Hz, 2H), 4.96 (m, 1H), 5.82 (dddd, $J=16.8$, 10.2, 6.6, 6.6 Hz, 1H), 7.19 (d, $J=9.2$ Hz, 1H), 7.38 (dd, $J=7.4$, 7.4 Hz, 1H), 7.59 (dd, $J=7.2$, 7.1 Hz, 1H), 7.67 (d, $J=8.0$ Hz, 1H), 7.96 (d, $J=8.4$ Hz, 2H); ^{13}C NMR (δ ppm): 33.67, 38.45, 115.12, 121.20, 125.83, 126.82, 127.00, 129.50, 130.10, 136.14, 137.70, 147.76, 161.87; EI-MS (70 eV, m/z) 183 (M^+, 71), 182 (100), 168 (53), 167 (32), 156 (23), 149 (20), 143 (18); ***E*-(2-quinolyl)propene**: ^{1}H NMR (δ ppm): 2.01 (d, $J=5.6$ Hz, 3H), 6.73 (d, $J=16.0$ Hz, 1H), 6.86 (dq, $J=16.0$, 5.6 Hz, 1H), 7.47 (dd, $J=7.6$, 7.5 Hz, 1H), 7.52 (d, $J=8.6$ Hz, 1H), 7.68 (ddd, $J=8.5$, 7.1, 1.2 Hz, 1H), 7.75 (d, $J=7.9$ Hz, 1H), 8.02 (d, $J=8.1$ Hz, 1H), 8.06 (d, $J=8.1$ Hz, 1H); ^{13}C NMR (δ ppm): 18.60, 118.70, 125.80, 127.40, 129.10, 129.50, 129.46, 130.40, 132.30, 132.70, 148.00, 156.40; ESI-MS (m/z) 170 (MH^+); **2-(2-quinolyl)propane**: ^{1}H NMR (δ ppm): 1.40 (d, $J=6.7$ Hz, 6H), 3.30 (hept, $J=6.8$ Hz, 1H), 7.35 (d, $J=8.6$ Hz, 1H), 7.48 (dd, $J=7.9$, 7.2 Hz, 1H), 7.68 (ddd, $J=6.9$, 6.8, 1.5 Hz, 1H), 7.77 (d, $J=8.0$ Hz, 1H), 8.05 (d, $J=8.9$ Hz, 1H), 8.09 (d, $J=8.6$ Hz, 1H); ^{13}C NMR (δ ppm): 22.24, 36.94, 118.96, 125.30, 126.67, 127.11, 128.79, 129.01, 136.01, 147.53, 167.24; ESI-MS (m/z) 172 (MH^+, 100); **1-(2-quinolyl)decane**: ^{1}H NMR (δ ppm): 0.87 (t, $J=6.6$ Hz, 3H), 1.20–1.48 (m, 14H), 1.81 (quint., $J=7.5$ Hz, 2H), 2.96 (t, $J=7.9$ Hz, 2H), 7.29 (d, $J=8.6$ Hz, 1H), 7.47 (dd, $J=7.9$, 7.2 Hz, 1H), 7.67 (ddd, $J=8.4$, 7.1, 1.2 Hz, 1H), 7.76 (d, $J=8.2$ Hz, 1H), 8.05 (d, $J=8.3$ Hz, 2H); ^{13}C NMR (δ ppm): 14.04, 22.62, 26.84, 29.26, 29.51, 30.02, 31.84, 39.34, 121.26, 125.50, 127.37, 127.13, 128.78, 129.18, 136.03, 147.83, 163.01; CI-MS (m/z) 270 (MH^+, 100); **1-(2-quinolyl)-2-methylpropene**: ^{1}H NMR (δ ppm): 2.01 (s, 3H), 2.17 (s, 3H), 6.52 (s, 1H), 7.32 (d, $J=8.4$ Hz, 1H), 7.47 (dd, $J=7.3$, 7.2 Hz, 1H), 7.67 (ddd, $J=7.1$, 6.9, 1.2 Hz, 1H), 7.75 (d, $J=7.8$ Hz, 1H), 8.04 (d, $J=8.4$ Hz, 1H), 8.06 (d, $J=8.4$ Hz, 1H); ^{13}C NMR (δ ppm): 19.78, 27.26, 122.17, 125.22, 125.50, 126.03, 127.14, 128.94, 129.06, 135.40, 142.20, 147.80, 157.51; ESI-MS (m/z) 184 (MH^+, 100).