Regioselective Addition of Grignard Reagents to New Lipophilic Isoquinolinium Salts Applied to the Synthesis of Stable Ethyl 1,2-disubstituted 1,2-Dihydroisoquinoline-3-carboxylates and Derivatives

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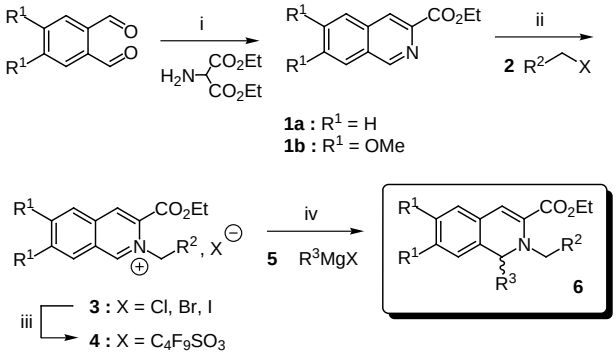
Abstract: New and stable ethyl 1,2-disubstituted 1,2-dihydroisoquinoline-3-carboxylates **6** and **12a** were synthesized in good yields by regioselective addition reactions of alkyl Grignard reagents to lipophilic and soluble isoquinolinium salts **4** and **11**. The salts **4** and **11** were obtained quantitatively and directly from isoquinoline-3-carboxylates **1**(**a,b**) with the corresponding alkyl halides **2** or symmetric alkyl dihalides **7** using solventless quaternization reaction conditions and were converted into the corresponding isoquinolinium perfuorobutanesulfonates **4** and **11a** by ionic metathesis.

Key words: 1,2-dihydroisoquinoline, Grignard reaction, lipophilic isoquinolinium salt, ionic methathesis, solvent-free quaternization

1,2-Dihydroisoquinoline-3-carboxylates[1] (DIC) and 1,2,3,4-tetrahydroisoquinoline-3-carboxylates[2] (TIC) have been recently a popular area in the synthesis of conformationally constrained peptides or non-peptides structures for SAR analysis. These peptidomimetics[3] often provide enhanced biological activities and greater proteolytic stabilities. There are at present several different methods for the preparation of substituted 1,2-dihydroisoquinoline derivatives which has often been considered to be unstable species: 1) addition reactions of organometallic reagents[4] such as organolithium, Grignard,[5] organozinc,[6] metallocarbene complexes,[7] and also allylsilanes[8] to isoquinolinium salts, 2) reduction of isoquinolines or isoquinolinium salts,[9] 3) construction of the 1,2-dihydroisoquinoline skeleton by the well-known Bischler-Napieralsky ring cyclization[10] or 4) Wittig reaction of *N*-alkoxycarbonylcarbamates with ω-halogenated phosphorus ylides.[11] Among these methods, the addition of Grignard reagents to Zincke's salts[12] provides a very practical entry to various chiral 1-substituted 1,2-dihydroisoquinolines[12] but these intermediates are unstable in air and are rather difficult to purify.

Our interest in this field was to develop a practical entry to stable 1,2-disubstituted 1,2-dihydroisoquinoline bearing an electron-attracting carboxyl function adjacent to the imino bond via Grignard reaction[13] using lipophilic isoquinolinium salts. Herein we report our preliminary results concerning synthesis of the hitherto unknown 1,2-disubstituted 1,2-isoquinoline-3-carboxylate and its derivatives. The sequence is outlined in Scheme 1.



Scheme 1 (i) EtONa (1.2 equiv.), dry EtOH, Δ, $MgSO_4$, 4 h. (ii) **2** (2.5 equiv.), 90 °C, 4 h. (iii) $nC_4F_9SO_3K$ (1.5 equiv.), dry EtOH, Δ, 12 h. (iv) **5** (4 equiv.), THF, 25 °C, 12 h. then saturated NH_4Cl.

The starting ethyl isoquinoline-3-carboxylate **1a** and ethyl 6,7-dimethoxy isoquinoline-3-carboxylate[14] **1b** were readily obtained on large scale by a "one pot" domino reaction[15] using diethyl aminomalonate and the respective 1,2-dialdehydes.

To prepare the *N*-substituted 3-ethoxycarbonyl-isoquinolinium salts **3** (Scheme 1), we have developed and tested two experimental procedures. In method A, a mixture of **1a** and alkyl halide **2** (2.5 equiv.) was refluxed in the appropriate solvent (acetone or ether[16]) with vigorous stirring during 3 days. Then, the solution was allowed to cool down at room temperature and the insoluble isoquinolinium salt **3**(**a-e**) was filtered off, washed twice with ether (20 mL) and dried under reduced pressure. In method B, the preparation of isoquinolinium salts **3**(**f-i**) was easily achieved without solvent by heating a mixture of **1b** with the appropriate alkyl halide **2** (2.5 equiv.) at 90 °C for a reaction time of 4 hours. The precipitated salt was also washed with ether (3 × 20 mL). The results summarized in Table 1, show that the *N*-substituted isoquinolinium salts **3**(**a-i**) were obtained in yields ranging from 60% to 96%. We therefore selected a lipophilic 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate group,[17] which, in addition to being less nucleophilic than the starting halide (X = I, Br, Cl), should provide salts **4** with better solubility in organic solvents, particularly in hot THF. As expected, these new salts **3** gave good yields for the *N*-substituted derivatives **4**(**a-d**) (Table 1) by simply stirring salts **3** with potassium perfluorobutanesulfonate (1.5 equiv.) in dry refluxing ethanol.[18] After elimination of ethanol in vacuo, formation of

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Table 1 Isoquinolinium Salts Prepared by Quaternization and Ionic Metathesis Reactions.

Salt	R^1	R^2	n	X	Reaction conditions	Yield (%)[a]
3a	H	H	-	I	Me_2CO, Δ, 72 h	76
3b	H	CO_2Et	-	Br	Et_2O, Δ, 72 h	75
3c	H	CN	-	Br	Et_2O, Δ, 72 h	96
3d	H	C_6H_5	-	Br	Et_2O, Δ, 72 h	82
3e	MeO	H	-	I	Me_2CO, Δ, 72 h	76
3f	MeO	CO_2Et	-	Br	90 °C, 4 h	86
3g	MeO	CN	-	Br	90 °C, 4 h	60
3h	MeO	C_6H_5	-	Br	90 °C, 4 h	76
3i	H	$CH=CH_2$	-	Br	Et_2O, Δ, 72 h	83
4a	H	H	-	NfO[b]	EtOH, Δ, 12 h	66
4b	H	CO_2Et	-	NfO[b]	EtOH, Δ, 12 h	83
4c	H	C_6H_5	-	NfO[b]	EtOH, Δ, 12 h	88
4d	MeO	C_6H_5	-	NfO[b]	EtOH, Δ, 12 h	76
10a	H	-	1	Br	90 °C, 4 h	90
10b	H	-	2	Br	90 °C, 4 h	75
11a	H	-	1	NfO[b]	EtOH, Δ, 12 h	91
14b	H	-	2	Cl	90 °C, 4 h	53
14b'	H	-	2	NfO[b]	EtOH, Δ, 12 h	93

[a] Isolated yield.
[b] NfO = 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate or perfluorobutanesulfonate.

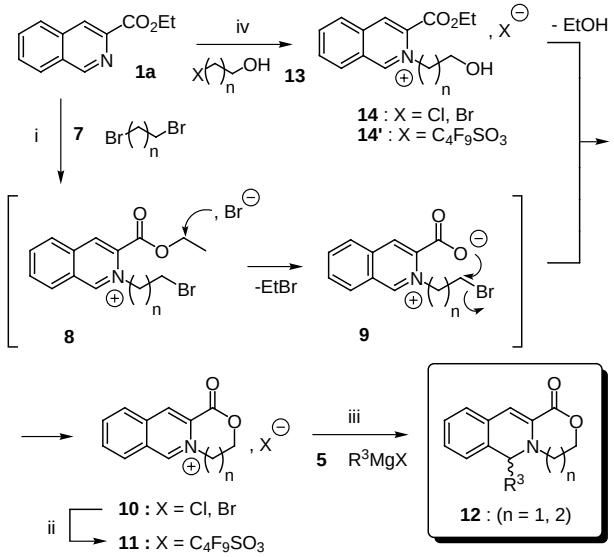
a precipitate, characterized as a crystalline solid, was obtained in ether at ambient temperature. The choice of the perfluorobutanesulfonate as counteranion was also guided by the fact that this permitted simple analysis of the isoquinolinium core by ^1H NMR spectroscopy.

With salts **4**(**a-d**) in hand, we then studied their reaction with alkyl, phenyl and benzyl Grignard reagents **5**. Reaction in a solvent such as Et_2O gave disappointing results due to the insolubility of these salts in this solvent. Thus, drop wise addition of a solution of salts **4** in dry THF to an excess (4 equiv.) of the corresponding alkyl Grignard reagent **5** at room temperature led, after a reaction time of 12 hours followed by addition of a saturated NH_4Cl solution in the crude reaction mixture, to the expected ethyl disubstituted 1,2-dihydroisoquinoline-3-carboxylates **6**(**a-e**) (Table 2) which were stable in air after purification by chromatography on silica gel. Their full structures were substantiated by the ^1H, ^{13}C NMR and HRMS analyses[19]. In contrast, when experiments were performed with a large excess of phenyl or benzylmagnesium bromide (4–16 equiv.), the corresponding 1,2-dihydroisoquinolines **6**(**f-h**) were recovered in poor yields (~5%) together with decomposition by-products of salts **4**, this may be due to the low reactivity of the electrophilic iminium moiety (C-1) bearing an electron withdrawing group in C-3 position.

Table 2 Ethyl 1,2-Dihydroisoquinoline-3-carboxylates **6**(**a-h**) and **12a** Prepared by Grignard Reaction from Salts **4**(**a-d**) and **11a**.

Product	R^1	R^2	n	R^3	Yield (%)a
6a	H	H	-	Et	82
6b	H	C_6H_5	-	Me	60
6c	MeO	C_6H_5	-	Me	51
6d	H	H	-	C_6H_5	(30)[b]
6e	H	$CH=CH_2$	-	Me	65
6f	H	C_6H_5	-	C_6H_5—≡—[c]	(30) 10[d,e]
6g	H	C_6H_5	-	$C_6H_5CH_2$	(5)[b]
6h	H	C_6H_5	-	C_6H_5	(5)[b]
12a	H	-	1	Me	53

[a] Isolated yield.
[b] Yield determined by 200 MHz ^1H NMR analysis of the crude reaction mixture.
[c] The reaction was performed using methylmagnesiumiodide and phenylacetylene.
[d] Yield in parentheses determined by 200 MHz ^1H NMR analysis of the crude reaction mixture and isolated yield after purification by chromatography on silica gel 60F 254 (Merck).
[e] For long storage, it is recommendable to handle **6f** under an inert atmosphere at 4 °C.



Scheme 2 *Reagents and reaction conditions :* (i) **7** (2.5 equiv.), 90 °C, 4 h. (ii) $nC_4F_9SO_3K$ (1.5 equiv.), dry EtOH, Δ, 12 h. (iii) **5** (4 equiv.), THF, 25 °C, 12 h. then saturated NH_4Cl. (iv) 2-bromoethanol **13a** (2.5 equiv.), 90 °C, 4 h; or 3-chloropropanol **13b** (2.5 equiv.), 90 °C, 3 days.

In a similar way, we have also studied the quaternization reaction of **1a** with 1,2-dibromoethane (**7a**) (n = 1) and 1,3-dibromopropane (**7b**) (n = 2) using solventless reaction conditions (Scheme 2). Reaction of **1a** with the dibromoalkanes **7** (2.5 equiv.) at 90 °C during 4 hours affords directly the respective precipitated 1-oxo-3,4-dihydro-1*H*-2-oxa-4a-azonia-anthracene bromide (**10a**)[20] and the 10-oxo-6,7,8,10-tetrahydro-9-oxa-5a-azonia-cyclohepta[*b*]naphthalene bromide (**10b**) in good yields (**10a**: 90% and **10b**: 75%) via the intermediates **8** and **9** which could not be isolated. We tried to analyze this domino reaction by ^{1}H NMR and we could observe the formation of **10** and the disappearance of the signal for the ethyl ester group (C-3) of **1a**. This "one-pot" process involves successively: (a) a quaternization reaction between **1a** and **7** to give in situ **8** followed by (b) a nucleophilic substitution to produce **9** which undergoes (c) lactonization to provide salt **10**.

We have also examined the direct synthesis of the lactone salts[21] **10** by a quaternization reaction with a mixture of **1a** and the respective halogenoalcohol **13(a,b)** (2.5 equiv.) using the same reaction conditions (Scheme 2). After 4 hours at 90 °C with 2-bromoethanol (**13a**)**,** the ^{1}H NMR spectrum of the crude reaction mixture exhibits signals which can be assigned to **10a** (n = 1), but with 3-chloropropanol (**13b**), **1a** was only converted into 3-ethoxycarbonyl-2-(3-hydroxy-propyl)-isoquinolinium chloride (**14b**) (n = 2) in moderate yield (53%) after a reaction time of 3 days (Table 1). Initial attempts to force the reaction to completion were unsuccessful (no amount of the corresponding lactone salt **11b** was detected in the ^{1}H NMR of the reaction mixture).

In the same way, subsequent anion methathesis of salt **10a** with $C_4F_9SO_3K$ (1.5 equiv.) in refluxed ethanol (12 hours) afforded the soluble salt **11a** in high yields but with **11b** the anion metathesis failed and gave exclusively the 3-ethoxy-2-(3-hydroxypropyl)-isoquinolinium perfluorobutanesulfonate (**14'b**, Table 1). Finally, regioselective addition of methylmagnesium iodide (4 equiv.) in dry THF at room temperature has also been successfully applied to the lipophilic salts **11a** after 12 hours. Under these conditions the new compound **12a** was obtained in moderate yield (53%) and was stable after purification by chromatography on silica gel.

In summary, we have developed an efficient method for the preparation of new and stable ethyl 1,2-disubstituted 1,2-dihydroisoquinoline-3-carboxylates[22] via regioselective addition reactions of Grignard reagents to the corresponding lipophilic isoquinolinium salts **4** and **11a**. The extension of this strategy to other nucleophilic reagents with chiral isoquinolium salts bearing an electron withdrawing group is underway.

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(16) Experimental procedure for the preparation of *3-ethoxycarbonyl-2-phenylmethyl-isoquinolinium bromide* (**3d**): A mixture of ethyl isoquinoline-3-carboxylate (**1a**; 1 g, 10 mmol) and benzyl bromide (**2d**; 1.7 g, 10 mmol) in dry Et_2O (25 mL) was refluxed with vigorous magnetic stirring during 3 days under nitrogen. The reaction mixture was allowed to cool down at ambient temperature. The insoluble salt **3** was filtered off, washed twice with Et_2O(20 mL) and dried in a dessicator over $CaCl_2$ which gave **3** in 90% yield as white needles (mp 132-134 °C). ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.32 (t, 3 H, *J* = 7 Hz); 4.42 (q, 2 H, *J* = 7 Hz); 6.63 (s, 2 H); 7.31 (m, 5 H, Ar); 8.08 (t, 1 H, *J* = 7.6 Hz, H-6, H-7); 8.29 (t, 1 H, *J* = 7.4 Hz, H-6, H-7); 8.46 (d, 1 H, *J* = 8 Hz, H-5, H-8); 8.97 (d, 1 H, *J* = 7.4 Hz, H-5, H-8); 8.98 (s, 1 H, H-4); 11.82 (s, 1 H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 14.00 (qt, *J* = 128, 2.4 Hz); 62.55 (tq, *J* = 149 Hz); 65.54 (tq, *J* = 149, 4.4 Hz); 128.26 (dm, *J* = 139 Hz); 128.46 (m, C_{ipso}, Ar); 128.56 (dd, *J* = 136, 4.3 Hz, C-2', C-3'); 129.30 (dd, *J* = 162, 4.6 Hz, C-2', C-3'); 129.60 (dm, *J* = 161 Hz, C-6, C-7); 130.44 (dm, *J* = 114 Hz, C-6, C-7); 132.27 (dd, 134, 4.5 Hz, C-5, C-8); 133.20 (m, C-4a, C-8a); 133.34 (m, C-4a, C-8a); 133.54 (dd, *J* = 167, 7.9 Hz, C-5, C-8); 136.76 (m, C-3); 138.70 (dd, *J* = 166, 8 Hz, C-4); 156.00 (dm, *J* = 195, 5.4 Hz, C-1); 161.00 (m, CO).

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(18) Experimental procedure for the preparation of *3-ethoxycarbonyl-2-phenylmethyl-isoquinolinium perfluorobutane sulfonate* (**4c**) by ionic metathesis: **4c** was prepared from a mixture of **3d** (1 g, 2.68 mmol) and $nC_4F_9SO_3K$ (2.3 g, 6.72 mmol) in dry refluxing EtOHwith vigorous magnetic stirring with a reaction time of 12 hours. After filtration and removal of solvent in a rotary evaporator, the crude reaction mixture was triturated with dry Et_2O (20 mL). After standing for 2 hours, the precipitated product was filtered off, washed with Et_2O (2 × 20 mL) and dried under reduced pressure. The salt **4** was obtained in 86% yield as colorless needles (mp 92-94 °C).

(19) Preparation of *ethyl 1-methyl-2-phenylmethyl-1,2-dihydro isoquinoline-3-carboxylate* (**6b**) by Grignard reaction: A solution of methylmagnesiumiodide (2.23 g, 13.44 mmol) in dry THF (20 mL) was added drop wise at room temperature under nitrogen during 30 min to a stirred suspension of 3-ethoxycarbonyl-2-phenylmethyl-isoquinolinium perfluorobutane sulfonate (**4c**; 0.5 g, 0.84 mmol) in anhydrous THF (10 mL). The mixture was stirred 12 hours at ambient temperature. The resulting mixture was poured into a vigorously stirred solution of aqueous saturated NH_4Cl. The organic phase was collected by decantation, dried with $MgSO_4$ and was concentrated under reduced pressure. After addition of CH_2Cl_2 (20 mL) to the crude reaction mixture, the organic solution was filtered off and after removal of solvent in vacuo, the crude product **6b** was purified by chromatography on silica gel 60F 254 (Merck)using methylene chloride–petroleum ether 40-60 (1:1) as eluent (R_f = 0.3), affording pure and stable compound **6b** (0.2 g, 80%) as brown viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.09 (d, 3 H, *J* = 7 Hz); 1.34 (t, 3 H, *J* = 7 Hz); 4.14–4.35 (m, 5 H); 6.89 (t, 1 H, *J* = 7.5 Hz, H-6, H-7); 6.98 (s, 1 H, H-4), 7.17–7.29 (m, 7 H, Ar); 7.41 (d, 1 H, *J* = 7 Hz, H-5, H-8). ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 14.32 (qt, *J* = 125, 2.4 Hz); 21.53 (qd, *J* = 124, 4 Hz); 55.69 (tm, *J* = 136, 4.9 Hz); 56.04 (dm, *J* = 133 Hz, C-1); 61.42 (tq, *J* = 148, 4.3 Hz); 117.30 (dd, *J* = 166, 3.4 Hz, C-4); 125.44; 125.54; 127.10; 127.20; 128.30; 128.40; 128.50; 130.20 (m, C_{ipso}, Ar); 134.80 (m, C-4a, C-8a); 135.10 (m, C-4a, C-8a); 139.30 (m, C-3); 165.60 (CO). HRMS, *m/z* = 307.3869 found (calculated for $C_{20}H_{21}NO_2$ requires 307.3863).

(20) Selected spectral data of *1-oxo-3,4-dihydro-1H-2-oxa-4a-azonia-anthracene bromide*(**10a**): ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 5.03 (t, 2 H, *J* = 7.4 Hz); 5.22 (t, 2 H, *J* = 7.4 Hz); 8.21 (t, 1 H, *J* = 7 Hz, H-8, H-9); 8.33 (t, 1 H, *J* = 7.2 Hz, H-8, H-9); 8.40 (d, 1 H, *J* = 8.4 Hz, H-7, H-10); 8.56 (d, 1 H, *J* = 8.1 Hz, H-7, H-10); 9.24 (s, 1 H, H-6); 9.89 (s, 1 H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 55.60 (tt, *J* = 150, 4.7 Hz, C-9, C-10); 68.70 (tt, *J* = 160, 4.4 Hz, C-9, C-10); 130.97 (m, C-4a, C-8a); 131.20 (m, C-4a, C-8a); 132.00 (dt, *J* = 140, 4.4 Hz, C-5, C-8); 133.72 (d, *J* = 170 Hz, C-6, C-7); 133.96 (dd, *J* = 175, 4.7 Hz, C-5, C-8); 137.00 (dd, *J* = 159, 4 Hz, C-6, C-7); 139.85 (C-3); 141.20 (dd, *J* = 190, 6 Hz, C-4); 153 (dm, *J* = 190 Hz, C-1); 161.80 (CO).

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