

CeCl₃·7H₂O/NaI-promoted Efficient Alkylation of Activated Quinoline and Isoquinoline

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Active methylene compounds undergo smooth addition to quinolines and isoquinolines activated by chloroformate in the presence of CeCl₃·7H₂O/NaI to afford 2-alkyl-1,2-dihydroquinoline and 1-alkyl-1,2-dihydroisoquinoline, respectively in excellent yields with high selectivity.

Addition reactions of activated aza-aromatics is of great importance for the synthesis of biologically active nitrogen heterocycles, including alkaloids.¹ Because of the activity of quinoline and isoquinoline derivatives as anti-bacterial, anti-malarial, and anti-inflammatory, the synthesis of their new analogues is of prime importance in the field of medicinal chemistry. A wide variety of 2-substituted quinoline and isoquinoline analogs are synthesized by using organometallic compounds via C–C bond formation.^{2–5} Addition of isocyanides to *N*-acylazinium salts has been reported as an alternative process for Reissert synthesis via Ugi-type reaction.⁶ Recently, alkylation of quinoline and isoquinoline activated by diethyl pyrocarbonate with alkylating agents has been reported using anhydrous LiCl.⁷ However, this method provide the products as a mixture of regioisomers and also found to be ineffective for electron-deficient quinolines. Thus, there is still scope to develop a simple and efficient route for the alkylation of *N*-acylated aza-aromatic system using cheap and readily available reagents.

Lanthanide salts are unique Lewis acids that are currently of great research interest. In particular, cerium(III) chloride (CeCl₃·7H₂O) has gained much popularity, owing to its unique reactivity, ease of handling, low toxicity, and moisture and air tolerance.⁸ It has been extensively used for various regio- and chemoselective organic transformations.⁹

In continuation of our interest toward the development of novel methodologies for the derivatization of quinoline and isoquinolines,¹⁰ we report herein the direct addition of alkylating agents to various quinolines and isoquinolines activated by ethyl chloroformate in the presence of CeCl₃·7H₂O to afford 2-alkyl-1,2-dihydroquinolines, and 1-alkyl-1,2-dihydroisoquinolines with high selectivity. For instance, when quinoline (**1**) activated by ethyl chloroformate was treated with diethyl malonate (**2**) in the presence of 30 mol % CeCl₃·7H₂O in dichloromethane at ambient temperature 2-alkyl-1,2-dihydroquinoline **3a** was obtained in 60% yield. However, the addition of catalytic amount NaI (5 mol %) improved the yield of **3a** to 80% (Scheme 1).

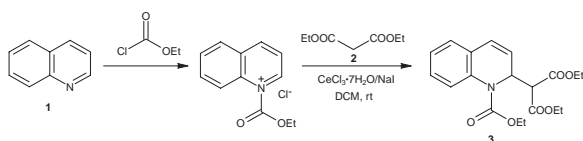
In a similar fashion, various alkylating agents bearing an active methylene group underwent smooth addition to *N*-acylated

quinolinium ions to produce the corresponding 2-alkyl-1,2-dihydroquinoline derivatives in high yields. In all the cases, addition took place at the 2-position of quinoline selectively. The reactions proceeded rapidly with electron-rich quinolines. It is noteworthy that electron-deficient nitro-substituted quinolines also reacted well to give the corresponding addition products. The reaction of *N*-acylquinolinium ion with dimedone also showed corresponding dihydroquinoline adduct in good yield. Similarly, isoquinolines also underwent smooth addition with active meth-

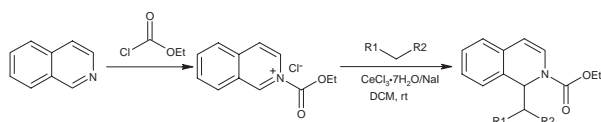
Table 1. CeCl₃·7H₂O/NaI-catalyzed alkylation of quinoline and isoquinoline activated by chloroformate

Entry	Aza-aromatics	alkylating agent	Product ^{a,b}	Time /h	Yield ^c /%
a		Diethyl malonate		3.4	80
b		Diethyl malonate		4.0	82
c		Diethyl malonate		4.0	78
d		Acetylacetone		4.4	70
e		Dibenzoylmethane		5.2	78
f		Benzyl picolinyl acetate		4.8	68
g		Dimedone		5.5	75
h		Diethyl malonate		6.0	60
i		Dimethyl malonate		6.2	88
j		Dibenzoylmethane		6.0	70
k		Methyl 4,4-dimethyl-3-oxopentanoate		5.8	65
l		Ethyl benzoylacetate		5.5	75
m		Methyl 4,4-dimethyl-3-oxopentanoate		5.4	80
n		Diethyl malonate		5.0	60
o		Diethyl malonate		5.4	58

^aR = CO₂Et. ^bAll products were characterized by ¹H NMR, IR, and MS spectroscopy. ^cIsolated and unoptimized yields after column chromatography.



Scheme 1.



Scheme 2.

ylene compounds leading to the formation of 1-alkyl-1,2-dihydroisoquinolines (Scheme 2). The products thus obtained were characterized by ^1H NMR, IR, and mass spectroscopy.

The reaction conditions are mild so that no side products or decomposition of the products is observed. Dichloromethane is the solvent of choice giving best results. Although these reactions can be accomplished using cerium chloride without NaI, long reaction times and low yields of products were observed when compared to $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}/\text{NaI}$ system. This clearly indicates that sodium iodide activates the CeCl_3 to accelerate the reaction. In the absence of CeCl_3 , the reaction did not occur. Among various rare earth metal salts such as YbCl_3 , YCl_3 , $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$, and SmCl_3 studied for this reaction, $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ was found to be more effective and superior in terms of conversion and reaction times. The scope and generality of this process is illustrated with respect to various substituted quinolines, isoquinolines, and alkylating agents and the results are summarized in Table 1.

In summary, we have described $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}/\text{NaI}$ -catalyzed alkylation of activated quinolines and isoquinolines, providing straightforward route for the synthesis of alkylated dihydroquinolines and dihydroisoquinolines with high regioselectivity which may be valuable synthetic intermediates for alkaloids and related nitrogen heterocyclic compounds.

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- General procedure:** To a stirred solution of quinoline or isoquinoline (130 mg, 1 mmol) in dichloromethane (2 mL) was added ethyl chloroformate (163 mg, 1.5 mmol) at ambient temperature. The reaction mixture was stirred for 30 min. To this mixture was added active methylene compound (161 mg, 1 mmol) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}/\text{NaI}$ (75 + 15 mg, 30 mol %). After completion of the reaction, as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (2×15 mL). The combined organic extracts were washed with 10% hypo solution, dried over Na_2SO_4 , concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh ethyl acetate–hexane (2:8) to afford the corresponding alkylated product. Spectral data for selected compound: **3a**: ^1H NMR (200 MHz) δ 1.19 (t, 3H, $J = 7.5$ Hz), 1.29 (t, 3H, $J = 7.5$ Hz), 1.33 (t, 3H, $J = 6.8$ Hz), 3.3 (d, 1H, $J = 9.8$ Hz), 3.96–4.33 (m, 6H), 5.66 (dd, 1H, $J = 6.0, 3.7$ Hz), 6.2 (dd, 1H, $J = 3.0, 6.0$ Hz), 6.54 (d, 1H, $J = 9.0$ Hz), 7.1 (d, 2H, $J = 4.6$ Hz), 7.23 (m, 1H), 7.53 (d, 1H, $J = 6.8$ Hz). IR (KBr): ν 2982, 1731, 1489, 1474, 1457, 1397, 1255, 1153, 1095, 1032, 764 cm^{-1} . FABMS: m/z : 361 (M^+), 288, 202, 130, 95, 81, 69, 55. **3g**: ^1H NMR (200 MHz, $\text{CDCl}_3 + \text{DMSO}$) δ 1.0 (s, 6H), 1.28 (t, 3H, $J = 7.2$ Hz), 2.1 (s, 2H), 2.27 (s, 2H), 4.17 (q, 2H, $J = 7.2$ Hz), 6.40 (s, 1H), 6.72 (s, 1H), 6.94 (m, 2H), 7.12 (m, 1H), 7.60 (d, 1H, $J = 9.0$ Hz), 10.4 (brs, 1H). IR (KBr): ν 3459, 2957, 1706, 1637, 1576, 1490, 1376, 1291, 1230, 1059, 757 cm^{-1} . FABMS: m/z : 420 (M^+), 346, 340, 307, 289, 280, 176, 165, 154, 136, 120, 107, 95, 89, 77, 67, 55. **3k**: ^1H NMR (300 MHz, CDCl_3) δ 1.06 (s, 9H), 1.38 (t, 3H, $J = 7.6$ Hz), 3.46 (s, 3H), 4.0 (d, 1H, $J = 6.8$ Hz), 4.30 (m, 2H), 5.74 (t, 1H, $J = 6.8$ Hz), 6.31 (dd, 1H, $J = 3.8, 6.0$ Hz), 6.6 (d, 1H, $J = 9.8$ Hz), 7.76 (d, 1H, $J = 9.0$ Hz), 7.98 (d, 1H, $J = 2.3$ Hz), 8.1 (dd, 1H, $J = 2.3, 6.8$ Hz). IR (KBr): ν 2974, 1715, 1610, 1578, 1521, 1485, 1434, 1343, 1278, 1239, 1158, 1044, 747 cm^{-1} . FABMS: m/z : 404 (M^+), 331, 247, 203, 175, 129, 77, 57. **3o**: ^1H NMR (300 MHz, CDCl_3) δ 1.10 (t, 3H, $J = 6.8$ Hz), 1.28–1.48 (m, 6H), 3.67 (d, 1H, $J = 9.0$ Hz), 4.0 (m, 2H), 4.15 (q, 2H, $J = 6.8$ Hz), 4.24 (q, 2H, $J = 6.8$ Hz), 6.09 (d, 1H, $J = 9.0$ Hz), 7.15 (s, 1H), 7.22 (t, 1H, $J = 7.5$ Hz), 7.26 (d, 1H, $J = 5.2$ Hz), 7.32 (t, 1H, $J = 7.5$ Hz), 7.50 (d, 1H, $J = 7.5$ Hz). IR (KBr): ν 2984, 1725, 1617, 1568, 1479, 1456, 1378, 1251, 1168, 1034, 762 cm^{-1} . FABMS: m/z : 439 (M^+), 282, 280, 238, 236, 210, 208, 191, 133, 123, 109, 95, 81, 69, 55.