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Syntheses of allyldihydroquinolines: indium-mediated allylations of EEDQ in the presence of acetic acid

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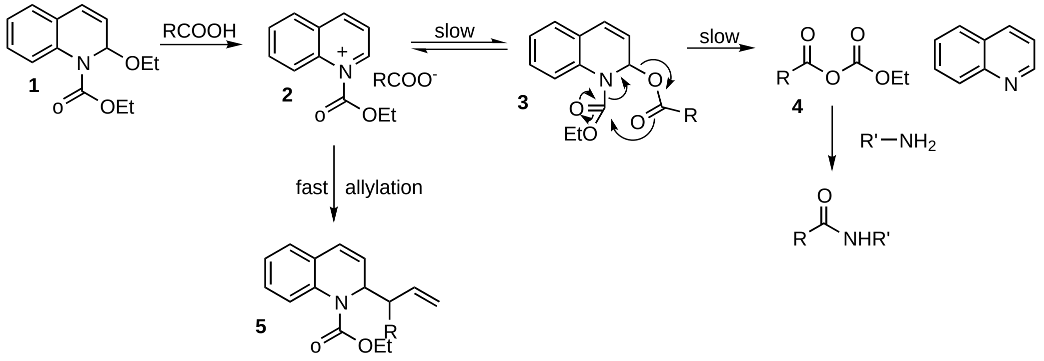
Abstract—Indium-mediated allylations of EEDQ with various allyl bromides in the presence of 1.2 equiv. of acetic acid at rt gave the corresponding allylated dihydroquinolines with high α selectivities in high yields. The allylations of EEDQ with limited allyltins and allylsilane in the presence of $BF_3{\cdot}Et_2O$ at rt gave the corresponding allylated products in high yields. © 2002 Elsevier Science Ltd. All rights reserved.

Addition reactions of activated aza-aromatics with organometallic reagents are of great importance for the synthesis of biologically active nitrogen compounds including alkaloids.[1] Generally, aza-aromatics were activated by chloroformate and acyl chloride. Nucleophilic reactions of allylic metal reagents such as allyltins and allylsilanes have been extensively studied to introduce allylic groups as a versatile carbon functionality.[2] The Yamaguchi group reported that allyltins react readily with activated aza-aromatics in chemo and regioselective manner, providing an efficient method for introducing allylic substituent into nitrogen heterocycles.[3] Although allylsilanes were widely utilized as an useful carbon nucleophiles, it has been proven that they are not nucleophilic enough to react with pyridine acylated by methyl chloroformate.[3a]

Considering that the allylsilanes are less reactive[4] and allyltins are toxic in addition to anhydrous condition and commercial availability of two reagents, an alternative and complementary allylating reagent which is nontoxic and reasonably reactive is needed to be developed. As the reagent, in situ generated allylindium has been emerged as a new protocol in allylation.[5]

EEDQ, 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline, has been known as a coupling reagent[6] in the peptide synthesis and as a reagent in the protection of 2-hydroxycarboxylic acid.[7] The two reactions are reported to proceed through a mixed carbonic anhydride **4** formed from carboxylic acid adduct **3**, which in turn is formed from *N*-acylquinolinium ion **2** as shown in Scheme 1. Involvement of *N*-acylquinolinium ion as an intermediate occurs to us that EEDQ could be allylated using allylating reagents under controlled condition. The success of allylation in the presence of a carboxylic acid as an activating agent are depending on the relative nucleophilicity of allylindium and carboxyl-



Scheme 1.

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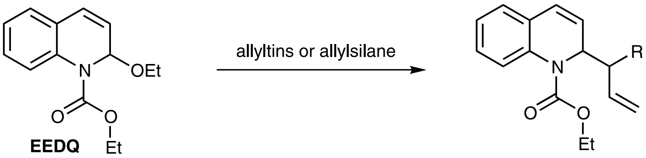
ate. If the nucleophilicity of allylindiums toward *N*-acylquinolinium ion **2** is better than that of a carboxylate, allylated dihydroquinolines could be obtained successfully.

Here, we report efficient indium mediated allylations of EEDQ with various allyl bromides and indium, and allylations of EEDQ with allyltins and allylsilane. EEDQ was allylated using various allyl bromides (1.2 equiv.) and indium (1.2 equiv.) in the presence of 1.2 equiv. of acetic acid in THF at rt to give the corresponding allylated dihydroquinolines in high yields (Scheme 2). EEDQ also was allylated using 1 equiv. of allyltributyltin, prenyltributyltin and allyltrimethylsilane in the presence of $BF_3 \cdot Et_2O$ (1.1 equiv.) in methylene chloride at rt to give the corresponding allylated dihydroquinolines in high yields (Scheme 3).

The indium-mediated allylations were studied systematically in the presence of various amounts of acetic acid as one of carboxylic acids (Table 1)[8] and in various solvent systems such as DMF, THF, EtOH and water (Table 2). At first, a systematic study using allyl bromide as a model was conducted to find the optimum amount of acetic acid in THF as shown in Table 1. In the absence of acetic acid, the reaction of EEDQ using 1.2 equiv. of allyl bromide and 1.2 equiv. of indium at rt after 24 h gave a mixture of α- and γ-allyldihydroquinolines in overall 25% yield.[9] The low yield seemed to be ascribed to the slow formation of *N*-acylquinolinium ion in the absence of activating reagent. The reaction gave allyldihydroquinolines as a mixture of α and γ regioisomers in 34 and 39% overall yields, respectively, in the presence of 0.1 and 0.5 equiv. of acetic acid (entries 2 and 3). In the presence of 1.2 and 2 equiv. of acetic acid, the reactions were complete in 1 h to give a mixture of α- and γ-allyldihydroquinolines in 93 and 91% overall yields, respectively. α- and γ-Allyldihydroquinolines in all four reactions were obtained in similar ratio (about 12:1), irrespective of overall yields. Therefore, 1.2 equiv. of acetic acid was an optimum amount of acetic acid.

The allylations of EEDQ with allyl bromide and prenyl bromide in the presence of 1.2 equiv. of acetic acid at rt were studied in various solvent systems such as DMF, ethanol, THF and water, and the results are shown in Table 2. Among four solvent systems, THF was identified to be the best solvent system. The allylations with allyl bromide and prenyl bromide in THF gave the corresponding allylated products in 93 and 84% yields, respectively (entry 3 of Table 2). The allylations of EEDQ with allyl bromide in DMF and ethanol were complete in 1 h (entries 2 and 4) in relatively low yields. The low yield in other solvent systems attribute to the formation of quinoline as a side product. For example, quinoline in the allylation of EEDQ with allyl bromide in water after 1 h was obtained in 42% yield (entry 1). Therefore, a choice of solvent was THF.

Under the optimum conditions, indium-mediated allylations of EEDQ with various allyl bromides gave the corresponding allylated dihydroquinolines with high α selectivities in high yields as shown in entries 1–7 of Table 3. Quinoline was formed in all of the allylations. The reaction of EEDQ with propargyl bromide gave a mixture of α-propargyldihydroquinoline and α-allenyldihydroquinoline in a 1:3.3 ratio in an overall 33% yield (entry 8). The allylation of EEDQ with



Scheme 3.

Table 1. Allylation of EEDQ using indium in THF

Entry	Acetic acid (equiv.)	Time (h)	Yield (%)[a]
1	None	24	25
2	0.1	24	34
3	0.5	24	39
4	1.2	1	93
5	2	1	91

[a] Isolated yields.

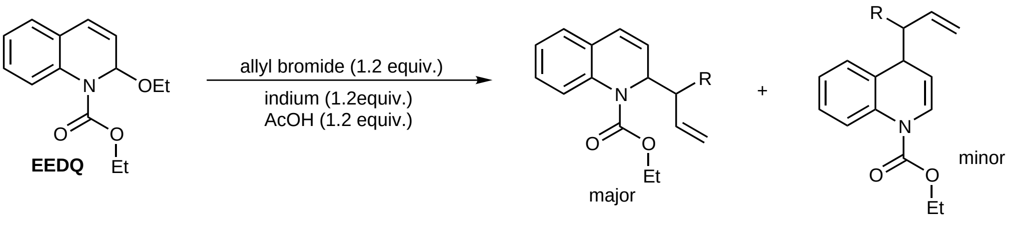
Table 2. Allylations of EEDQ in various solvent systems[a]

Entry	Solvent	Time (h)	Yield (%)[b]
1	Water	1	30
2	Ethanol	1	74 (44)[c]
3	THF	1	93(84)[c]
4	DMF	1	74 (5)[c]

[a] Indium (1.2 equiv.), allyl bromides (1.2 equiv.) and acetic acid (1.2 equiv.) were used.

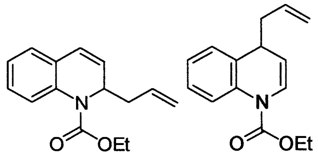
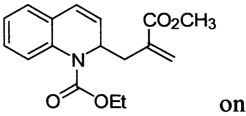
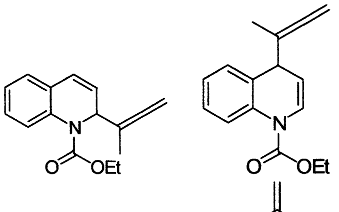
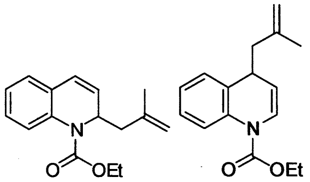
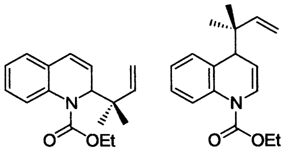
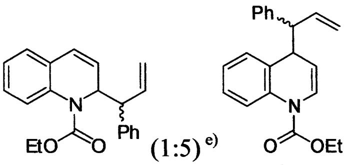
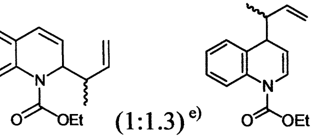
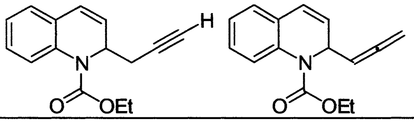
[b] Isolated yields in the reaction of allyl bromide.

[c] Isolated yields in the reaction of prenyl bromide.



Scheme 2.

Table 3. The allylations of EEDQ with various allyl bromides

Entry	Allyl bromides	Allylated dihydroquinolines	Time	Yield (%)[a]
1	Allyl bromide		1 h	93 (12.4:1)[c]
2	Methyl 2-bromomethylacrylate	 only α regioisomer	30 min	99
3	1-bromo-2-butyne		24 h	87 (100)[b]
4	Methallyl bromide		50 min	86 (15.4:1)[c]
5	Prenyl bromide		15 min	74 (9:1)[c]
6	Cinnamyl bromide	 (1:5)[e] (1:1.5)[e]	15 min	85 (4:1)[c]
7	Crotyl bromide	 (1:1.3)[e] (1:1.5)[e]	20 min	82 (9:1)[c]
8	Propargyl bromide		40 min	33 (1:3.3)[d]

a) Isolated yields. b) When 1-bromo-2-butyne (2 equiv.) and indium (2 equiv.) were used, α and γ allylated dihydroquinolines were obtained in 24:1 ratio after 24 h in quantitative overall yield. c) Ratio of α:γ regioisomers d) Ratio of α-propargyl and α-allenyldihydroquinolines. e) Ratio of two diastereoisomers, which were not assigned yet.

cinnamyl bromide gave a mixture of α and γ regioisomer in 4:1 ratio, each of which is consisted of two diastereoisomers in about 1:5 and 1:1.5 ratio, respectively (entry 6). The reaction of crotyl bromide also gave a mixture of α and γ regioisomers in 9:1 ratio, each of which is consisted of two diastereoisomers in about 1:1.3 and 1:1.5 ratio, respectively (entry 7). The ratios of two diastereoisomers and two regioisomers were determined by the ^{1}H NMR spectrum.

While allylations of quinoline acylated with phenyl chloroformate using allyltin and allylsilane have been reported,[3f] the allylations of EEDQ with allyltin and allylsilane have not been known, to the best of our knowledge. EEDQ was allylated using allyltins (1 equiv.) and allylsilane (1 equiv.) in the presence of $BF_3{\cdot}Et_2O$ (1.1 equiv.) as a Lewis acid and the results are shown in Table 4. The reactions of allyltins were complete in 15 min at rt to give the corresponding

Table 4. Allylation of EEDQ with allyltin and allylsilane in the presence of $BF_3{\cdot}Et_2O$

Entry	Substrate	Time	Yield (%)[a]
1	Allyltrimethylsilane	2.5 h	89
2	Allyltributyltin	15 min	94
3	Prenyltributyltin	15 min	100 (3.6:1)[b]

[a] Isolated yields.

[b] Ratio of α and γ regioisomers.

allylated dihydroquinolines in high yields. The allylation of EEDQ with allyltributyltin and allyltrimethylsilane gave only α-allyldihydroquinoline in high yield. The reaction of prenyltributyltin gave a mixture of α- and γ-prenyldihydroquinolines in 3.6:1 ratio. Further studies on the allylation of EEDQ and its analogs with various allyltins and allylsilanes are under investigation.

In conclusion, indium-mediated allylations of EEDQ with a variety of allyl bromides in the presence of indium and acetic acid gave the corresponding allylated dihydroquinolines with high α selectivities in high yields. However, the reaction of propargyl bromide gave α-allenyldihydroquinoline and α-propargyldihydroquinoline in low overall yield. The reaction of EEDQ with allyltin, prenyltin and allylsilane gave the corresponding allylated products in high yields.

Experimental

A typical procedure of indium-mediated allylations of EEDQ: To a solution of EEDQ (50 mg, 0.20 mmol) in HPLC grade THF (3 ml) was added allyl bromide (22 μl, 0.24 mmol), indium (28 mg, 0.24 mmol) and acetic acid (14 μl, 0.24 mmol) sequentially. The resulting solution was stirred for 1 h and the reaction was monitored by TLC using a solution of ethyl acetate and hexane (1:4). The reaction was concentrated under reduced pressure. The concentrate was chromatographed on silica gel using a solution of ethyl acetate and hexane (1:10) to give a mixture of α- and γ-allyldihydroquinolines in 12.4:1 ratio in 93% overall yield (45.9 mg).

A typical procedure of allylations of EEDQ using allyltributyltin and allyltrimethylsilane: To a solution of EEDQ (50 mg, 0.20 mmol) in HPLC grade of methylene chloride (3 ml) was added allyltributyltin (65 μl, 0.20 mmol), $BF_3{\cdot}Et_2O$ (28 μl, 0.22 mmol, 1.1 equiv.) sequentially. The resulting solution was stirred for 15 min (reaction was monitored by TLC using a solution of ethyl acetate and hexane (1:2)) and the reaction was concentrated under reduced pressure. The concentrate was chromatographed on silica gel using a solution of ethyl acetate and hexane (1:10) to give an α-allyldihydroquinoline in 94% yield (46.4 mg).

Acknowledgements

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