COMMUNICATION

OBC
www.rsc.org/obc

Indium mediated allylation of quinoline and isoquinoline activated by phenyl chloroformate

Seung Hwan Lee, Young Sang Park, Mi Hae Nam and Cheol Min Yoon*
Graduate School of Biotechnology, Korea University, Seoul, Korea.
E-mail: cmyoon@korea.ac.kr; Fax: +82-2-3290-3433

Received 7th April 2004, Accepted 22nd June 2004
First published as an Advance Article on the web 9th July 2004

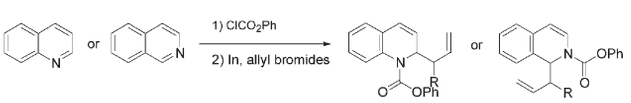
Quinoline and isoquinoline activated by phenyl chloroformate were allylated using indium and allyl bromides in THF at room temperature to give the corresponding allyldihydroquinoline and allyldihydroisoquinoline in good to high yields.

Introduction

The quinoline and isoquinoline ring systems are an important structural unit in naturally occurring alkaloids and synthetic analogues with interesting biological activities. Therefore, the development of new and efficient synthetic routes for the preparation of their analogs is of importance in both synthetic organic chemistry and medicinal chemisty.[1] One method for the preparation of quinoline and isoquinoline analogs is C–C bond formation using organometallic compounds. Addition reactions of organometallic reagents with aza-aromatics activated by acyl chlorides have been of great importance for the synthesis of a variety of biologically active nitrogen heterocycles, including alkaloids.[2] Recently, organometallic reagents such as allylsilane and allyltin have been widely utilized as useful carbon nucleophiles.[3] However, the reagents suffer from several problems such as poor nucleophilicity,[4] toxicity and their limited commercial availabilities.[3f] A fatal drawback of allylation using allylsilane has been observed in the allylation of activated isoquinoline using allylsilane, which gave a benzoisoquinuclidine derivative instead of allylated dihydroisoquinoline as a major product.[3f] A solution for these problems is allylation using an indium and allyl bromide protocol, which has been employed in the allylation of carbonyls with success.[5]

Results and discussion

We have recently reported that various allyl bromides and indium readily react with EEDQ (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline) in THF in the presence of 1.2 equiv. of glacial acetic acid at rt to give allyldihydroquinolines in a regioselective manner.[6] As a result of ongoing research into indium mediated allylation, we wish to report the indium-mediated allylation of quinoline and isoquinoline activated by phenyl chloroformate in THF (Scheme 1). Allyldihydroquinoline and allyldihydroisoquinoline were successfully prepared under our indium mediated allylation condition.



Scheme 1

Quinoline and phenyl chloroformate were chosen as a model substrate and an activating agent for the optimization of allylation at the beginning of the research. When an allylindium suspension prepared by stirring a solution of indium (2 equiv.) and allyl bromide (3 equiv.) in DMF at rt for 20 min was allowed to react with *N*-phenoxycarbonylquinolinium salts prepared by the reaction of quinoline with phenyl chloroformate in DMF for 3 min at 0 °C (Grignard type), 2-allyl-1,2-dihydroquinoline was obtained after 16 h in 34.2% yield (entry 1, Table 1). However, direct addition of indium and allyl bromide to phenoxycarbonylquinolinium salts increased the yield to 52.6% after 16 h at rt (Barbier type). The allylation was examined in several solvents such as THF, DCM and ethanol; THF was found to be most efficient solvent as shown in Table 1.

Table 1 Allylation of quinoline using allyl bromide and indium in various solvents[a]

Entry	Solvent	Time/h	allyldihydroquinoline[b](%)
1	DMF (Grignard type)	16	34.2
2	DMF (Barbier type)	16	52.6
3	THF (Barbier type)	0.5	81.0
4	DCM (Barbier type)	16	6.2
5	Ethanol (Barbier type)	24	No reaction

[a] Quinoline (0.77 mmol), phenyl chloroformate (1 equiv.), allyl bromide (3 equiv.), indium (2 equiv.) and solvent (4 ml) were used in the reaction. [b] Isolated yield of only 2-allyl-1,2-dihydroquinoline. Trace amount of 4-allyl-1,4-dihydroquinoline was formed and not separated.

With these results in hand, the allylations of quinoline and isoquinoline acylated by ethyl chloroformate or phenyl chloroformate were attempted using various amounts of indium and allyl bromide and the representative results are shown in Table 2. While the reaction of quinoline and isoquinoline acylated by ethyl chloroformate (1.1 equiv.) with indium (1.1 equiv.) and allyl bromide (1.5 equiv.) in THF at rt gave 2-allyl-1,2-dihydroquinoline and 1-allyl-1,2-dihydroisoquinoline in 12.7% and 35.7% yields respectively (entry 1), the reaction using 2 equiv. of indium and 3 equiv. of allyl bromide gave the corresponding dihydroquinoline and dihydroisoquinoline in high yields (entry 2). Isoquinoline was allylated faster than the quinoline under the reaction conditions. When phenyl chloroformate instead of ethyl chloroformate was utilized for the activation of quinoline and isoquinoline, reaction times were reduced, along with improved yields (entries 3, 4). It is noteworthy that the indium mediated allylation of isoquinoline under our conditions is the only way for the preparation of allylated isoquinoline *via* allylation.

Allylations of quinoline and isoquinoline activated by phenyl chloroformate with various allyl bromides were then carried out under our optimum conditions and the results are summarized in Table 3. The reaction of quinoline acylated phenyl chloroformate with allyl bromide proceeds smoothly to afford the 1,2-adduct, along with a small amount of the 1,4-adduct, depending on the allyl bromide (entries 1–4). However the major product in the reaction of activated quinoline with phenyl bromide under our reaction condition was the 1,4-adduct, probably due to steric effects (entry 5). The isoquinoline was allylated with various allyl bromides to give the corresponding 1-allylated isoquinolines in good to high yields (entries 1–5). The propargylation of activated quinoline with propargyl bromide gave 2-propargyldihydroquinoline as a major product with 4-propargyldihydroquinoline and 4-allenyldihydroquinoline as minor products (entry 6). The reaction of activated isoquinoline also gave the 1-propargyldihydoroisoquinoline as a major product, along with 1-allenyldihydroisoquinoline as a minor product (entry 3). However, the reaction of activated quinoline and isoquinoline with 1-bromo-2-butyne gave γ-allenyldihydroquinoline, with the 1,2-adduct as the major product, and γ-allenyldihydroisoquinoline under our reaction conditions respectively (entry 7).

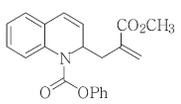
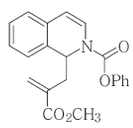
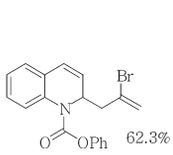
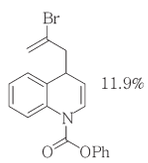
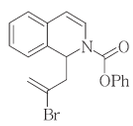
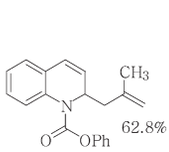
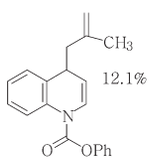
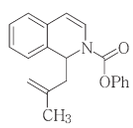
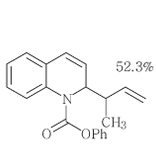
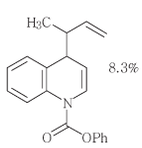
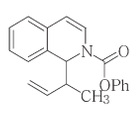
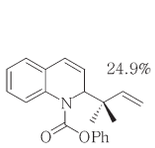
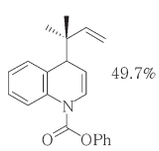
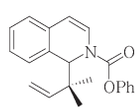
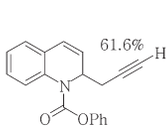
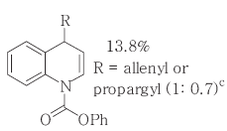
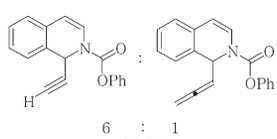
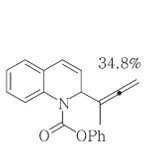
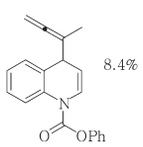
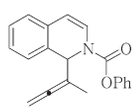
DOI: 10.1039/b405217j

Table 2 Allylation of quinoline and isoquinoline with allyl bromide and indium in THF[a]

Entry	Alkyl chloroformate	Indium (equiv.)	Allyl bromide (equiv.)	2-Allyl-1,2-dihydro-quinoline %[b](Time)	1-Allyl-1,2-dihydrioiso-quinoline %[b](Time)
1	Ethyl	1.1	1.5	12.7 (1.5)[c] (24 h)	35.7 (1 h)
2	Ethyl	2	3	84.8 (7.2)[c] (24 h)	80.8 (1 h)
3	Phenyl	1.1	1.5	52.5(1.9)[c] (1 h)	66.8 (0.5 h)
4	Phenyl	2	3	88.8(3.5)[c] (0.5 h)	92.8 (0.5 h)

[a] Quinoline (0.77 mmol), chloroformate (1.1 equiv.), allyl bromide, indium and THF (4 ml) were used in the reaction. [b] Isolated yield of 1,2-adduct. [c] Isolated yield of 1,4-adduct.

Table 3 Indium-mediated allylation of quinoline or isoquinoline in THF[a]

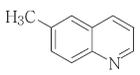
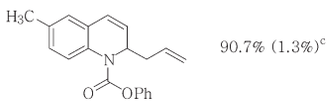
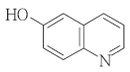
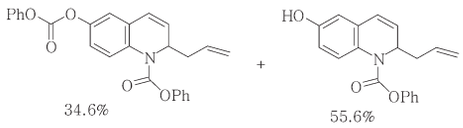
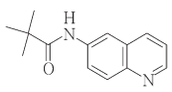
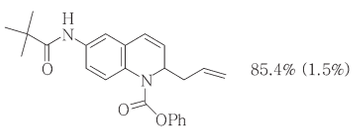
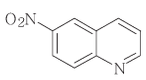
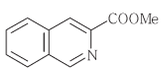
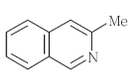
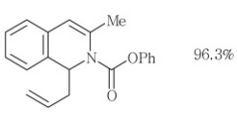
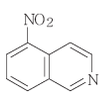
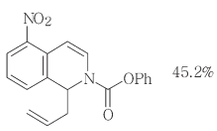
Entry	Allyl bromides	Allylquinolines[b]	Allylisoquinolines[b]
1	Methyl-2-(bromomethyl)acrylate	 95.5%	 90.5%
2	2,3-Dibromopropene	 62.3%  11.9%	 82.0%
3	Methallyl bromide	 62.8%  12.1%	 91.4%
4	Crotyl bromide	 52.3%  8.3%	 75.4%
5	Prenyl bromide	 24.9%  49.7%	 63.9%
6	Propargyl bromide	 61.6%  13.8% R = allenyl or propargyl (1: 0.7)[c]	 6 : 1 94.2%
7	1-Bromo-2-butyne	 34.8%  8.4%	 74.7%

[a] The reaction time was 0.5 h. [b] Isolated yields. [c] Ratio of 1,4-propargyl and 1,4-allenyl adduct was determined by ^{1}H NMR.

For the extension to our method to quinoline and isoquinoline derivatives, allylation of several quinolines and isoquinolines with allyl bromide was attempted under our optimum reaction conditions and the results are shown in Table 4. The electron sufficient quinoline and isoquinoline acylated with phenyl chloroformate in THF were efficiently allylated in the presence of allyl bromide and indium to give the corresponding dihydroquinoline and dihydroisoquinoline in good to high yields (entries 1, 2, 3 and 6). However, the reaction of electron deficient quinoline and isoquinoline was not working at all (entries 4 and 5) or it gave the corresponding allylated product in low yield (entry 7), due to the low nucleophilicity of the nitrogens of quinoline and isoquinoline. The 2.2 equiv. of phenyl chloroformate was used in the reaction of 6-hydroxyquinoline due to the hydroxy group and the reaction gave a mixture of allylhydroxydihydroquinoline and allyldihydroquinoline phenyl carbonate in high yield (entry 2).

In summary, the indium mediated allylation reaction of quinoline and isoquinoline activated by phenyl chloroformate with various allyl bromides and propargyl bromides in THF efficiently give the corresponding allylated dihydroquinolines and dihydroisoquinolines in good and high overall yields. The indium mediated allylation of isoquinoline under our conditions gave

Table 4 Allylations of the substituted quinolines or isoquinolines with allyl bromide

Entry	Substrate	Allylquinolines or allylisoquinolines[a]
1		 90.7% (1.3%)[c]
2[b]		 34.6% + 55.6%
3		 85.4% (1.5%)
4		No reaction
5		No reaction
6		 96.3%
7		 45.2%

[a] Isolated yields. [b] Phenyl chloroformate (2.2 equiv.), indium (2 equiv.) and allyl bromide (3 equiv.) were utilized. [c] Parenthesis yield is that of 1,4-adduct.

the corresponding allylated adducts in high yield, which is not available using the mild allylating agent, allylsilane. Our method was identified to be efficient for the allylation of electron sufficient quinoline and isoquinoline after activation by phenyl chloroformate.

Experimental

General procedure

To a solution of quinoline or isoquinoline (0.77 mmol) in HPLC grade THF (4 mL) was added phenyl chloroformate (1.1 equiv.) at room temperature. After stirring at that temperature for 0.5 h, indium (2 equiv.) and allyl bromide (3 equiv.) were added to the solution of acylated quinoline and isoquinoline solution. The resulting mixture was stirred at room temperature for 30 min. The reaction was monitored by TLC using an eluent of ethyl acetate and *n*-hexane (1 : 10). The reaction mixture was concentrated and purified by silica gel column chromatography with ethyl acetate and *n*-hexane (1 : 20) to give the corresponding adducts.

Acknowledgements

The authors wish to acknowledge the financial support of the Korea Science and Engineering Foundation (KOSEF) made in the program year 2003.

Notes and references

1 M. Balasubramanian and J. G. Keay in *Comprehensive Heterocyclic Chemistry II*, ed. A. P. Katrizky, V. W. Rees and E. F. Scriven, Pyridines and their Benzo Derivatives: Application, Pergamon, Oxford, 1996, vol. 5, pp. 245–300.

2 For a review see: (*a*) D. M. Stout and A. I. Meyers, *Chem. Rev.*, 1982, **82**, 223; (*b*) D. L. Comins and P. J. Sajan in *Comprehensive Heterocyclic Chemistry II*, eds A. P. Katrizky, V. W. Rees and E. F. Scriven, Pyridines and their Benzo Derivatives: Reactivity at the Ring, Pergamon, Oxford, 1996, vol. 5, p. 37. ; For recent examples, see: (*c*) D. L. Comins, Y. Zhang and S. P. Joseph, *Org. Lett.*, 1999, **1**, 657 and references cited therein; (*d*) T. Nishikawa, M. Yoshikai, K. Obi, T. Kawai, R. Unno, T. Jom ori and M. Isobe, *Tetrahedron*, 1995, **51**, 9339 and references cited therein; (*e*) P. Magnus, J. Rodríguez-Lopez, K. Mulholland and I. Matthews, *J. Am. Chem. Soc.*, 1992, **114**, 382; (*f*) M. F. Braña, M. Moran, M. J. Pérez de Vega and I. Pita-Romero, *J. Org. Chem.*, 1996, **61**, 1369; (*g*) T. Itoh, M. Miyazaki, K. Nagata and A. Ohsawa, *Tetrahedron*, 2000, **56**, 4383; (*h*) For a recent review of the allylation reaction: Y. Yamamoto and N. Asao, *Chem. Rev.*, 1993, **93**, 2207.

3 (*a*) R. Yamaguchi, M. Moriyasu, M. Yoshioka and M. Kawanisi, *J. Org. Chem.*, 1988, **53**, 3507; (*b*) R. Yamaguchi, K. Mochizuki, S. Kozima and H. Takaya, *J. Chem. Soc., Chem. Commun.*, 1993, 981; (*c*) B. Hatano, Y. Haraguchi, S. Kozima and R. Yamaguchi, *Chem. Lett.*, 1995, 1003; (*d*) Y. Haraguchi, S. Kozima and R. Yamaguchi, *Tetrahedron: Asymmetry*, 1996, **7**, 443 and references cited therein. See also Ref. 2e; (*e*) T. Itoh, H. Hasegawa, K. Nagata and A. Ohsawa, *J. Org. Chem.*, 1994, **59**, 1319; (*f*) R. Yamaguchi, T. Nakayasu, B. Hatano, T. Nagura, S. Kozima and K.-I. Fujita, *Tetrahedron*, 2001, **57**, 109.

4 It has been reported that allyltrimethylsilane is *ca.* 10^4 times less reactive than allyltributyltin toward diarylcarbenium ions: G. Hagen and H. Mayr, *J. Am. Chem. Soc.*, 1991, 4954.

5 The indium-mediated allylation of carbonyl compounds: (*a*) C. J. Li and T. H. Chan, *Tetrahedron Lett.*, 1991, **32**, 7017; (*b*) T.-P. Loh and X.- R. Li, *Tetrahedron Lett.*, 1997, **38**, 869; (*c*) V. J. Bryan and T. H. Chan, *Tetrahedron Lett.*, 1996, **37**, 5341; (*d*) for a review: C. J. Li and T. H. Chan, *Tetrahedron*, 1999, **55**, 11149 and references cited therein; (*e*) T. P. Loh, Q. Y. Hu and J. J. Vittal, *Synlett*, 2000, **4**, 523; (*f*) T. P. Loh, J. R. Zhou and X. R. Li, *Tetrahedron Lett.*, 1999, **40**, 9333; (*g*) for a review: P. Cintas, *Synthesis*, 1995, 1087.

6 J. H. Lee, J. S. Kweon and C. M. Yoon, *Tetrahedron Lett.*, 2002, **43**, 5771.