JOC*Note*

Gold(III) Chloride-Catalyzed Three-Component Reaction: A Facile Synthesis of Alkynyl Derivatives of 1,2-Dihydroquinolines and Isoquinolines†

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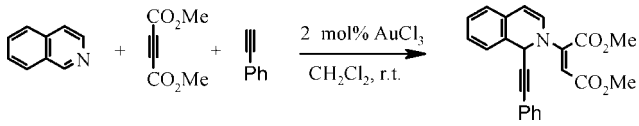

Gold(III) chloride is found to be an effective catalyst for the addition of alkynes on activated quinoline/isoquinolines to produce a series of alkynyl-substituted 1,2-dihydroquinolines and isoquinolines in a single-step operation. The easy availability of starting materials, convenient synthetic procedure, operational simplicity, and high regioselectivity makes this strategy very useful for the preparation of enyne derivatives of aza-aromatic compounds.

The use of gold salts has been dramatically increased in organic syntheses due to their unique Lewis acidic nature.[1] Especially, gold(III) compounds are being considered as potential Lewis acids to activate alkynes under extremely mild conditions.[2] In particular, gold(III) chloride has been widely used for a variety of organic transformations.[2]

Activated aza-aromatic systems such as quinolines and isoquinolines are useful building blocks in organic synthesis, especially for the synthesis of various biologically active nitrogen-containing alkaloids.[3,4]

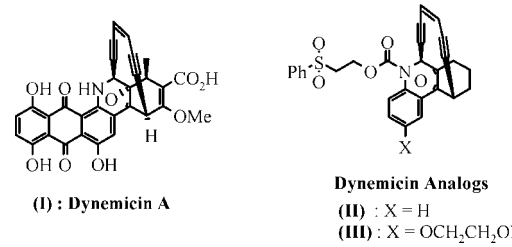

FIGURE 1. Structure of biologically active dynemicin A (**I**) and its analogues (**II** and **III**).

In particular, addition of alkynes to activated aza-aromatic systems is an important carbon−carbon bond-forming reaction for the synthesis of enediyne alkaloids such as dynemicin A and its analogues (Figure 1).[5] However, only a few methods are reported for the alkynylation of activated aza-aromatic systems.[3c,5a,6] In most cases, alkynyl Grignard reagents, alkynyltin, and alkynylsilanes have been utilized to introduce alkynyl functionality into quinoline systems.[7,8] Generally, chloroformates or acid chlorides are used as activating agents for quinolines and isoquinolines.[3]

Huisgen et al.[9a,b] have reported the formation of 1,4-dipoles from isoquinoline and dimethyl acetylenedicarboxylate (DMAD) and their trapping by phenyl isocyanate, diethyl mesoxalate, and dimethyl azodicarboxylate to generate six-membered heterocycles. Recently, we have also found that dimethyl acetylenedicarboxylate is an effective reagent for the coupling of indoles with quinolines and isoquinolines.[10] This result provided an

* Address correspondence to this author. Fax: 91-40-27160512.
† Dedicated to Prof. E. J. Corey on the occasion of his 80th birthday.
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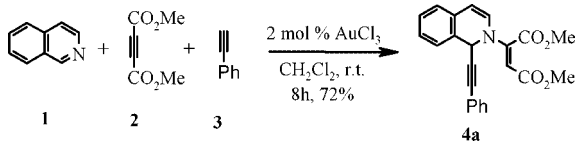
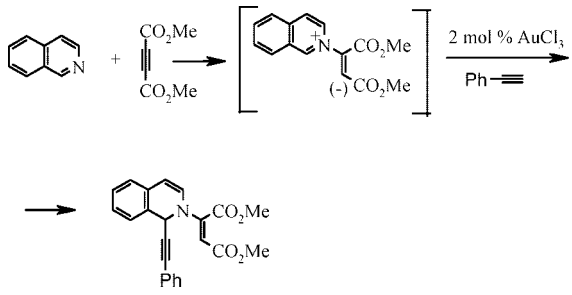
SCHEME 1. Preparation of Product 4a



SCHEME 2. A Plausible Reaction Mechanism for the Alkynylation of Isoquinoline



inspiration to study the annulation of aryl alkynes with quinoline and isoquinoline activated by dimethylacetylene dicarboxylate. However, attempted annulation of isoquinoline (**1**) with dimethyl acetylenedicarboxylate (**2**) and phenylacetylene (**3**) in the presence of 2 mol % gold(III) chloride led to formation of alkyne addition product instead of the anticipated cyclization. The reaction was complete in 8 h to furnish dimethyl 2-(1-(phenylethynyl)isoquinolin-2(1*H*)-yl)maleate **4a** in 72% yield (Scheme 1).

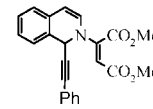
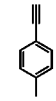
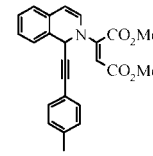
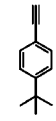
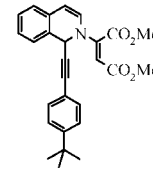
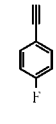
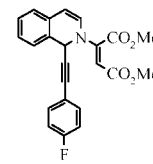
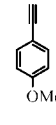
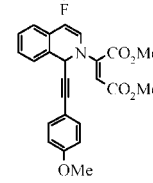
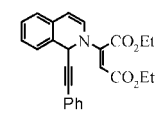
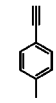
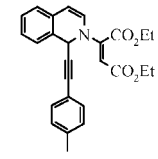
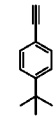
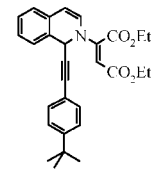
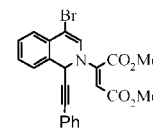
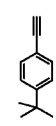
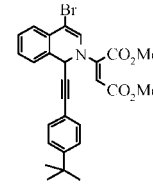
The structure of **4a** was established by using various ^{1}H, ^{13}C NMR, IR, and HRMS. This result provided incentive for an extensive study. Interestingly, various ethynylbenzenes such as 1-ethynyl-4-methylbenzene, 1-*tert*-butyl-4-ethynylbenzene, 1-ethynyl-4-fluorobenzene, and 1-ethynyl-4-methoxybenzene underwent smooth coupling with activated isoquinoline to produce the corresponding 1-alkynyl-substituted 1,2-dihydroisoquinolines in good to excellent yields (entries **b**−**e**, Table 1).

Like DMAD, diethyl acetylenedicarboxylate also participated in this reaction to afford the corresponding alkynyl derivatives of 1,2-dihydroisoquinolines (entries **f**−**h**, Table 1). However, in case of 4-bromoisoquinoline, the desired products were also obtained in fairly good yield (entries **i** and **j**, Table 1).

Mechanistically, the reaction may proceed via the formation of a zwitterionic intermediate,[11] which reacts subsequently with phenylacetylene activated by Au(III) to furnish the desired product (Scheme 2).

Like isoquinolines, quinoline also coupled effectively with dimethylacetylene dicarboxylate and ethynylbenzene under identical conditions. The reaction went to completion in 9.0 h and the desired alkyne addition product, **6a**, was obtained in 82% yield (Scheme 3, Table 2)

TABLE 1. Gold(III) Chloride-Catalyzed Three-Component Coupling Reaction[a,b]

Entry	Isoquinoline 1	Acetylene-dicarboxylate 2	Ethynyl-benzene 3	Product[a] 4	Time (h)	Yield (%)[b]
a					8.0	72
b		"			5.0	78
c		"			3.5	92
d		"			7.5	80
e		"			4.5	92
f					7.5	70
g		"			4.5	78
h		"			4.0	90
i					8.5	63
j					5.0	72

[a] All products were characterized by NMR, IR, and mass spectrometry. [b] Isolated yields after purification.

Similarly, various ethynylbenzenes were coupled effectively with activated quinolines to furnish the corresponding adducts

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SCHEME 3. Preparation of Product 6a

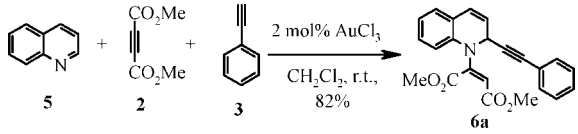
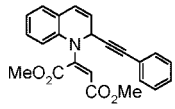
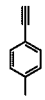
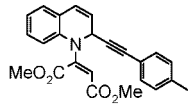
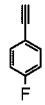
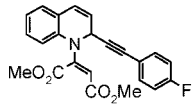
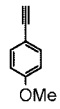
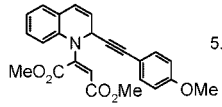
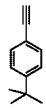
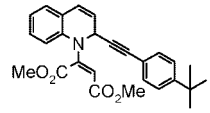
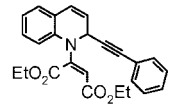
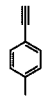
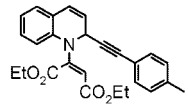
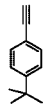
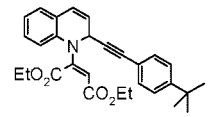


TABLE 2. Gold(III) Chloride-Catalyzed Three-Component Coupling Reaction[a,b]

Entry	Quinoline 5	Acetylene-dicarboxylate 2	Ethynyl-benzene 3	Product[a] 6	Time (h)	Yield (%)[b]
a					9.0	82
b	"	"			4.0	85
c	"	"			8.0	74
d	"	"			5.5	89
e	"	"			3.5	92
f	"				8.5	68
g	"	"			5.0	88
h	"	"			3.5	90

[a] All products were characterized by NMR, IR, and mass spectrometry. [b] Isolated yields after purification.

in good to excellent yields (entries **b**−**h**, Table 2). This method worked well for both electron-rich as well as electron-deficient substrates. Various functional groups such as bromo, fluoro, and methoxy derivatives are well tolerated under the reaction conditions (Tables 1 and 2). This method offers several advantages such as high yields of products, mild reaction conditions, greater regioselectivity, cleaner reaction profiles, and operational simplicity. As solvent, dichloromethane appeared to give the best results. Among various Lewis acid catalysts such as $GaCl_3$, $InCl_3$, $BiCl_3$, $NbCl_5$, $ZrCl_4$, $TaCl_5$, and $CeCl_3 \cdot 7H_2O$, $AuCl_3$ was found to be the most effective catalyst in terms of conversion. In the absence of catalyst, no desired product was obtained. However, aliphatic alkynes failed to undergo addition under similar conditions.

The structure and configuration of product **6e** was also confirmed by single-crystal X-ray analysis.[12] The scope and generality of this process is illustrated with respect to various isoquinolines, quinolines, and ethynylbenzenes and the results are presented in Tables 1 and 2.

In summary, we have developed a novel three-component reaction capable of coupling of ethynylbenzenes with quinoline and isoquinolines activated by acetylenedicarboxylate at room temperature using 2 mol % of gold(III) chloride catalyst. In addition to its simplicity and mild reaction conditions, this method provides good yields of products with high regioselectivity, which makes it a useful and attractive process for the alkynylation of quinolines and isoquinolines in a single-step operation.

Experimental Section

Typical Procedure. To a stirred solution of dialkyl acetylenedicarboxylate (1.2 mmol), ethynylbenzene (1.0 mol), and gold(III) chloride (2 mol %) in CH_2Cl_2 (5 mL) at 0 °C under nitrogen atmosphere for 30 min was added quinoline/isoquinoline (1.0 mmol) and the resulting mixture was stirred at room temperature for the appropriate time (see Tables 1 and 2). After completion of the reaction, as indicated by TLC, the reaction mixture was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with water followed by brine and dried over anhydrous Na_2SO_4, which was filtered off. Removal of solvent followed by purification on silica gel column with a mixture of EtOAc−hexanes (10%) afforded pure product. Solid compounds were recrystallized with CH_2Cl_2−hexane (5%).

Dimethyl 2-(1-(Phenylethynyl)isoquinolin-2(1*H*)-yl)maleate (4a; Table 1). Pale yellow solid, mp 143−145 °C; IR (KBr) ν 2924, 2363, 1733, 1597, 1445, 1381, 1163, 1036, 978, 904, 811, 762, 691, 537 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, J = 1.5, 7.5 Hz, 1H), 7.37−7.31 (m, 2H), 7.25−7.18 (m, 5H), 7.09−7.05 (m, 1H), 6.29 (d, J = 7.5 Hz, 1H), 5.91 (d, J = 7.5 Hz, 1H), 5.74 (s, 1H), 5.43 (s, 1H), 3.95 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (proton decoupled, 75 MHz, CDCl3) δ 167.1, 165.0, 149.1, 131.8, 128.9, 128.6, 128.1, 127.6, 126.2, 125.1, 124.9, 121.9, 108.9, 92.4, 86.0, 84.6, 53.2, 51.3, 50.5; LCMSD *m/z* 396 $(M + Na)^+$; HRMS (ESI) calcd for $C_{23}H_{19}NaNO_4$ 396.1211, found 396.1207.

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Supporting Information Available: Characterization data and ^1H and ^{13}C NMR spectra for compounds **4a**−**j** and **6a**−**h**), experimental procedure for general reactions, and X-ray data of compound **6e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Please see the Supporting Information.