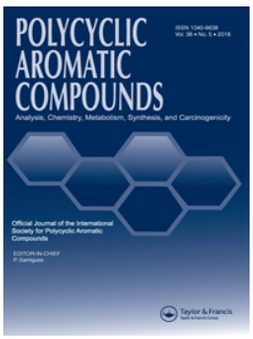

Polycyclic Aromatic Compounds

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Palladium Catalyzed Domino Sonogashira Coupling of 2-Chloro-3-(Chloromethyl)Quinolines with Terminal Acetylenes Followed by Dimerization

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ABSTRACT

A domino Sonogashira coupling of 2-chloro-3-(chloromethyl)quinolines and terminal acetylenes and then dimerization is described. This palladium-catalyzed reaction gave novel dimer quinolinium salts in good to high yield. Based on empirical evidence, a plausible mechanism was provided. The produced quinolinium salt are amenable to further synthetic elaborations such as reactions with phenoxide and thiophenoxide to yield the corresponding ether and thioether.

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Sonogashira cross-coupling; palladium catalyzed reaction; domino reaction; quinolines

Introduction

Heterocyclic compounds with quinoline subunits are among several compounds of interest due to their pharmacological properties as evidenced by the occurrence in alkaloids molecules.[1] So far 15 approved anticancer drugs include the quinoline core.[2]

The triple bond functional group has a special place in the synthesis of different heterocyclic compounds.[3] Extensive efforts have been devoted to develop synthetic routes to incorporate triple bond transformations into complex heterocyclic compounds. Over the past years, metal-catalyzed Sonogashira coupling reaction of terminal alkynes, which is a synthetic tool for C-C bond formation, has been widely studied.[4] Several reports starting from alkynylation of 2-chloroquinolines resulted in poly-heterocycles such as: benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines,[5] 3-phenylbenzo[*b*][1,6]naphthyridines,[6] pyranoquinolinones,[7] benzo[*b*]oxazolo[2,3-*f*][1,6]naphthyridine,[8] 1,2-dihydrobenzo[1,6]naphthyridines,[9] and quino[2,3-*b*]carbazoles.[10]

In this context, Gao groups have developed a practical strategy for the construction of natural products containing indolizinone or quinolizinone scaffolds and their analogs, which proceeded via a cascade exo hydroamination followed by spontaneous lactamization.[11] They applied this method to the synthesis of camptothecin, 22-hydroxyacuminatine, oxypalmatine, norketoyobyrine, naucleficine and nauclefine.[11] Verma and coworkers have established an iodine-catalyzed reaction regarding to the synthesize of 4-iodo-pyrano[4,3-*b*]quinolines and ortho-alkynyl esters from ortho-alkynyl aldehydes.[12] Interestingly, Samala et al. have disclosed that four, five and six membered cyclic amino acids reacted with 2-alkynyl aryl aldehyde to yield the corresponding 1*H*-benzo[*g*]indoles, tetrahydrobenzo[*h*] quinolines, and naphtho[1,2-*b*]azepines.[13] In contrast condensation of 2-alkynyl pyridine/quinoline aldehydes with proline furnished the corresponding hexahydropyrrolo[2,1-*b*]oxazoles.

Choosing a versatile starting material can provide access for the synthesis of various useful molecules. During the past two decades 2-chloroquinoline-3-carboxaldehydes have gained more

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attraction as starting material to synthetic chemists to construct the diverse quinoline-based molecules.[14]

In our further research on quinolines chemistry,[15] herein we wish to report palladium catalyzed Sonogashira reaction followed by a subsequent dimerization of 2-chloro-3-(chloromethyl)-quinolines **1**.

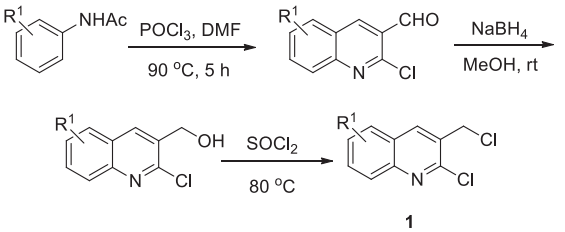
Results and discussion

We prepared 2-chloro-3-(chloromethyl)-quinolines **1** as starting material from acetanilides with different substituents as outlined in Scheme 1.[16]

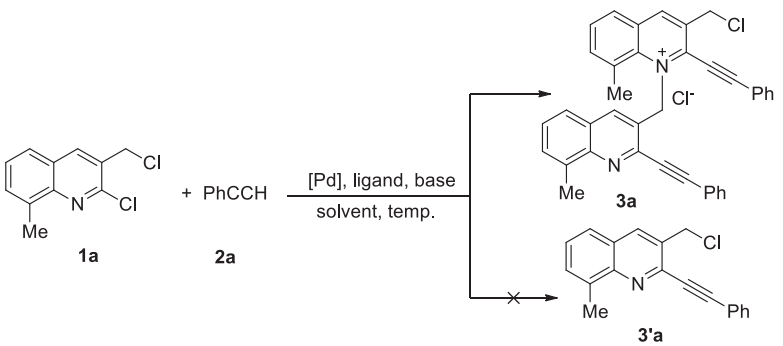
A series of experiments were performed with 2-chloro-3-(chloromethyl)-8-methylquinoline **1a** and phenylacetylene **2a** as the model reaction. Pleasingly, this reaction in the presence of $PdCl_2$, PPh_3 and TEA in toluene, gave **3a** instead of the expected simple Sonogashira coupling product **3'a** (Scheme 2).

Thus, we chose to optimize the model reactions with different palladium sources, ligands, bases, solvents, and temperatures. The reaction with $PdCl_2$, PPh_3, TEA in CH_3CN under air atmosphere gave no product but under N_2 atmosphere, even at room temperature, produced **3a** in 70% yield (Table 1, entries 1-3). Elevating the temperature to 80 °C in CH_3CN increased the yield to 88% (Table 1, entry 4). Screening of solvents revealed that CH_3CN is the optimal choice yielding a high yield within a short reaction time(Table 1, entries 5-8). This may be due to the fair interaction of lone pair of nitrogen in acetonitrile with Pd. Using alternative catalytic systems such as: $Pd(OAc)_2$, $Pd(OAc)_2$/CuI or $PdCl_2$/CuI showed no significant difference with $PdCl_2$ (Table 1, 9-11). Application of $P(CycHex)_3$, TMEDA, or L-proline as ligands considerably diminished the yields of the desired product **3a** (Table 1, entries 12-14). TEA as organic base was more efficient than the inorganic bases evaluated (Table 1, entries 15-18).

Overall, the best yield was achieved by performing the reaction with $PdCl_2$, PPh_3, and Et_3N in CH_3CN at 80 °C under nitrogen atmosphere for 3 h (Table 1, entry 4). Our next task was to



Scheme 1. Synthesis of starting materials 2-chloro-3-(chloromethyl)quinolines **1**.



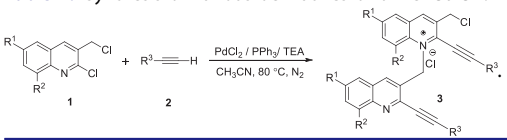
Scheme 2. Sonogashira coupling of **1a** and **2a** and then dimerization.

Table 1. Optimization of the reaction condition.

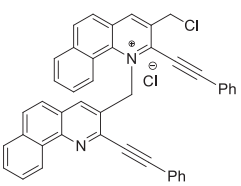
Entry	Solvent	Base	Catalyst/ Ligand	Time(h)	Yield[a,b] (%)
1	CH_3CN	TEA	$PdCl_2$	24[c, d]	–
2	CH_3CN	TEA	$PdCl_2$/ PPh_3	24[c, d]	–
3	CH_3CN	TEA	$PdCl_2$/ PPh_3	24	70[c]
4	CH_3CN	TEA	$PdCl_2$/ PPh_3	3	88
5	DMF	TEA	$PdCl_2$/ PPh_3	6	70
6	DMSO	TEA	$PdCl_2$/ PPh_3	9	66
7	Toluene	TEA	$PdCl_2$/ PPh_3	12	30
8	CH_2Cl_2	TEA	$PdCl_2$/ PPh_3	15	30
9	CH_3CN	TEA	$PdCl_2$/ CuI/ PPh_3	8	35
10	CH_3CN	TEA	$Pd(OAc)_2$/ PPh_3	5	76
11	CH_3CN	TEA	$Pd(OAc)_2$/ CuI/ PPh_3	8	65
12	CH_3CN	TEA	$PdCl_2$/ $P(Cy)_3$	8	27
13	CH_3CN	TEA	$PdCl_2$/ TMEDA	10	20
14	CH_3CN	TEA	$PdCl_2$/ L-proline	10	30
15	CH_3CN	K_2CO_3	$PdCl_2$/ PPh_3	10	50
16	CH_3CN	Cs_2CO_3	$PdCl_2$/ PPh_3	9	45
17	CH_3CN	*t*-BuOK	$PdCl_2$/ PPh_3	24	23
18	CH_3CN	*t*-BuONa	$PdCl_2$/ PPh_3	24	27

[a]All reactions were carried out using **1a** (1 mmol), **2a** (1.2 mmol), catalyst (4 mol%), ligand (8 mol%), base (2 mmol), and solvent (2.0 mL) and stirred under N_2 atm., at 80 °C unless otherwise noted.
[b]Isolated yields.
[c]At room temperature.
[d]Air atmosphere.

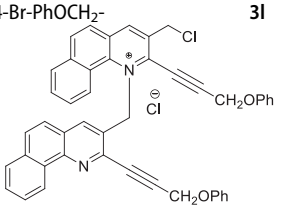
Table 2. Synthesis of various derivatives of dimer **3a**-**3n**.



Entry	R1	R2	R3	Product	Yielda (%)
1	H	Me	Ph	**3a**	88
2	Me	H	Ph	**3b**	86
3	Cl	H	Ph	**3c**	75
4	H	H	Ph	**3d**	85
5	OMe	H	Ph	**3e**	83
6	Br	H	Ph	**3f**	80
7	Me	H	$PhOCH_2$-	**3g**	78
8	H	H	$PhOCH_2$-	**3h**	84
9	H	Me	$PhOCH_2$-	**3i**	85
10	H	H	4-Me-$PhOCH_2$-	**3j**	79
11	Me	H	4-Me-$PhOCH_2$-	**3k**	85
12	H	H	4-Br-$PhOCH_2$-	**3l**	86

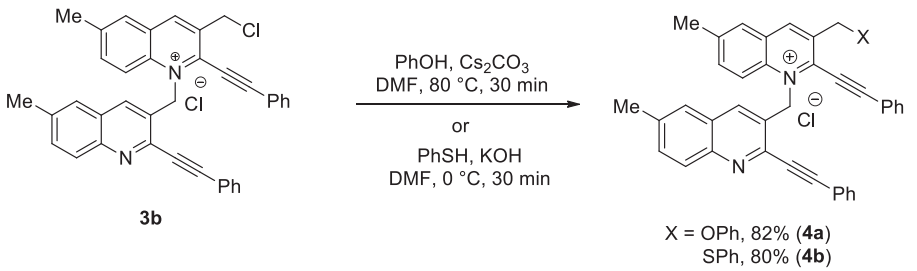


3m, 87%

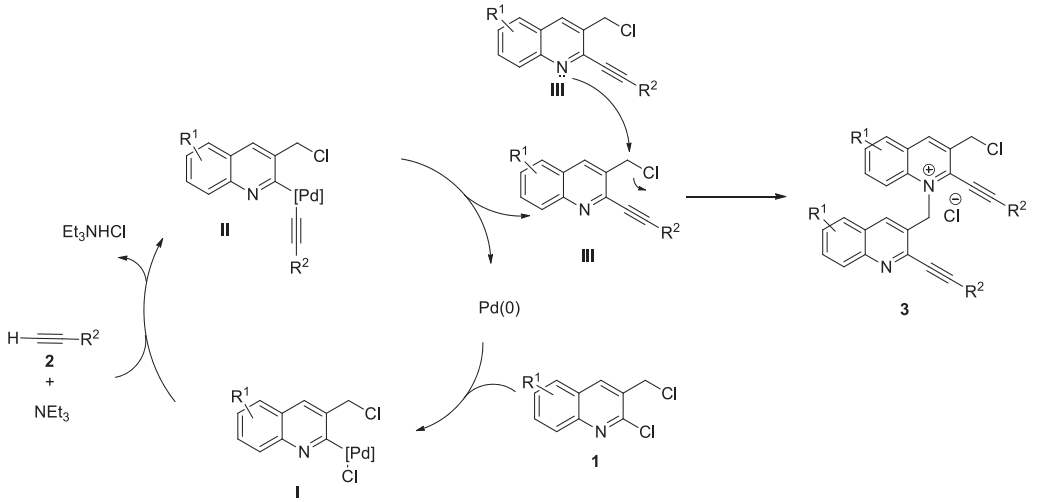


3n, 81%

evaluate the scope of this optimized methodology for a range of 2-chloro-3-(chloromethyl)quinolines **1** and terminal acetylenes (Table 2). Quinoline **1** containing methyl, methoxy, chlorine and bromine substituents reacted properly with phenylacetylene to furnish corresponding dimers **3a**-**f** (Table 2, entries 1-6). Furthermore, aliphatic acetylenes were also well tolerated in the synthesis of corresponding salts **3g**-**l** in good to high yields (Table 2, entries 7-12). The scope of the



Scheme 3. Nucleophilic substitution on aliphatic methylene chloride of compound **3b**.



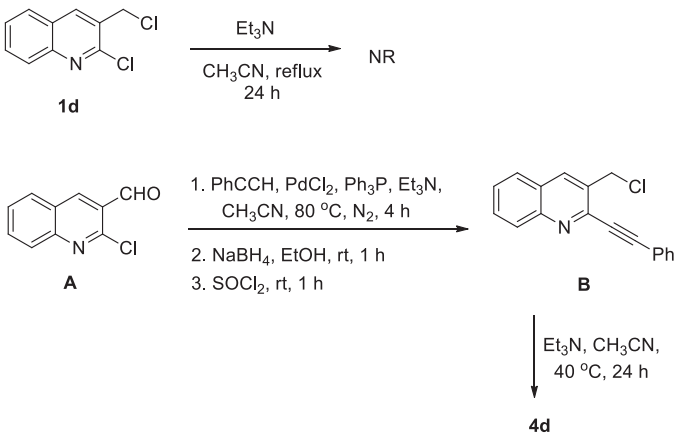
Scheme 4. The plausible mechanism for the synthesis of **3**.

reaction was also expanded to include 2-chloro-3-(chloromethyl)benzo[*h*]quinoline as a coupling partner; this produced compounds **3m** and **3n** in 81%–87% yields respectively with phenylacetylene and propargyl phenoxide (Table 2).

Investigating the conversion of the produced salts **3** into more complicated quinoline derivatives was performed by the reacting **3b** with phenol and thiophenol under basic conditions which afforded the corresponding ether **4a** and thioether **4b** (Scheme 3).

The proposed mechanism for the reaction is shown in Scheme 4. The general mechanism starts from the in-situ generation of the Pd(0) complex with PPh_3, followed by the oxidative addition of the Ar-Cl bond of the quinoline heterocycle to form **I**. Addition of terminal acetylene to intermediate **I** assisted by Et_3N generated the complex **II** which, by reductive elimination, led to compound **III**. Finally, dimerization of **III** via nucleophilic substitution of nitrogen of one molecule to Csp^3-Cl of another one formed the salt **3** (Scheme 4).

With regards to investigating the mechanism described above, reactions in Scheme 5 were performed. Treatment of 2-chloro-3-chloromethylquinoline with Et_3N in refluxing CH_3CN did not yield product even after 24 h (Scheme 5). This may be due to the existence of an electron withdrawing Cl in the 2 position of quinoline which reduced activation of nitrogen toward nucleophilic substitution. In addition, 3-(chloromethyl)-2-(phenylethynyl)quinoline (**B**), which has alkyne as electron releasing group, in the presence of Et_3N tended to dimerize to **4d**. Notably increasing the temperature to reflux converted **B** to unidentified polymer.



Scheme 5. Control experiments.

Conclusions

In summary, because of the importance of quinoline core and the ability of 2-chloro-3-(chloromethyl)quinolines to expand into more complex compounds, the primary materials of **1** were subject of reaction with terminal alkynes in a Sonogashira reaction. Surprisingly, in addition to the Sonogashira coupling, the corresponding adducts were dimerized in-situ to afford novel attractive molecules **3**. Interestingly, the product **3b** reacted efficiently with phenoxide and thiophenoxide to yield the corresponding ether and thioether respectively.

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