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Tetrahedron Letters 45 (2004) 1881–1884
Tetrahedron Letters

Synthesis of substituted quinolines by iron-catalyzed coupling reactions between chloroenynes and Grignard reagents

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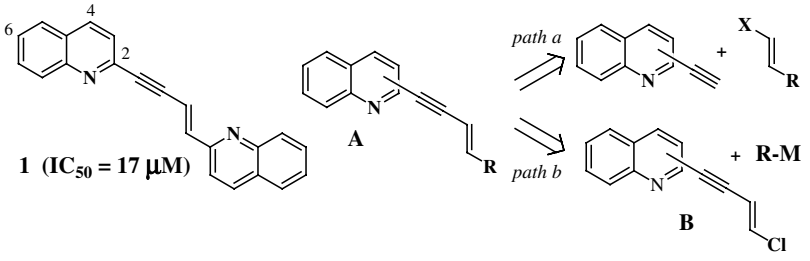
Received 1 December 2003; revised 23 December 2003; accepted 5 January 2004

Abstract—This letter reports the preparation of quinolines, substituted at the 2- or 3-position by a 4-substituted but-3-en-1-yne group, by the environmentally friendly iron(III)-catalyzed coupling reaction of Grignard reagents with 1-chloro-4-(2-quinolyl)but-1-en-3-yne. The extension and the scope of this non-toxic and chemoselective procedure to various functionalized unsaturated vinyl chlorides are described.

Natural 2-substituted quinolines, isolated from a Bolivian plant, *Galipea longiflora*, have shown interesting in vitro and in vivo leishmanicide activities.[1] We have thus undertaken a structure–activity relationship study and have synthesized numerous quinolines.[2] Interestingly, we have found that besides antiprotozoal activity,[3] some of them have displayed interesting anti-retroviral properties against HIV-1[3] and HTLV-1 transformed cells.[4] The SAR studies have highlighted the crucial role of unsaturation (e.g., double or triple bond) at the 2-position of the quinoline ring, for biological activity. Thus, we were interested by the leishmanicide activity of compound **1** ($IC_{50} = 17\,\mu M$ against amastigotes forms of *L. infantum*) which is close to the reference product, meglumine antimonate (Glucantime®) used in chemotherapy ($IC_{50} = 7\,\mu M$), and wanted to prepare quinolines bearing an enyne moiety of general structure **A** (Scheme 1).



Scheme 1.

Keywords: Grignard reagents; Iron; Quinolines; Anti-leishmania; Enynes; Vinyl chlorides.
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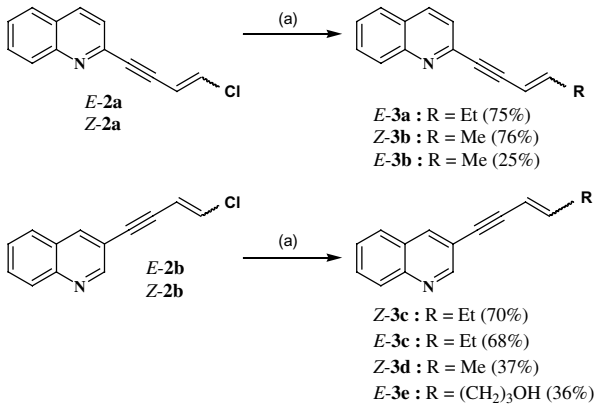
doi:10.1016/j.tetlet.2004.01.019

Among the several methods available for the synthesis of enynes, the Sonogashira–Linstrumelle coupling of 1-alkynes with vinyl halides (iodides, bromides, chlorides, and triflates) represents one of the most useful approaches to such unsaturated compounds (path a).[5] However, when compounds **A** bearing various R substituents at the double bond are needed, this method is less suitable since vinyl halides are not commercially available and often require multistep sequence syntheses. From the standpoint of flexibility, a method that employed a common starting material as a precursor would have an obvious advantage. In this work, we focused our attention on a straightforward approach based on the use of substituted chloroenynes **B**, which could represent useful building blocks for the introduction of a range of substituents R on the double bond by a transition metal catalyzed coupling reaction with organometallic compounds (path b).

Previously, we showed that the carbon–chlorine bond in chloroenynes and related compounds is not inert to further coupling reactions and under appropriate transition metal catalysis (e.g., Ni, Pd, or Mn), these compounds react rapidly and cleanly with organometallic reagents to afford efficiently the corresponding coupling products.[6] As the quinolyl enyne **A** to be prepared will be directly tested in several biological tests, we decided to avoid the use of classical metal catalysis of known or suspected toxicity. Recently a new environmentally friendly procedure using the non-toxic iron(III) acetylacetonate was reported allowing the coupling of Grignard reagents with simple halogenoalkenes (e.g., chloro and bromoalkenes) in a stereoselective manner.[7] Therefore, we turned our attention to investigate the reactivity of chloroenynes **B** and related compounds toward Grignard reagents in the presence of the non-toxic iron(III) acetylacetonate catalysis. The results of this study are now reported.

E- and *Z*-chloroenynes **2a** were prepared as already reported,[8] via a Sonogashira–Linstrumelle coupling reaction between a 2-quinolyl-alkyne and *E*- or *Z*-1,2-dichloroethylene. Then, several *E*- or *Z*-2-substituted quinolines **3a**–**b** were prepared in good yields by reaction of 1.5 equiv of the required alkyl Grignard reagent with the corresponding chloroenynes **2a** under stirring for 15 min at 0 °C in THF, in the presence of a catalytic amount of $Fe(acac)_3$ (3 mol%) and 15 equiv of NMP (Scheme 2). It is important to note that primary alkyl Grignard reagents react in good yields, with retention of the double bond configuration. Methyl was transferred as well as other primary alkyl Grignards, if used in large excess (the low yield observed for the formation of *E*-**3b** may be rationalized by the low scale of this single experiment, vide infra). Quinolines **3c**–**e**, substituted at the 3-position, were also prepared in good yields by this method, starting from the corresponding chloroenynes **2b**. It is worth noting that a functionalized alkyl Grignard reagent (3-hydroxypropyl)[9] also gave the expected adduct in a moderate but unoptimized 36% yield.

We then decided to study the reaction and wanted to generalize it to several 4-substituted chloroenynes **2**

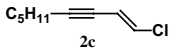
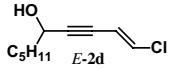
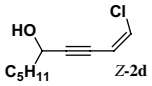
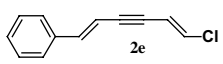
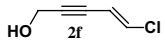
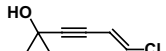
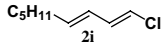


Scheme 2. Reagents and conditions: (a) RMgCl (1.5 equiv), Fe(acac) (3 mol%), THF, NMP (15 equiv), −10 to 0 °C, 15 min to 1 h.

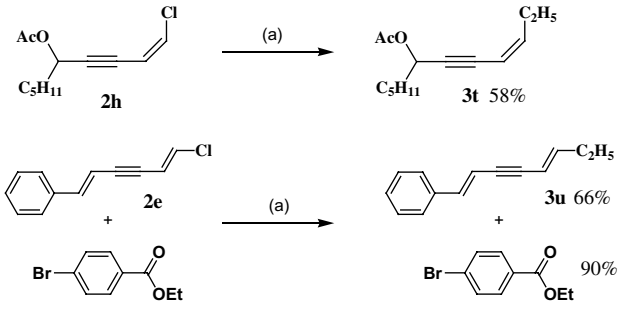
(Table 1). Chloroenynes **2c**–**h** were again prepared as already reported,[8] by Sonogashira–Linstrumelle coupling reactions between the corresponding alkyne and 1,2-dichloroethylene. When 1.5 equiv of the alkyl Grignard reagent were reacted with chloroenynes **2c**–**g** as described above [15 min to 1 h at 0 °C in THF, in the presence of a catalytic amount of $Fe(acac)_3$ and 15 equiv of NMP], the expected adducts **3** were obtained in good yields and with retention of the configuration of the double bond. In a similar manner, pure *E*,*E*-diene **3v** was prepared stereoselectively and efficiently from the corresponding *E*,*E*-chlorodiene **2i** (entry 17). Primary alkyl Grignard reagents (methyl, ethyl, as well as long alkyl chain aliphatic reagents) are transferred in high yields. Secondary and tertiary alkyl Grignards also gave the expected adducts in good yields (entries 2, 4, 6, 8, 12, 15, 16). Interestingly, the isopropyl Grignard reagent can be transferred, even though it is prone to give reduced products by β-elimination (entry 15).[2b] Free propargyl alcohols were tolerated, but required the use of an excess of Grignard reagent (3 equiv), in order to obtain the desired coupled product in good yields. It is worth noting that the functionalized alkyl Grignard reagent (3-hydroxypropyl)[9] also gave the expected adduct in good yield (entry 9).

When the propargyl acetate **2h** was treated under the reaction conditions described above, we were pleased to observe that the expected cross-coupled product **3t** was obtained in reasonable yield (58% unoptimized). This result must be emphasized since the cross-coupling reactions of Grignard reagents under palladium catalysis gives complex mixtures. In the following example, it was also interesting to note that the reaction was highly chemoselective since an activated aryl bromide did not react under the reaction conditions, even though they were reported to be alkylated by Grignard reagents in the presence of iron(III) salts.[10] Indeed, when 1.3 equiv of the ethyl Grignard reagent was allowed to react with an equimolar mixture of chloroenyne **2e** and ethyl *p*-bromobenzoate, the expected enyne **3u** was obtained in 66% yield (compare with 71% obtained from $C_{12}H_{25}MgBr$, in Table 1 entry 7). No product resulting from cross-coupling reaction of the aromatic ring was detected by ^1H NMR spectroscopy of the crude mixture.

Table 1. Fe(acac)$_3$ catalyzed cross-coupling reactions between alkyl Grignard reagents and unsaturated vinyl chlorides **2**[a]

Entry	Chloroenynes **2**[b]	RMgX (equiv)	Yield of **3** (%)[c]	Compounds
1		$C_{12}H_{25}MgBr$ (1.5)	68	**3f**
2	**2c**	*c*-$C_6H_{11}MgBr$ (1.5)	74	**3g**
3		$C_{12}H_{25}MgBr$ (3)	76	**3h**
4	*E*-**2d**	*c*-$C_6H_{11}MgBr$ (3)	72	**3i**
5		$C_{12}H_{25}MgBr$ (3)	74	**3h**
6	*Z*-**2d**	*c*-$C_6H_{11}MgBr$ (3)	82	**3i**
7		$C_{12}H_{25}MgBr$ (1.5)	71	**3j**
8	**2e**	*c*-$C_6H_{11}MgBr$ (1.5)	76	**3k**
9		$ClMgO(CH_2)_3MgCl$ (1.5)	63	**3l**
10	 **2f**	$C_{12}H_{25}MgBr$ (3)	85	**3m**
11		$C_{12}H_{25}MgBr$ (3)	88	**3n**
12		*c*-$C_6H_{11}MgBr$ (3)	61	**3o**
13		C_2H_5MgBr (3)	73	**3p**
14	**2g**	CH_3MgBr (10)[d]	70	**3q**
15		*i*-C_3H_7MgCl (3)	75	**3r**
16		*t*-C_4H_9MgBr (3)[e]	65	**3s**
17	 **2i**	C_2H_5MgBr (1.5)	79	**3v**

[a] For a general procedure, see Ref. 11.
[b] Prepared according to Ref. 8.
[c] Isolated yield based on **2**. All new compounds exhibited satisfactory spectral properties and isomeric purity (>97%).
[d] CH_3MgBr in diethyl ether.
[e] *t*-C_4H_9MgBr in pentane/THF.



Scheme 3. Reagents and conditions: (a) C_2H_5MgBr (1.3 equiv), Fe(acac) (3 mol%), THF, NMP (15 equiv), −10 to 0 °C, 1 h.

Furthermore, ethyl *p*-bromobenzoate was recovered unchanged in 90% yield (Scheme 3).

In conclusion, we describe herein a very efficient synthesis of quinolines substituted at the 2- or 3-position by a 4-substituted but-3-en-1-yne group (the structure–activity relationship study will be presented in a following paper). The key step involves the efficient iron(III)-catalyzed cross-coupling reaction of a chloroenyne with an alkyl Grignard reagent.[11] This reaction which is very general and stereospecific, requires very mild conditions (0 °C in a few minutes). Moreover, this process is chemoselective since several functional groups are tolerated (e.g., propargyl acetate, ethyl benzoate, aryl bromide, and hydroxyl). Further developments will be disclosed in due course.

Acknowledgements

The CNRS is gratefully acknowledged for financial support of this research. We wish to thank G. Pembouong and A. Garlot for their technical help, J.-C. Jullian for the NMR experiments, and Dr. A. Fournet for his interest in this study.

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11. Typical procedure and selected spectroscopic data: In a round-bottomed flask, under a nitrogen atmosphere, containing the chloroenyne **2** (1 mmol) and $Fe(acac)_3$ (10.6 mg, 0.03 mmol) was added NMP (2.2 mL, 22.2 mmol) and THF (1.2 mL). The temperature was cooled to 0 °C (with an ice bath), and the desired Grignard reagent (1.5 mmol) was added dropwise (for hydroxyl chloroenynes, 3 mmol of Grignard reagent was added). The red colored solution turned dark brown to black (depending on the Grignard reagent). The reaction mixture was stirred for 30 min to 1 h, until the disappearance of starting material, as judged by TLC. A 1 M aqueous HCl solution (5 mL) was then added, and the two layers separated. After extraction of the organic layer by EtOAc (2×20 mL), the combined organic layers were washed three times with water, then dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was then purified by silica gel column chromatography to yield the expected adducts (see the table for yields).
(*E*)-6-Quinol-2-ylhex-3-en-5-yne **3a**: ^{1}H NMR (200 MHz, δ ppm) 8.06 (br d, $J = 6.4$ Hz, 2H); 7.72 (m, 2H); 7.48 (m, 2H); 6.49 (dt, $J = 15.9$, 6.7 Hz, 1H); 5.75 (dt, $J = 15.9$, 1.1 Hz, 1H); 2.21 (m, 2H); 1.05 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (50 MHz, δ ppm) 149.3; 148.1; 143.8; 136.0; 129.9; 129.2; 127.4; 126.9; 126.8; 124.1; 108.1; 89.3; 88.1; 26.4; 12.7. ESI-MS (m/z) 208 (MH^+, 100).
(*Z*)-5-Quinol-2-ylpent-2-en-4-yne **3b**: ^{1}H NMR (200 MHz, δ ppm) 8.11 (d, $J = 4.2$ Hz, 1H); 8.09 (d, $J = 4.1$ Hz, 1H); 7.78 (d, $J = 8.1$ Hz, 1H); 7.71 (t apparent, $J = 7.5$ Hz, 1H); 7.52 (m, 2H); 6.19 (dq, $J = 10.8$, 6.9 Hz, 1H); 5.78 (dd, $J = 10.8$, 1.1 Hz, 1H); 2.04 (dd, $J = 6.8$, 1.0 Hz, 3H). ^{13}C NMR (50 MHz, δ ppm) 148.3; 143.9; 141.2; 136.0; 129.9; 129.4; 127.4; 127.0; 126.9; 124.2; 109.6; 93.9; 86.9; 16.5. ESI-MS (m/z) 216 ($M+Na^+$, 30), 194 (MH^+, 100).
(*E*)-6-Quinol-3-ylhex-3-en-5-yne **3c**: ^{1}H NMR (200 MHz, δ ppm) 8.90 (d, $J = 1.7$ Hz, 1H); 8.19 (d, $J = 1.3$ Hz, 1H); 8.07 (d, $J = 8.3$ Hz, 1H); 7.70 (m, 2H); 7.54 (m, 1H); 6.40 (dt, $J = 15.9$, 6.7 Hz, 1H); 5.75 (dt, $J = 15.9$, 0.8 Hz, 1H); 2.24 (m, 2H); 1.08 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (50 MHz, δ ppm) 152.0; 147.8; 147.0; 137.8; 129.8; 129.2; 127.4; 127.3; 127.1; 117.8; 108.2; 91.7; 85.1; 26.3; 12.8. ESI-MS (m/z) 208 (MH^+, 100).
(*Z*)-5-Quinol-3-ylpent-2-en-4-yne **3d**: ^{1}H NMR (200 MHz, δ ppm) 8.92 (br s, 1H), 8.21 (br s, 1H); 8.09 (br d, $J = 8.4$ Hz, 1H); 7.77 (d, $J = 7.9$ Hz, 1H); 7.71 (dd, $J = 7.7$, 7.4 Hz, 1H); 7.56 (dd, $J = 7.5$, 7.3 Hz, 1H); 6.14 (dq, $J = 10.7$, 6.9 Hz, 1H), 5.77 (br d, $J = 11.1$ Hz, 1H), 2.02 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR (50 MHz, δ ppm) 151.5; 148.3; 141.3; 136.0; 129.9; 129.3; 127.4; 127.0; 126.9; 124.2; 109.6; 92.9; 87.4; 16.8. ESI-MS (m/z) 194 (MH^+, 100).
(*E*)-7-Quinol-3-ylhept-4-en-6-yn-1-ol **3e**: ^{1}H NMR (200 MHz, δ ppm) 8.88 (br s, 1H), 8.17 (br s, 1H); 8.06 (d, $J = 8.4$ Hz, 1H); 7.74 (d, $J = 8.1$ Hz, 1H); 7.68 (dd, $J = 7.1$, 8.2 Hz, 1H); 7.53 (dd, $J = 7.1$, 7.9 Hz, 1H), 6.35 (dt, $J = 15.8$, 7.1 Hz, 1H), 5.77 (d, $J = 15.9$ Hz, 1H); 3.70 (t, $J = 6.3$ Hz, 2H); 2.31 (dt, $J = 7.2$, 7.4 Hz, 2H); 1.73 (quint, $J = 6.8$ Hz, 2H). ^{13}C NMR (50 MHz, δ ppm) 152.0; 146.5; 145.5; 137.9; 129.9; 129.2; 127.5; 127.3; 127.2; 117.7; 109.7; 91.5; 85.3; 61.9; 29.6; 26.9. ESI-MS (m/z) 238 (MH^+, 100).