Rapid One-Pot Synthesis of Antiparasitic Quinolines Based upon the Microwave-Assisted Coupling–Isomerization Reaction (MACIR)

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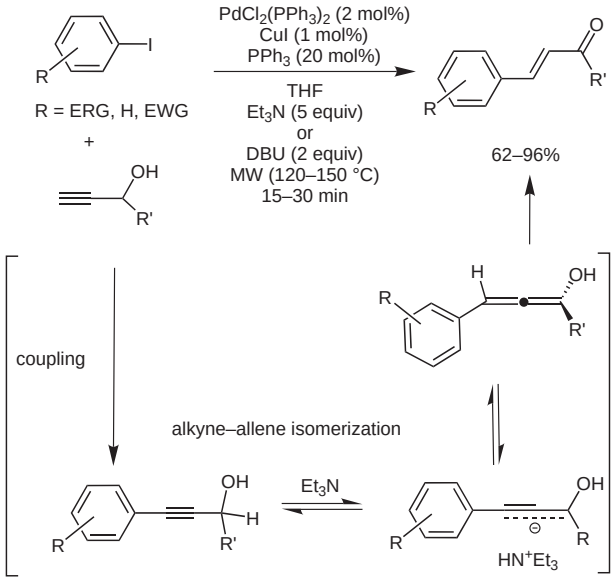
Received 5 November 2007

Abstract: 2-Substituted quinolines and related derivatives can be rapidly prepared from (hetero)aryl halides and propargyl alcohols in the sense of a one-pot microwave-assisted coupling–isomerization reaction (MACIR). First biological tests against trypanosomes and protozoans have revealed antiparasitic activity in the lower micromolar range.

Key words: alkynes, antiparasitic activity, catalysis, cross-couplings, isomerizations, microwave reactions

Quinolines represent an important class of heterocycles, and the quinoline skeleton is present in various natural products, especially in alkaloids. Among them quinine is an active ingredient for the treatment of malaria.[2] Despite its relatively low efficacy and tolerability, quinine still plays an important role in the treatment of multiresistant malaria, one of the world's most devastating infectious diseases.[3] Therefore, the design of many drugs and affordable chemotherapies are based upon synthetic quinoline derivatives, such as chloroquine, mefloquine, quinacrine.[4] In addition, chimanine alkaloids are also effective against parasitic diseases such as leishmaniasis and trypanosomiasis.[5] Besides, *leishmania*-HIV co-infection has been regarded as an emerging infectious disease. Several 2-substituted quinolines[6] have been shown to possess in vitro activity against causal agents of cutaneous leishmaniasis, visceral leishmaniasis, African trypanosomiasis and Caga's disease as well as against HIV-1 replication. Thus, substituted quinolines are generally attractive as antimalarials, antibacterials, protein kinase inhibitors, NADH models, and as agrochemicals. In addition, they are also interesting as ligands for transition-metal complexes[7] as well as general synthetic blocks.[8] Numerous elegant syntheses have been developed for quinolines, however, the exploration of diversity-oriented synthetic routes for this class of compounds still remains a challenge. Quite some syntheses of quinolines are based upon the condensation of anilines, as the nitrogen component, and an electrophilic three-carbon unit, such as in Skraup, in Doebner–von Miller, in Combes, and in Conrad–Limpach syntheses[9] which are highly convergent. Even milder, regioselective, and practical syntheses for these heterocycles can be envisioned by the aid of metal-catalyzed coupling circumventing the often harsh conditions in classical quinoline construction.[10,11] An interesting access to 2-substituted quinolines makes use of a base-mediated consecutive isomerization and cyclization sequence of 3-(2-aminophenyl)-1-arylprop-2-yn-1-ols that are easily available by Sonogashira coupling of iodo aniline with propargyl alcohols after prolonged reaction time (7–20 h) at elevated temperature (180 °C), or upon using strong bases (KOH).[12] Recently, we have extended the coupling–isomerization reaction (CIR),[13] a straightforward enone synthesis by Sonogashira coupling of (hetero)aryl halides and propargyl alcohols with concomitant base-catalyzed propargyl alcohol–enone isomerization, by dielectric heating for electronically diverse substrates to a general microwave-assisted CIR (MACIR; Scheme 1).[14] Generally, the CIR is a suitable entry to multicomponent syntheses of heterocycles.[15] Here, we communicate an application of MACIR to the synthesis of antiparasitic quinolines and first biological data.



Scheme 1 Microwave-assisted coupling–isomerization reaction (MACIR)

In systematic studies on CIR accelerated by dielectric heating, we recently found that not only electron-withdrawing but also electro-neutral and even electron-rich (hetero)aryl halides can be successfully reacted propargyl alcohols in the sense of the CIR-chalcone synthesis.[14b] Indeed, subjecting *o*-amino (hetero)aryl halides **1** and propargyl alcohols **2** to the MACIR conditions, after 30

SYNLETT 2008, No. 3, pp 0359–0362
Advanced online publication: 23.01.2008
DOI: 10.1055/s-2008-1032067; Art ID: G35807ST
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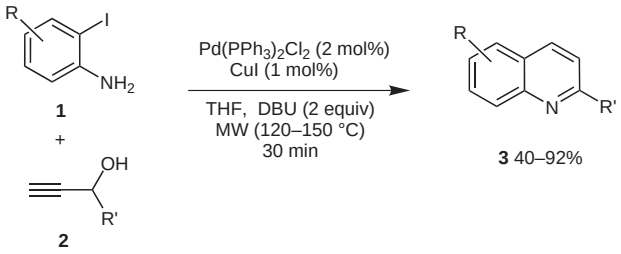
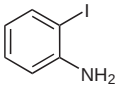
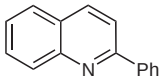
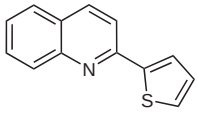
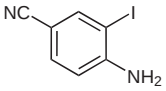
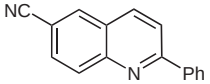
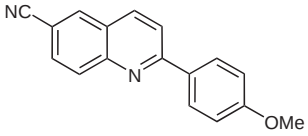
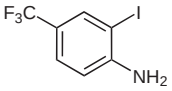
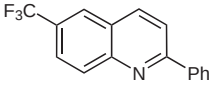
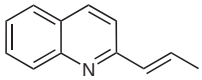
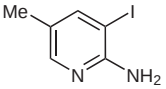
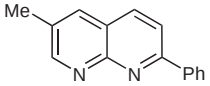
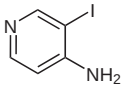
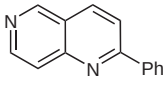
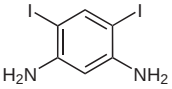
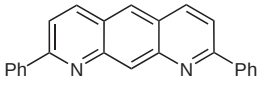
minutes reaction time, the corresponding quinoline derivatives **3** were obtained in good to excellent yields (Scheme 2, Table 1).[16,17] Besides extensive spectroscopic analyses (^{1}H, ^{13}C and DEPT, COSY, and HETCOR NMR experiments, mass spectrometry) the structure was unambiguously confirmed by an X-ray crystal structure analysis of the compound **3c** (Figure 1).[18]



Scheme 2 One-pot MACIR synthesis of 2-substituted quinolines

Table 1 MACIR Synthesis of 2-Substituted Quinolines **3**[a]

Entry	2-Iodoaniline **1**	Propargyl alcohol **2**	Quinoline **3** (yield, %)[b]
1	 **1a**	**2a** R′ = Ph	 **3a** (81)
2	**1a**	**2b** R′ = 2-thienyl	 **3b** (80)
3	 **1b**	**2a**	 **3c** (70)
4	**1b**	**2c** R′ = 4-MeOC$_6$H$_4$	 **3d** (57)
5	 **1c**	**2a**	 **3e** (92)
6	**1a**	**2d** R′ = *trans*-prop-1-enyl	 **3f** (40)
7	 **1d**	**2a**	 **3g** (79)
8	 **1e**	**2a**	 **3h** (78)
9	 **1f**	**2a**	 **3i** (64)

[a] Reaction conditions: (hetero)aryl halide **1** (1.0 equiv), propargyl alcohol **2** (1.05 equiv), Pd(PPh$_3$)$_2$Cl$_2$ (0.02 equiv), CuI (0.01 equiv), DBU (2 equiv, 0.7 M in THF), heating in a sealed vessel at 150 °C in a Smith Synthesizer single-mode microwave cavity for 30 min.
[b] Yields refer to isolated yields of compound **3** after flash chromatography on silica gel to be ≥95% pure as determined by NMR spectroscopy.

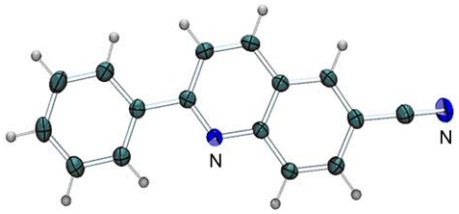


Figure 1 Molecular structure of **3c**

Without isolation of intermediates, both the CIR and the cyclocondensation take place in one step. Mechanistically, the formation of the quinoline core presumably occurs via a base-mediated *trans–cis* isomerization equilibrium under the microwave irradiation, followed by a concluding intramolecular condensation step. Interestingly, naturally occurring quinoline alkaloids, such as 2-phenyl quinoline (**3a**) or chimanine B (**3f**) can be prepared very easily, very quickly, and in good yields. Starting with the 1,5-diamino 2,4-diiodobenzene (**1f**), in the sense of a pseudo three-component reaction, the expected pyridoquinoline derivative **3i** is accessible.

Many quinolines have already been shown to possess antileishmanial activity in vitro tests (IC_{50} = 12-100 μM).[6] Therefore, we have tested the 2-substituted quinoline derivatives **3** at two concentrations with respect to their antiparasitic activity, i.e. against trypanosomes (*trypanosoma brucei rhodesiense*, *trypanosoma cruzi*, *leishmania donovani*), and protozoans (*plasmodium falciparum*), all of them are responsible for the plagues of tropical diseases such as sleeping sickness, leishmaniasis, or malaria. Among the tested quinolines some representatives display antiplasmodial activity at higher micromolar levels. Therefore, the IC_{50} values against *plasmodium falciparum* were determined for all quinoline derivatives **3**. The naphthyridine **3g** showed also moderate activity against *plasmodium falciparum* at lower micromolar concentration (IC_{50} 1.64 mg/mL).

In conclusion, we have developed a rapid and efficient one-pot quinoline synthesis on the basis of MACIR of the *o*-amino (hetero)aryl halides with propargyl alcohols within 30 minutes and in good to excellent yields. First biological tests against selected parasites have revealed the potential of new quinoline derivatives as antiparasitic agents. Further studies directed to expand the synthetic scope and the screening for compounds with higher activity are currently in progress.

Acknowledgment

Financial support of the Deutsche Forschungsgemeinschaft is gratefully acknowledged. We also cordially thank Ms Annette Loos for experimental assistance, Dr. Elisabeth Davioud-Charvet for valuable discussions, and BASF AG for the generous donation of chemicals.

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(16) **Typical Procedure (3g, Table 1, Entry 7)**
A magnetically stirred solution of **1d** (234 mg, 1.00 mmol), **2a** (139 mg, 1.05 mmol), $(PPh_3)_2PdCl_2$ (20 mg, 0.02 mmol), and CuI (2 mg, 0.01 mmol) in degassed DBU (2 mmol) and THF (1.5 mL) was stirred under nitrogen in a heavy-walled SmithCreator process vial in the microwave cavity at 150 °C for 30 min. After cooling to r.t. EtOAc (40 mL) and H_2O (40 mL) were added and the aqueous layer was extracted with EtOAc. The combined organic phases were dried with $MgSO_4$ and the solvents were removed in vacuo. The residue was chromatographed on silica gel (hexane–EtOAc, 5:1) and recrystallized from EtOH or pentane–$CHCl_3$ (1:1) to give 174 mg (79%) of **3g** as light yellow crystals, mp 142 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.54 (s, 3 H), 7.44–7.54 (m, 3 H), 7.91 (d, *J* = 1.5 Hz, 1 H), 7.94 (d, *J* = 8.3 Hz, 1 H), 8.13 (d, *J* = 8.3 Hz, 1 H), 8.28 (dd, *J* = 8.3, 1.5 Hz, 2 H), 8.96 (d, *J* = 2.1 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6 (CH_3), 119.6 (CH), 121.3 (C_q), 127.8 (CH), 128.8 (CH), 129.9 (CH), 131.5 (C_q), 135.2 (CH), 137.1 (CH), 138.7 (C_q), 154.8 (C_q), 155.8 (CH), 159.3 (C_q). MS: (EI, 70 eV): *m/z* (%) = 220.1 (100) [M^+], 205.1 (10) [$M^+ - CH_3$], 77 (12) [$C_6H_5^+$]. IR (KBr): ν = 3027, 1604, 1581, 1546, 1503, 1481, 1458, 1434, 1321, 1278, 1140, 1025, 898, 814, 766, 739, 703, 678, 568 cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_2$ (220.3): C, 81.79; H, 5.49; N, 12.72. Found: C, 81.71; H, 5.38; N, 12.79.

(17) All compounds have been fully characterized by ^{1}H, ^{13}C and DEPT, COSY, NOESY, HETCOR and HMBC NMR experiments, IR, mass spectrometry, HRMS, and/or combustion analyses.

(18) CCDC-669319 (**3c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; or deposit@ccdc.cam.ac.uk].

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