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Tetrahedron Letters 47 (2006) 2539–2542
Tetrahedron Letters

# Synthesis and biological evaluation of allenic quinazolines using palladium-catalyzed hydride-transfer reaction

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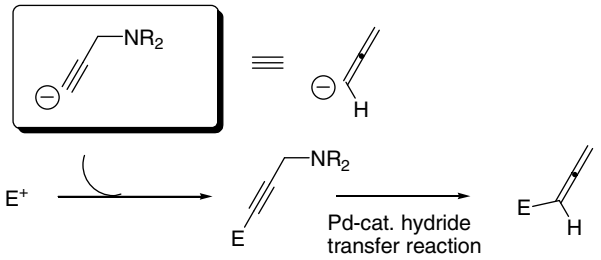
Received 9 January 2006; revised 6 February 2006; accepted 9 February 2006
Available online 24 February 2006

**Abstract**—Allenic quinazolines **13a**–**h** were designed as mimics of Tarceva, which is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, and synthesized from the corresponding 4-(iodoanilino)quinazolines or 4-(iodophenoxy)quinazolines with *N*,*N*-dicyclohexylprop-2-ynylamine by the Sonogashira coupling followed by palladium-catalyzed hydride-transfer reaction. Cell growth inhibition of **13a**–**h** toward A431, Kato III, SKBR3, and HepG2 was examined. Among the compounds synthesized, **13a** showed a similar cell growth inhibition to Tarceva. Moreover, **13d** and **13h** exhibited a specific growth inhibition toward Kato III cells ($IC_{50} = 12$ and 4.7 μM, respectively), although a significant inhibition toward other three cell lines was not observed at a 100 μM concentration of compounds.


Since interesting biological activities have been observed in a substantial number of allenes in recent years,[1] many attempts have been made to introduce an allenic moiety into the backbone of certain pharmacologically active molecules in order to develop new biological and pharmacological properties.[2] Recent advances of pharmacologically active allenes focus mainly on inhibitors of enzymes including allenic steroids,[3] prostaglandines[4] and amino acid[5] and nucleoside analogues.[6] Therefore, development of simple protocols for the introduction of an allene moiety into pharmacologically active molecules is an important subject in pharmaceutical drug design.[7] We recently found that propargylic amines underwent the hydride-transfer reaction in the presence of a palladium catalyst to afford allenes.[8] In this transformation, propargylic amine can be handled as an allenyl anion equivalent and introduced into various electrophiles to be transformed into allenes (Scheme 1). The allene transformation can be utilized for the synthesis of heterocyclic allenes,[9] and the use of two cyclohexyl groups substituted on the nitrogen of propargylic amines enabled us to handle the transformation under mild conditions to afford the conjugated ene–allenes.[10]

On the other hand, the epidermal growth factor receptor (EGFR) protein tyrosine kinase (PTK) is one of the important kinases that plays a fundamental role in signal transduction pathways. Since Fry et al. discovered that the 4-anilinoquinazoline (PD 153035) possesses a specific inhibitory activity toward EGFR tyrosine kinase,[11] various 4-anilinoquinazoline derivatives have been synthesized so far based upon the 4-anilinoquinazoline framework, and Iressa[12] and Tarceva[13] have been found to be effective for nonsmall cell lung cancer and recently approved for clinical use. We focused on the acetylene moiety of Tarceva and decided to introduce an allenic moiety into the aniline ring of 4-anilinoquinazolines. In this letter, we report the synthesis and biological evaluation of 4-(allenylanilino)quinazolines and 4-(allenylphenoxy)quinazolines using the palladium-catalyzed hydride-transfer reaction.




**Scheme 1.** Allenyl anion equivalent.

Allenic quinazolines were synthesized from the corresponding iodides and dicyclohexylpropargylamine

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doi:10.1016/j.tetlet.2006.02.043

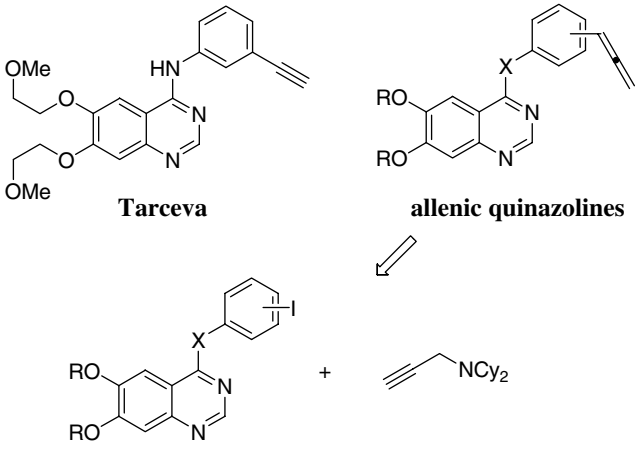
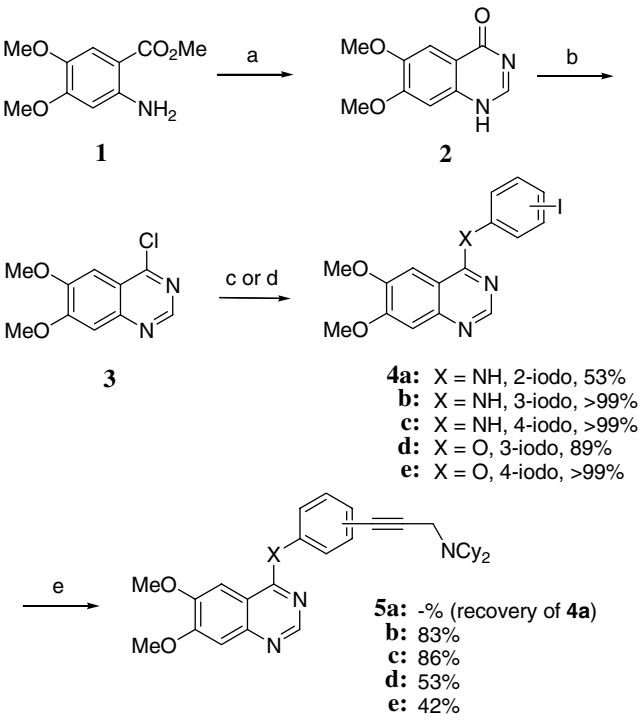



**Chart 1.**




**Scheme 2.** Reagents and conditions: (a) $NH_2CHO$, 190 °C, 87%; (b) $POCl_3$, diisopropylethylamine, toluene, reflux, 93%; (c) 2-, 3-, or 4-iodoaniline, isopropanol, reflux; (d) 3- or 4-iodophenol, $K_2CO_3$, isopropanol, reflux; (e) *N*,*N*-dicyclohexylprop-2-ynylamine, $Pd(PPh_3)_4$ (5 mol %), CuI (10 mol %), tetraethylamine, $CH_3CN$, 60 °C.

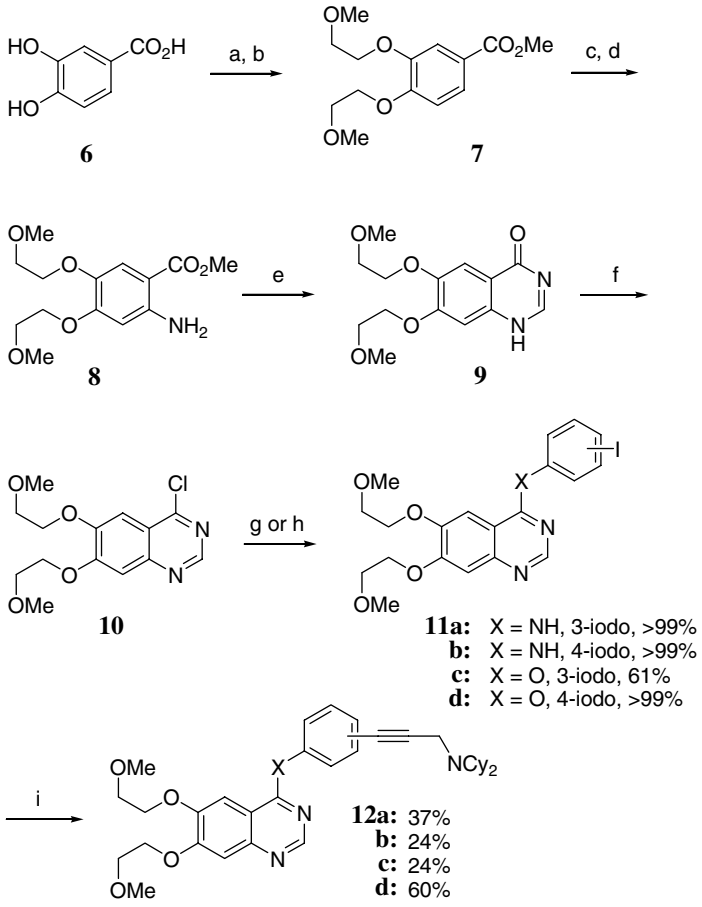
via the Sonogashira coupling followed by the hydride transfer reaction as shown in Chart 1. Synthesis of 4-iodoanilinoquinazolines was accomplished according to the reported procedures with modification.[14] Cyclization of methyl 2-amino-4,5-dimethoxybenzoate **1** with formamide gave quinazolinone **2**, which was treated with $POCl_3$ to afford 4-chloro-6,7-dimethoxyquinazoline **3** in 93% yield. Nucleophilic substitution of **3** with 2-, 3-, and 4-iodoanilines gave the iodoanilinoquinazolines, **4a**–**c**. In the similar manner, the iodophenoxyquinazolines, **4d** and **4e**, were obtained from **3** by treated with 3- and 4-iodophenols. We next examined the introduction of a propargylic amine moiety as an allene precursor into the iodides **4a**–**e** using the Sonogashira coupling reaction. Although the iodide **4a** did not undergo the Sonogashira coupling with *N*,*N*-dicyclohexylprop-2-ynylamine in the presence of palladium catalyst, the corresponding allene precursors **5b**–**d** were obtained from **4b**–**d** in 42–86% yields (Scheme 2).

6,7-Bis(2-methoxyethoxy)quinazoline derivatives **12a**–**d** were also synthesized from 3,4-dihydroxybenzoic acid **6**. Esterification of **6** followed by ether formation with 1-bromo-2-methoxyethane gave **7**. Nitration at 2-position of **7** followed by hydrogenation under Pd/C afforded **8**, which was converted to 6,7-bis(2-methoxyethoxy)-4-chloroquinazoline **10** through quinazolinone **9**. The chloroquinazoline **10** was treating with 3- and 4-iodoanilines to give the corresponding iodoanilinoquinazolines, **11a** and **11b**, quantitatively. In the similar manner, the iodophenoxyquinazolines, **11c** and **11d**, were obtained from **10** by treated with 3- and 4-iodophenols. The iodides **11a**–**d** underwent the Sonogashira coupling with *N*,*N*-dicyclohexylprop-2-ynylamine in the presence of palladium catalyst to give the corresponding allene precursors **12a**–**d** in 24–60% yields (Scheme 3).

We next investigated the synthesis of various allenic quinazolines **13** from the corresponding allene precursors **5b**–**d** and **12a**–**d** via palladium-catalyzed hydride-transfer reaction as shown in Table 1. The reaction of **5b** proceeded in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %) and $(C_6F_5)_2PC_2H_4P(C_6F_5)_2$ (10 mol %) in $CHCl_3$ at 100 °C, giving the 6,7-dimethoxy-4-(3-allenylanilino)quinazoline **13a** in 66% yield (entry 1). This reaction condition was previously investigated in the synthesis of heterocyclic allenes.[9] Not only the anilino quinazoline **5c** but also the phenoxyquinazolines **5d** and **5e** underwent the hydride-transfer reaction (entries 2–4). In the similar manner, 6,7-bis(2-methoxyethoxy)quinazoline derivatives **13e**–**h** were also obtained from **12a**–**d** in 39–61% yields (entries 5–8).

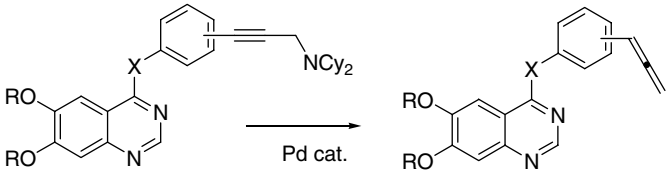
Cell growth inhibition of the allenic quinazolines **13a**–**h** was investigated using various human cancer cell lines. The results are summarized in Table 2. The compound **13a** exhibited relatively high cell growth inhibition toward all cell lines and gave $IC_{50}$ values of 1.8–9.0 μM, which are similar to those of Tarceva. Compounds **13b**,**e**, and **13f** showed lower growth inhibitions toward HepG2 cells in comparison with A431, Kato III, and SKBR3 cells. Surprisingly, highly specific growth inhibition toward Kato III cells, in which fibroblast growth factor receptors (FGFRs) are highly expressed, was observed in compounds **13d**, and **13h**. $IC_{50}$ values of **13d** and **13h** toward Kato III cells were 12 and 4.7 μM, respectively, although a significant inhibition toward other three cell lines was not observed at a 100 μM concentration of compounds.

In conclusion, we succeeded in the synthesis of allenic quinazolines **13a**–**h** from 4-(iodoanilino)quinazolines and 4-(iodophenoxy)quinazolines using the Sonogashira coupling and palladium-catalyzed hydride-transfer reactions. The current synthesis proved utility of the




**Scheme 3.** Reagents and conditions: (a) $H_2SO_4$, MeOH, reflux, 98%; (b) 1-bromo-2-methoxyethane, $K_2CO_3$, TBAI, acetone, reflux, 99%; (c) $HNO_3$, $Ac_2O$, rt, 85%; (d) $H_2$, 10% Pd/C, EtOH, quant.; (e) $NH_2CHO$, 160 °C, 90%; (f) $POCl_3$, diisopropylethylamine, toluene, reflux, quant.; (g) 3- or 4-iodoaniline, isopropanol, reflux; (h) 3- or 4-iodophenol, $K_2CO_3$, isopropanol, reflux; (i) *N*,*N*-dicyclohexylprop-2-ynylamine, $Pd(PPh_3)_4$ (5 mol %), CuI (10 mol %), triethylamine, $CH_3CN$, 60 °C.

**Table 1.** Synthesis of allenes **13** from **5b–d** or **12a–d** via palladium-catalyzed hydride transfer reaction[a]




**5b-e** or **12a-d** **13**

| Entry | | Structure of **13** | | | Yield (%) |
|---|---|---|---|---|---|
| | | R | X | Position[b] | |
| 1 | **13a** | $CH_3$ | NH | 3′ | 66 |
| 2 | **13b** | $CH_3$ | NH | 4′ | 39 |
| 3 | **13c** | $CH_3$ | O | 3′ | 46 |
| 4 | **13d** | $CH_3$ | O | 4′ | >99 |
| 5 | **13e** | $CH_3OC_2H_4$ | NH | 3′ | 49 |
| 6 | **13f** | $CH_3OC_2H_4$ | NH | 4′ | 39 |
| 7 | **13g** | $CH_3OC_2H_4$ | O | 3′ | 55 |
| 8 | **13h** | $CH_3OC_2H_4$ | O | 4′ | 61 |

[a] The reactions were carried out in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %) and $(C_6F_5)_2PC_2H_4P(C_6F_5)_2$ (10 mol %) in $CHCl_3$ at 100 °C in a vial tube.

[b] The position of an allene moiety substituted on the aniline group of **13** is indicated.

palladium-catalyze allene-transformation reaction for introduction of an allene moiety into pharmacologically active molecules. Among the compound synthesized, **13a** showed a similar cell growth inhibitory activity to Tarceva. Moreover, **13d** and **13h** exhibited a specific growth inhibition toward Kato III cells. Since FGF

**Table 2.** Cell growth inhibition of compounds **13a–h** ($IC_{50}/\mu M$)[a]

| Compounds | A431[b] | Kato III[c] | SKBR3[d] | HepG2[e] |
|---|---|---|---|---|
| **13a** | 1.8 | 8.7 | 5.3 | 9.0 |
| **13b** | 22 | 17 | 18 | >100 |
| **13c** | 28 | 2.3 | >100 | 98 |
| **13d** | >100 | 12 | >100 | >100 |
| **13e** | 2.2 | 9.3 | 3.7 | 38 |
| **13f** | 7.2 | 5.8 | 12 | 52 |
| **13g** | 15 | 12 | 41 | 14 |
| **13h** | >100 | 4.7 | >100 | >100 |
| Tarceva | 2.3 | 3.3 | 9.3 | 8.2 |

[a] Cells were incubated with the medium containing the compounds at various concentrations for 3 days at 37 °C in $CO_2$ incubator. $IC_{50}$ values show a concentration of compounds that resulted in 50% of the cell number of untreated cultures.

[b] Human vulval squamous carcinoma cell.

[c] Human stomach cancer cell.

[d] Human breast cancer cell.

[e] Human liver cancer cell.

receptors are expressed highly in Kato III cells, this result may propose a possibility of **13d** and **13h** as potent inhibitors of FGFR tyrosine kinases. Inhibitory activities of these compounds toward various kinases as well as mechanistic details of the specific inhibition toward Kato III cells are now under investigation in our laboratory.

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