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An efficient synthesis of 4-alkyl-2(1*H*)-quinazolinones and 4-alkyl-2-chloroquinazolines from 1-(2-alkynylphenyl)ureas

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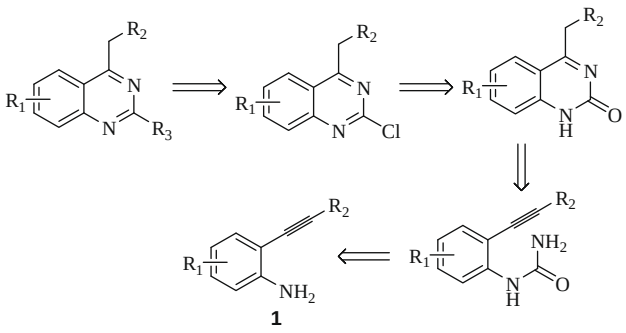
ABSTRACT

An efficient synthesis of 4-alkyl-2(1*H*)-quinazolinones has been achieved by cyclization of 1-(2-alkynylphenyl)ureas (**2** R_2 = alkyl) in dichloroethane catalyzed by TfOH. In the case of aryl substitution (**2** R_2 = aryl), a mixture of quinazolinone tautomers is obtained in dichloroethane with TFA as co-solvent. Chlorination of the resulting mixture affords 4-alkyl-2-chloro-quinazolines as sole products.

Quinazoline and quinazolinone derivatives have attracted considerable interest for medicinal chemists due to their broad spectrum of biological activities such as anticancer, diuretic, anti-inflammatory, anticonvulsant, and antihypertensive activities.[1] Although there are numerous methods for the syntheses of quinazoline and quinazolinone derivatives, no general and practical methods for the syntheses of diversified 4-alkylquinazolines and 4-alkyl-2(1*H*)-quinazolinones are available.[2] Herein we report a novel strategy for the conversion of readily available 2-alkynylanilines **1** to diversified 4-alkyl-2-chloroquinazolines and 4-alkylquinazolinones which could be served as precursors for the synthesis of 4-alkyl-2-substituted quinazolines (Scheme 1).

2-Alkynylanilines **1** with various alkyl and aryl substituents at the other end of triple bond were first transformed to their corresponding urea derivatives according to the literature method with minor modification in good to almost quantitative yields (Table 1).[3] Anilines with aryl substituents worked better than those with alkyl substituents (Table 1, entries 8–14). The ratio of HOAc to H_2O was determined by the solubility of **1** in the co-solvent. The reaction was very clean and the crude products were pure enough for further reaction without purification after normal work-up in most cases.

The reaction conditions were optimized with 1-(2-(1-hexynyl)phenyl)urea **2a** as substrate and the results are summarized in Table 2. The solvent was screened first in the presence of 2.0 equiv of TfOH as a catalyst (Table 2, entries 1–6).[4] Dichloroethane (DCE) was superior to other solvents and afforded the desired product in good yield (85%, Table 2, entry 1). The yield was lower in dichloromethane under reflux overnight probably due to its lower boiling point (Table 2, entry 2). A range of acids were tested with DCE as a solvent (Table 2, entries 9–13). Among these acids, concentrated sulfuric acid can produce the product in reasonable yield



Scheme 1. Retrosynthetic analysis of 4-alkylquinazolines.

(62%, Table 2, entry 12).[5] The reaction was also conducted with TFA and HOAc as solvents. HOAc cannot catalyze the reaction at all. Although as high as 81% of product can be isolated in TFA as a solvent, the yield was much lower using 2.0 equiv of TFA in DCE (Table 2, entries 8 and 9). The results suggested that stronger acid TfOH was more efficient in this reaction. The amount of TfOH was also optimized from catalytic (0.1 equiv) to excess (3.0 equiv). The yield can be maximized to 91% with 1.5 equiv of TfOH (Table 2, entry 17).

With the optimized conditions established, 1-(2-alkynylphenyl)ureas **2** with alkyl substituents were tested first. Good to excellent yield of 2-(1*H*)-quinazolinones **3** with a variety of alkyl groups on the C-4 was obtained (Table 3, entries 1–4). Substitutions on the aromatic ring affected the yields very sensitively (Table 3, entries 5 and 6). Electron-donating group (methyl) favored the reaction while electron-withdrawing group (chloro) disfavored the reaction dramatically (28%).[6]

When cyclization of **2h** with a phenyl substituent was applied under the same condition, an unexpected indole derivative **4h** was obtained in 71% yield (Scheme 2). When the acidity of the cat-

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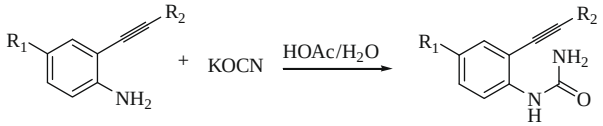
Table 1
Synthesis of 1-(2-alkynylphenyl)ureas **2** from 2-alkynylanilines **1**[a]

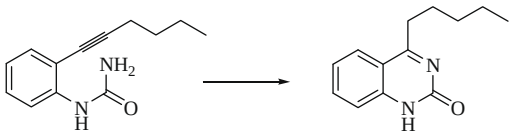


1 **2**

Entry	R_1	R_2	$HOAc/H_2O$	Product	Yield (%)
1	H	*n*-Bu	2:1	**2a**	88[b]
2	H	*t*-Bu	3:1	**2b**	70[b]
3	H	Bn	2.5:1	**2c**	97[c]
4	H	Cyclohexyl	3:1	**2d**	81[b]
5	H	TMS	2:1	**2e**	95[c]
6	Me	TMS	4:1	**2f**	98[c]
7	Cl	TMS	4:1	**2g**	98[c]
8	H	Ph	3:1	**2h**	95[c]
9	H	4-BrC_6H_4	5:1	**2i**	98[c]
10	H	4-ClC_6H_4	5:1	**2j**	99[c]
11	H	3-ClC_6H_4	4:1	**2k**	96[c]
12	H	2-ClC_6H_4	4:1	**2l**	95[c]
13	Me	Ph	5:1	**2m**	98[c]
14	Cl	Ph	5:1	**2n**	96[c]
15	H	4-MeC_6H_4	5:1	**2o**	98[c]
16	H	4-$MeOC_6H_4$	4:1	**2p**	99[c]

[a] To a suspension of 2-alkynylanilines **1** (0.5 mmol) in water (2.0 mL) was added HOAc under sonication until the starting material was all dissolved. A solution of KOCN (3.0 equiv) in minimum amount of H_2O was added to the above-mentioned solution and was stirred for about 20 min at ambient temperature.
[b] Purified by column chromatography.
[c] Extracted with EtOAc and washed with H_2O, saturated $NaHCO_3$, and brine, and used without further purification.

Table 2
Cyclization of 1-(2-(1-hexynyl)phenyl)urea **2a** under various conditions[a]



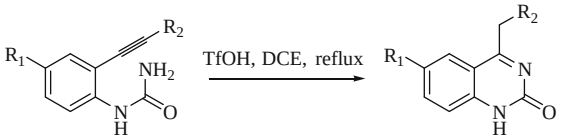
2a **3a**

Entry	Solvent	Acid (equiv)	Yield[b] (%)
1	DCE	TfOH (2.0)	85
2	DCM	TfOH (2.0)	69
3	EtOH	TfOH (2.0)	32
4	Ether	TfOH (2.0)	Trace
5	*n*-Hexane	TfOH (2.0)	34
6	Acetonitrile	TfOH (2.0)	Trace
7	AcOH	AcOH (solvent)	Trace
8	TFA	TFA (solvent)	81
9	DCE	TFA (2.0)	28
10	DCE	*p*-TsOH (2.0)	9
11	DCE	$BF_3{\cdot}OEt_2$ (2.0)	Trace
12	DCE	Concd H_2SO_4 (2.0)	62
13	DCE	TMSOTf (2.0)	31
14	DCE	TfOH (0.1)	9
15	DCE	TfOH (0.5)	14
16	DCE	TfOH (1.0)	63
17	**DCE**	**TfOH** (1.5)	**91**
18	DCE	TfOH (2.5)	86
19	DCE	TfOH (3.0)	68

[a] Heating a solution of 1-(2-(1-hexynyl)phenyl)urea **2a** (0.5 mmol) in individual solvent (3 mL) to reflux in the presence of acid catalyst overnight.
[b] Isolated yield.

alyst was reduced from TfOH to TFA, the expected quinazolinone **3h** was indeed produced but together with its tautomer **5**. We failed to separate them in pure form. They equilibrated to the mixtures again soon after column chromatography. The tautomers were treated with $POCl_3$ and 2-chloro-4-benzylquinazoline **6h**

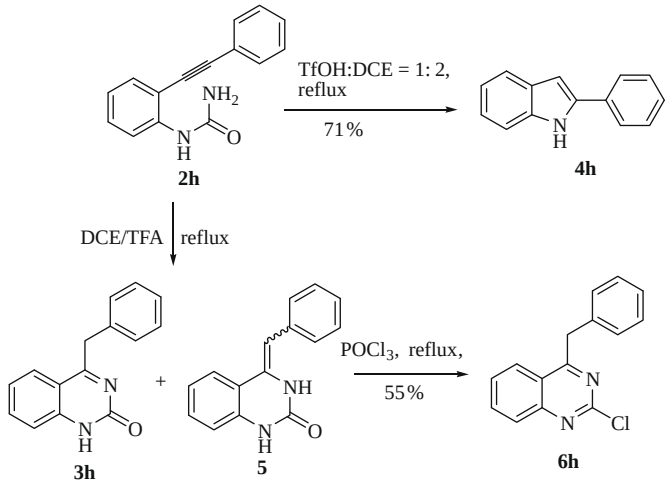
Table 3
TfOH-catalyzed cyclization of 1-(2-alkynylphenyl)ureas **2** in DCE[a]



2 **3**

Entry	**2**	Product **3**	Yield[b] (%)
1	**2b**	**3b,** R_1 = H, R_2 = *t*-Bu	91
2	**2c**	**3c,** R_1 = H, R_2 = Bn	79
3	**2d**	**3d,** R_1 = H, R_2 = cyclohexyl	98
4	**2e**	**3e,** R_1 = H, R_2 = H	75
5	**2f**	**3f,** R_1 = Me, R_2 = H	89
6	**2g**	**3g,** R_1 = Cl, R_2 = H	28

[a] Heating a solution of 1-(2-alkynylphenyl)ureas **2** (0.5 mmol) in DCE (3 mL) to reflux in the presence of TfOH (0.75 mmol) overnight.
[b] Isolated yield.

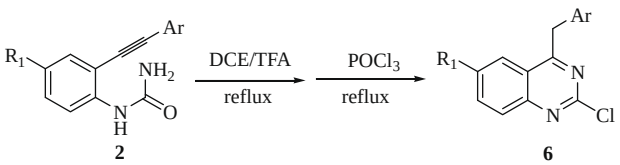


Scheme 2. Cyclization of 1-(2-(2-phenylethynyl)phenyl)urea **2h** under different conditions.

was formed as a sole product in 55% overall yield from **2h**. The aromaticity of the quinazoline locked the double bond inside the ring.

The two-step strategy was then applied to other aryl substituted 1-(2-alkynylphenyl)ureas **2i–2n** (Table 4). Functionalities

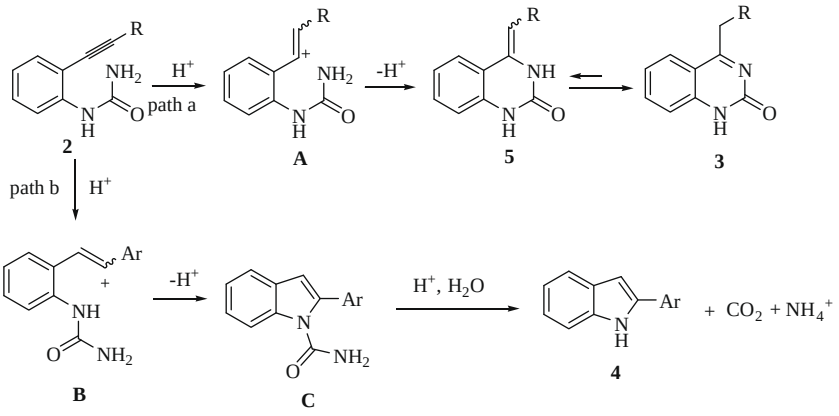
Table 4
TFA-catalyzed cyclization of 1-(2-alkynylphenyl)ureas **2** and subsequent chlorination with $POCl_3$[a]



2 **6**

Entry	**2**	Product **6**	Yield[b] (%)
1	**2i**	**6i,** R_1 = H, Ar = 4-BrC_6H_4	70
2	**2j**	**6j,** R_1 = H, Ar = 4-ClC_6H_4	67
3	**2k**	**6k,** R_1 = H, Ar = 3-ClC_6H_4	71
4	**2l**	**6l,** R_1 = H, Ar = 2-ClC_6H_4	80
5	**2m**	**6m,** R_1 = Me, Ar = Ph	49
6	**2n**	**6n,** R_1 = Cl, Ar = Ph	Trace

[a] Heating a solution of 1-(2-alkynylphenyl)ureas **2** (0.5 mmol) in TFA (1 mL) and DCE (2 mL) to reflux. After normal work-up, the crude product was treated with $POCl_3$ under reflux.
[b] Isolated yield.



Scheme 3. Mechanism of cyclization of 1-(2-alkynylphenyl)ureas **2** under different acids.

such as chloride and bromide on the aromatic ring away from the urea moiety tolerated (Table 4, entries 1–4), while chloro substitution on the left aromatic ring (R_1) ruined the reaction (Table 4, entry 6). Electron-donating groups such as methyl and methoxy in substrates **2o** and **2p** favored the formation of indoles exclusively even under the 'milder' conditions (result not shown).[7]

The possible reaction mechanism is depicted in Scheme 3. When R is an alkyl group, formation of **A** is preferred since the vinyl cation intermediate can be stabilized by the neighboring aromatic group. Subsequent cyclization leads to **5** which tautomerizes to its more stabilized form **3**. When R is an aryl group, competitive formation of **B** is preferred followed by five-membered indole formation. The carboxamide moiety on nitrogen of indole is easily cleaved under strong acid in the presence of moisture. Path b is especially favored when the Ar is substituted with an electron-donating group, such as methyl and methoxy in **2o** and **2p**. When changing TfOH to milder acid TFA, path a is possible even for some aryl-substituted 1-(2-alkynylphenyl)ureas **2**. However in this case, tautomerization of **5** to **3** is not exclusively since the double bond can also be stabilized by the aromatic group.

In summary, we have demonstrated an efficient method for the synthesis of 4-alkyl-2(1*H*)-quinazolinones and 4-alkyl-2-chloroquinazolines from 1-(2-alkynylphenyl)ureas **2**. Substitution on the other end of the triple bond is decisive for the acid applied. 1-(2-Alkynylphenyl)ureas **2** can be prepared in high yields from readily available 2-alkynylanilines. The construction of a focused library of 4-alkyl-2-substitutedquinazolines from products of current method is underway in our laboratories.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.130.

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6. *General procedure for compounds* **3**: A solution of 1-(2-alkynylphenyl)ureas **2** (0.5 mmol) in DCE (3 mL) was heated to reflux in the presence of TfOH (0.75 mmol) overnight. Ethyl acetate was added and the mixture was washed successively with saturated $NaHCO_3$, H_2O, and brine. The organic layer was separated and dried over Na_2SO_4. The concentrated residue was purified by column over silica gel. Compound **3a**: ^{1}H NMR (400 MHz, CDCl3): δ 12.99 (br, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 3.11 (t, J = 7.6 Hz, 2H), 1.92–1.84 (m, 2H), 1.47–1.36 (m, 4H), 0.92 (t, J = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.5, 158.6, 142.0, 135.0, 125.9, 123.2, 116.9, 115.8, 35.5, 31.8, 27.6, 22.5, 14.0; MS (EI, *m/z*) 216 $[M]^+$; HRMS (EI) calcd for $C_{13}H_{16}N_2O$: 216.1257 $[M]^+$, found: 216.1256.
7. *General procedure for compounds* **6**: A solution of 1-(2-alkynylphenyl)ureas **2** (0.5 mmol) in TFA (1 mL) and DCE (2 mL) was heated to reflux overnight. After removal of most solvents, ethyl acetate was added and the mixture was washed with saturated $NaHCO_3$, H_2O, and brine. The solution was dried over Na_2SO_4 and concentrated under vacuum. To the completely dried residue was added $POCl_3$ (3 mL) and stirred under reflux overnight. The excess $POCl_3$ was evaporated under vacuum and the residue was diluted with EtOAc. The mixture was washed with saturated $NaHCO_3$, H_2O, and brine, successively. The organic layer was separated and dried over Na_2SO_4. The concentrated residue was purified by column chromatography over silica gel. Compound **6h**: ^{1}H NMR (400 MHz, CDCl3): δ 8.13 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.86 (t, J = 7.2 Hz, 1H), 7.59 (t, J = 6.8 Hz, 1H), 7.32–7.26 (m, 4H), 7.21 (t, J = 6.0 Hz, 1H), 4.60 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 157.0, 152.3, 136.9, 134.8, 128.9, 128.7, 128.4, 128.0, 127.0, 125.6, 122.4, 41.3; MS (EI, *m/z*) 254 $[M]^+$; HRMS (EI) calcd for $C_{15}H_{11}N_2Cl$: 254.0605 $[M]^+$, found: 254.0604.