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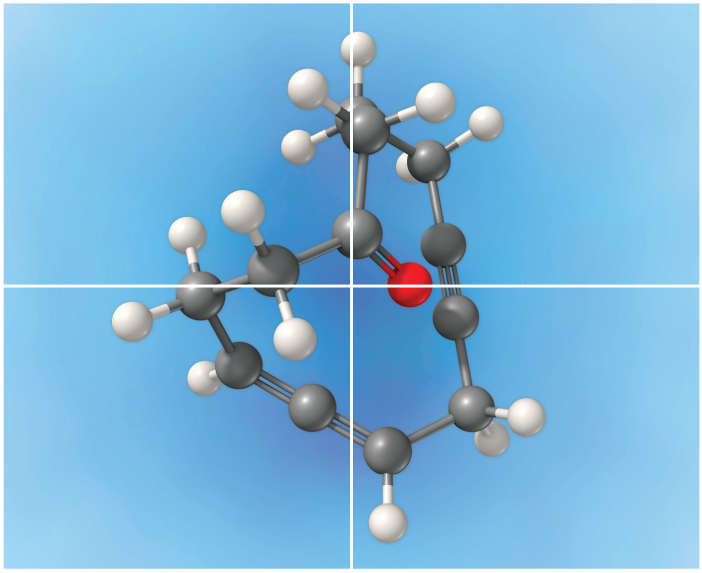

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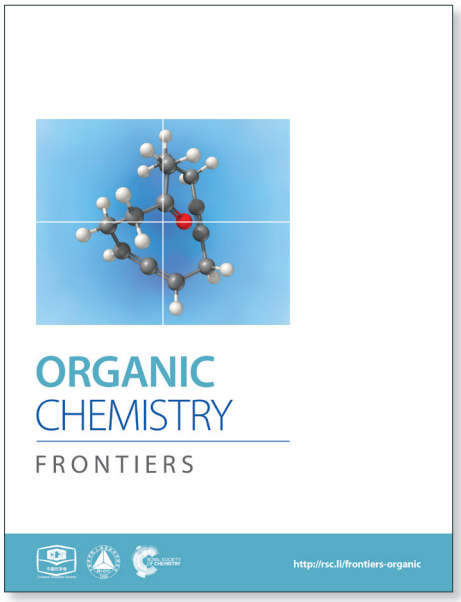

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ARTICLE

Cleavage of the C-C Triple Bond of the Ketoalkynes: Synthesis of 4(3*H*)-Quinazolinones

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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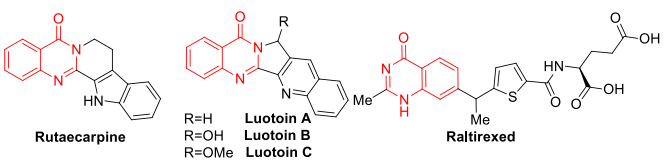
A novel protocol for the synthesis of 4(3*H*)-quinazolinones via selectively cleavage of the triple bond of ketoalkynes under oxidant-, metal-, and ligand-free conditions has been developed. Various 4(3*H*)-quinazolinones were obtained through fragmentation of C-C triple bond and formation of two C−N bonds.

Quinazolinones widely present in natural products, such as Rutaecarpine from a Chinese herbal drug named Wu-Chu-Yu was used to treat headache and cholera;[1] Luotonin A from a Chinese plant (*Peganumn nigellastrum*) showed cytotoxicity to the murine leukemia P388 cell line;[2] and Raltitrexed (brand name: Tomudex) have played an effective role in clinical therapy.[3] They also exhibit wide range of bioactivities, such as anticonvulsant,[4] antiviral,[5] anti-inammatory,[6] antifungal,[7] antimicrobial,[8] and antimalarial.[9] As a result, tremendous synthetic efforts have been made for building such a core. The condensation of aldehydes with *o*-aminobenzamides followed by oxidation has been used in the industries.[10] Recently, the transition metal-catalyzed synthesis of quinazolines has made great progress. Zhou and Fang built such a structure via Iridium-catalyzed hydrogen transfers.[11] Yokoyama and Hidemasa described a Pd-catalyzed benzylic C−H amidation with benzyl alcohols.[12] Zhu and other groups developed Pd-catalyzed CO insertion to construct quinazolin-4(3*H*)-ones.[13] Very recently, copper or iron-catalyzed C−N coupling of 2-halobenzoic acids or 2-halobenzamides with amidines to form quinazolines has been developed by Shafir, Buchwald and other groups.[14] These procedures rely on metal catalysts and excessive oxidant or base. Suitable ligands or microwaves were also necessary in some cases. The reaction of *β*-diketones with *o*-aminobenzamide to produce 4(3*H*)-quinazolinones has been mentioned in literatures.[15] However, the generality of the *β*-diketones was limited and low efficiency were observed when 1,3-diarylpropane-1,3-diones were used as the starting materials. We reasoned that 1,3-diarylpropane-1,3-dione perhaps hardly generate enaminone intermediate. Recently, we easily synthesized a series of heterocycles, such as pyrroles, chromones and triazoles,[16] from the ketoalkynes through an enaminone intermediate, which could be generated *in situ* from the reaction of ketoalkyne with *o*-aminobenzamide in the presence of suitable additives. Herein, we report a new strategy for the synthesis of 2-arylquinazolin-4(3*H*)-one from ketoalkynes *via* C−C triple bond cleavage.

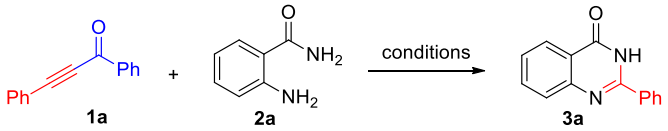


Scheme 1. Examples illustrating the importance of quinazolinones

In our initial studies, *o*-aminobenzamide **1a** and 1,3-diphenylprop-2-yn-1-one **2a** were chosen as model substrates to

optimize the reaction parameters. The desired product 2-phenylquinazolin-4(3*H*)-one **3a** were obtained by using TFA as an additive in THF, as well acetophenone as a byproduct. No product was detected in the absence of TFA. Different solvents were tested

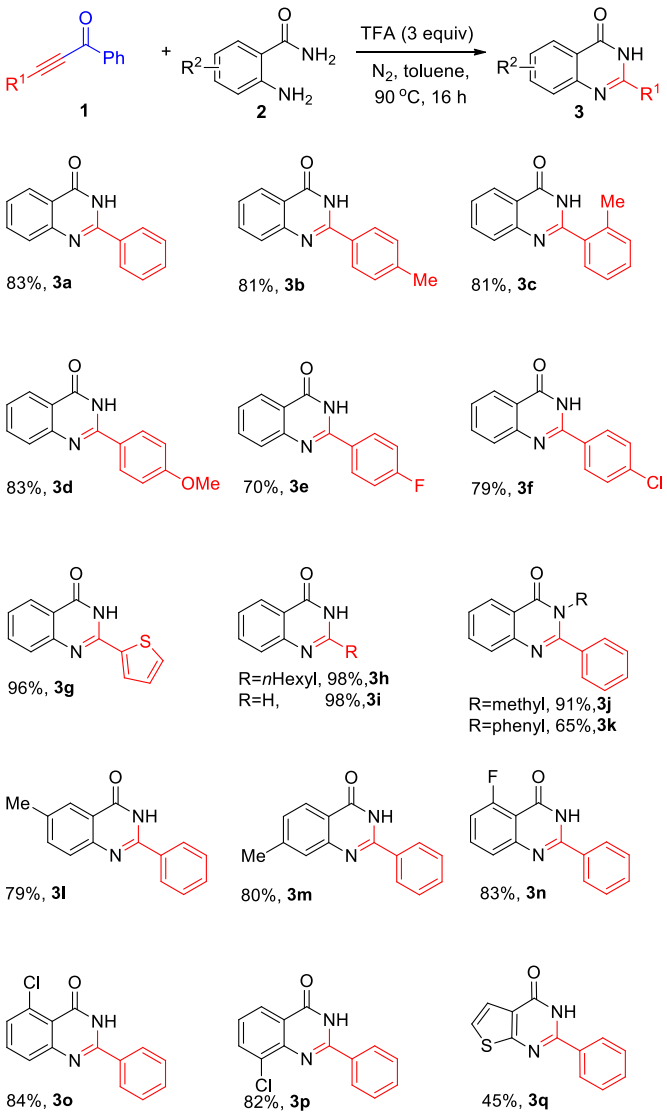
Table 1. Optimizing Reaction Parameters for the Condensation of *o*-Aminobenzamides **1a** with 1,3-Diphenylprop-2-yn-1-one **2a**[a]



Entry	Additive (equiv)	Solvent	Yield[b] (%)
1	TFA (5)	THF	78
2	TFA (5)	DMSO	79
3	TFA (5)	ethanol	79
4	TFA (5)	DCM	71
5	TFA (5)	DMF	40
6	TFA (5)	H_2O	38
7	TFA (5)	toluene	83
8	TFA (5)	NMP	55
9[c]	TFA (5)	DCM	67
10	TFA (4)	toluene	82
11	**TFA (3)**	**toluene**	**83**
12	TFA (2)	toluene	78
13[e]	TFA (3)	toluene	62
14[d]	TFA (5)	toluene	30
15	E_3N (5)	toluene	0
16	LiO*t*Bu (5)	toluene	0

[a] Reaction conditions: **1a** (0.65 mmol), **2a** (0.5 mmol), dry solvent (2 mL), 90 ℃, overnight, N_2. [b] Isolated yields based on **2a**. [c] 60 ℃, 16 h. [d] RT [e] **1a** : **2a** = 1:1.

Scheme 2. Substrate scope.[a]

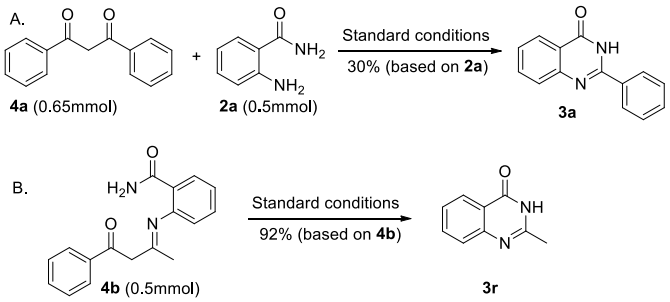


[a] Reaction conditions: **1a** (0.65 mmol), **2a** (0.5 mmol), TFA (1.5 mmol), dry toluene (2 mL), 90 ℃, 16 h. Isolated yields based on **2a**.

with 5 equiv of TFA at 90 °C (Table 1, entries 1−9). The highest yield was obtained in toluene (83%). Ethanol and DMSO led to **3a** in 79% yield (Table 1 entries 2, 3). The yield decreased significantly when NMP, DMF, and H_2O were used as the reaction media. Then the additive loading was investigated. This transformation was not affected when the acid additive was decreased to 3 equiv (Table 1, entry 11). However, further decreasing loading of TFA resulted in

relatively lower yield of **3a** (Table 1, entry 12). 1 Equiv of **1a** made the yield of **3a** decrease to 62% (entry 13). When the reaction temperature was decreased to room temperature, only 30% yield of 2-aryl-4(3*H*)-quinazolinone was obtained (Table 1, entry 14). The base, such as E_3N and LiO*t*Bu, did not favour this transformation (Table 1, entries 15-16). Therefore, the optimal reaction conditions were identified as follows: 3 equiv of TFA at 90 ^oC in toluene, overnight.

Having the optimal reaction conditions in hand, the scope and generality of the substrates were investigated. As shown in Scheme 2 (**3a**–**o**), good to excellent yields were provided for the most substrates examined. 1,3-Diphenylprop-2-yn-1-one and diarylprop-2-yn-1-one bearing electron-donating groups in the 3-aryl ring, such as methyl and methoxyl, proceeded well, affording 2-arylquinazolin-4(3*H*)-ones **3a**–**d** in good yields (Scheme 1). Meanwhile, *o*-methyl-substituted substrates conducted smoothly and resulted in the desired 4(3*H*)-quinazolinones in 81% yield (Scheme 2, **3b vs 3c**), implying that influence of steric hindrance of ketoalkynes was not significant. In addition, ketoalkynes with electron-withdrawing groups (fluoro- and chloro-) also reacted well and furnished the desired products **3e**, **3f** in 70% and 79% yield, respectively. Heteroaryl- and aliphatic ketoalkyne were also applicable under the standard reaction conditions. For instance, 1-phenyl-3-(thiophen-2-yl)prop-2-yn-1-one, 1-phenylnon-2-yn-1-one and 1-phenylprop-2-yn-1-one gave the corresponding quinazolin-4(3*H*)-ones **3g**, **3h**, **3i** in 96%, 98%, and 98% yield, respectively. We next examined reactions of N-substituted 2-aminobenzamides, such as 2-amino-N-methylbenzamide and 2-amino-N-phenylbenzamide. The corresponding products **3j**, **3k** could be afforded in 91% and 65% yields, respectively. Next, the scope of the coupling reaction of substituted *o*-aminobenzamides **2l**–**p** was further examined. We were pleased to find that *o*-aminobenzamide with 3-chloro, 4-methyl, 5-methyl, 6-chloro, and 6-fluoro groups also worked well and provided quinazolin-4(3*H*)-one derivatives **3l**–**p** in 79%–84% yields. To our delight, 2-aminothiophene-3-carboxamide could be a suitable substrate and resulted in the desired product in 45% yield (Scheme 2, **3o**).



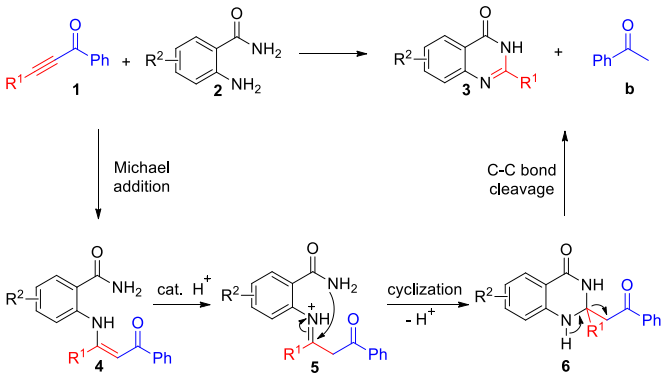
Scheme 3. Control Experiment

To clarify the reaction mechanism, 1.5 equiv of 1,3-diphenylpropane-1,3-dione (Scheme 3, **4a**) was treated with *o*-aminobenzamide under the standard reaction conditions. 4(3*H*)-Quinazolinone **3a** was isolated only in 30% yield. These results indicated that *β*-diketones as the possible intermediates of this metal-free C–C triple bond cleavage reaction was excluded. Meanwhile, a relatively accessible key intermediate (E)-2-(4-oxo-4-phenylbutan-2-ylideneamino) benzamide was successfully synthesized and resulted in the desired 4(3*H*)-quinazolinones in 92% yield under the standard reaction conditions. Based on the results obtained above and the literature[17], a plausible reaction mechanism was proposed and shown in Scheme 4. With the help of TFA, the condensation reaction of **1** with **2** would generate the enaminone intermediate **4**. Then, intramolecular nucleophilic addition of **4** produced the intermediate **6**. Then the C–C bond cleavage reaction occurred to generate the product **3**.

In summary, we have demonstrated that the novel metal-free C–C triple bond cleavage reaction proceeded efficiently with TFA, affording 2-aryl(alkyl)-quinazolin-4(*3H*)-ones in moderate to excellent yields. In addition, the scope of this reaction was

successfully expanded to heteroaryl ketoalkyne and 2-aminothiophene-3-carboxamide. Currently, we are exploring the application of the proposed cleavage of the C−C triple bond with TFA to the synthesis of the pharmaceutical molecules.

Scheme 4. Plausible Reaction Mechanism



Acknowledgements

This work was supported by Program for Minjiang Scholar program (10BS216), Xiamen Southern Oceanographic Center (13GYY003NF16), NSF of China (21202048), and Promotion Program for Young and Middle-aged Teacher in Science and Technology Research of Huaqiao University (ZQN-PY120).

Notes and references

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†Electronic Supplementary Information (ESI) available: Experimental details. See DOI:10.1039/b000000x

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