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A Novel Three-Component One-Pot Reaction Involving Alkynes, Urea or Thiourea, and Aldehydes

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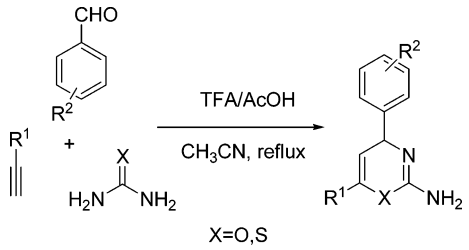
ABSTRACT



A novel three-component, one-pot condensation yielding 2-amino-4*H*-1,3-oxazines or 2-amino-4*H*-1,3-thiazines from alkynes, urea or thiourea, and aldehydes is described.

With the emphasis on the search for atom-efficient transformations of easily available starting materials into complex organic molecules,[1] reactions that provide maximum diversity are especially desirable. Here, expeditious domino[2] and multicomponent[3] reactions (MCRs) have emerged as powerful strategies. Consistently, several reported MCRs feature Diels−Alder chemistry with heterodiene[4] building blocks for the synthesis of heterocyclic six-membered rings.

Recently, we reported a highly chemoselective multicomponent Biginelli-type condensation, extending the scope of the Biginelli reaction through the use of cycloalkanones instead of 1,2-dicarbonyl compounds.[5] In continuation of our interest in MCRs, here we describe the first one-pot reaction of alkynes, urea or thiourea, and aldehydes, providing a series of 2-amino-4*H*-1,3-oxazines or 2-amino-4*H*-1,3-thiazines. 4*H*-1,3-Oxazines and 4*H*-1,3-thiazines are important synthetic intermediates in organic synthesis,[6] and these skeletons have been found in a few biologically relevant compounds[7] and vulcanization accelerators.[8]

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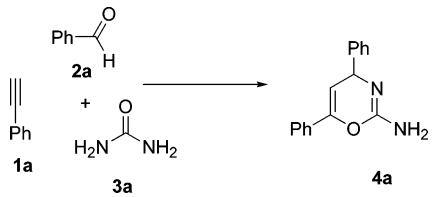
In the first step, we submitted a CH_3CN/DMF (2/1) solution of phenylacetylene, urea, and benzaldehyde in the presence of TMSCl to the reflux temperature. Unfortunately, no reaction was observed, even if Pd/TMSCl was employed in the reaction. To effect the reaction, various catalysts were screened (Table 1). To our surprise, the TFA−AcOH mixture

Table 1. Effect of Reaction Conditions on the New Multicomponent Reaction for the Synthesis of **4a**[a]



entry	solvent	catalysts	yield[b]
1	CH_3CN/DMF (2/1)	TMSCl (1 mL)	0%
2	CH_3CN/DMF (2/1)	TMSCl (1 mL), Pd	0%
3	CH_3CN/DMF (2/1)	AcOH (2 mL)	0%
4	CH_3CN/DMF (2/1)	TFA (2 mL)	0%
5	CH_3CN/DMF (2/1)	TFA/AcOH (1 mL/3 mL)	60%
6	CH_3CN	TFA/AcOH (1 mL/3 mL)	78%
7	CH_3CN	TFA/AcOH (1 mL/1 mL)	65%
8	CH_3CN	TFA/AcOH (1 mL/3 mL)	50%[c]

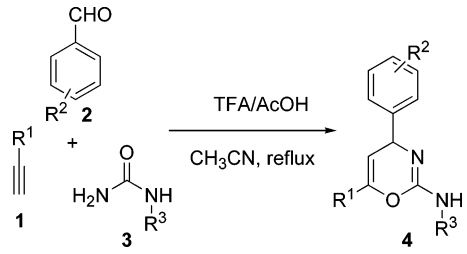
[a] Phenylacetylene **1a** (2 mmol), benzaldehyde **2a** (2 mmol), and urea **3a** (3 mmol), reflux, 10 h. [b] Isolated yields. [c] At room temperature, 48 h.

had a dramatic influence on the reaction. Although no product could be isolated with either TFA or AcOH alone, we obtained moderate yields of 4,6-diphenyl-2-amino-4*H*-1,3-oxazine **4a** by using a mixture of TFA−AcOH.

To test the efficiency of these conditions, we examined the effects of different ratios of TFA−AcOH and different solvents on this novel MCR (Table 1). The best result was achieved by carrying out the reaction with a 1:3 volume ratio of TFA−AcOH in refluxing acetonitrile for 10 h (Table 1, entry 6).[9] It is noteworthy that the reaction went to completion at room temperature, but this procedure required long reaction times (Table 1, entry 8).

To test this procedure, the scope of the reaction was then investigated with various alkynes, aldehydes, and urea or substituted ureas under the established protocol. All reactions proceeded smoothly to give the corresponding 2-amino-4*H*-1,3-oxazines (**4a**−**n**) in moderate to good yields (Table 2).

Table 2. Multicomponent Reaction of Aryl Alkynes, Urea or Substituted Ureas, and Aryl Aldehydes for the Synthesis of 2-Amino-4*H*-1,3-oxazines **4a**−**n**[a]



entry	R^1	R^2	R^3	yield[b] (%)
4a	C_6H_5	H	H	78
4b	C_6H_5	4-Me	H	80
4c	C_6H_5	4-F	H	81
4d	C_6H_5	2-MeO	H	75
4e	C_6H_5	3-NO_2	H	82
4f	4-MeC_6H_5	H	H	84
4g	4-MeC_6H_5	4-Me	H	81
4h	4-MeC_6H_5	2-Cl	H	82
4i	4-MeC_6H_5	4-Cl	H	79
4j	4-MeC_6H_5	3-NO_2	H	87
4k	4-FC_6H_5	4-F	H	55
4l	4-FC_6H_5	4-NO_2	H	53
4m	C_6H_5	4-F	Me	69
4n	C_6H_5	4-F	Et	67

[a] Reaction conditions: **1** (2 mmol), **2** (2 mmol), and **3** (3 mmol), reflux, 10 h. [b] Isolated yields.

All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, ESI-MS, and HRMS analysis. Compounds **4c** and **4n**

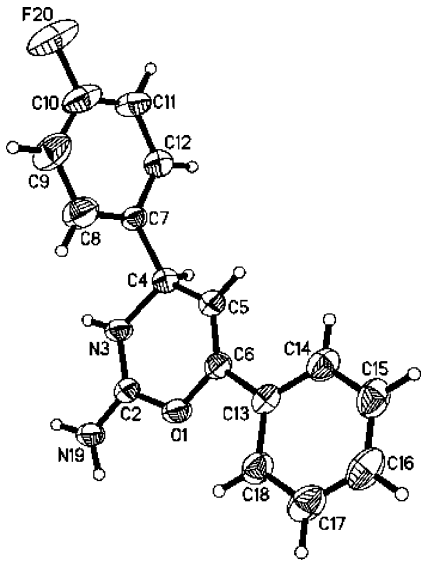


Figure 1. X-ray crystal structure of **4c**.

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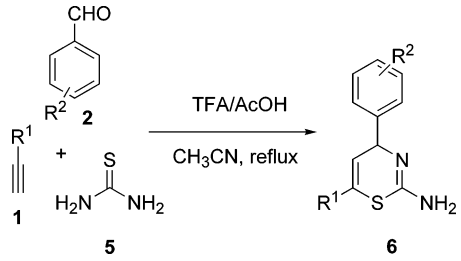
(9) **General Procedure for a Representative Example.** A solution of phenylacetylene **1a** (2 mmol), benzaldehyde **2a** (2 mmol), and urea **3a** (3 mmol) in anhydrous acetonitrile (3 mL) containing trifluoroacetic acid (1 mL) and AcOH (3 mL) was refluxed until the reaction was completed (TLC). The reaction mixture was then washed with ice−water and ice-cold 2 M NaOH. The solvent was evaporated, and the residue was washed with acetone. The solid product was recrystallized from MeOH to give pure product **4a**. Mp: 217−219 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.39 (br s, 2H), 7.75 (m, 2H), 7.44 (m, 8H), 6.38 (d, J = 4 Hz, 1H), 5.46 (d, J = 4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 156.1, 144.5, 140.7, 130.5, 130.2, 129.6, 129.3, 129.2, 127.6, 124.8, 102.0, 52.3. IR (KBr): 3037, 1721, 1673, 1205, 1135 cm^{-1}. MS (ESI) m/z: 251 ([M + H]$^+$). HRMS (ESI): [M + H]$^+$ found, 251.1174; calcd for $C_{16}H_{15}N_2O$, 251.1179.

were additionally confirmed by X-ray crystal structure analysis (Figure 1).

Encouraged by the results obtained with urea, we turned our attention to thiourea (Table 3). Thiourea followed the same general rules as ureas, giving the corresponding 2-amino-4*H*-1,3-thiazines (**6a**−**h**) in moderate yields. The structures of the products were established by spectroscopic analysis.

Table 3. Multicomponent Reaction of Aryl Alkynes, Thiourea, and Aryl Aldehydes for the Synthesis of 4*H*-1,3-Thiazines **6a**−**h**[a]



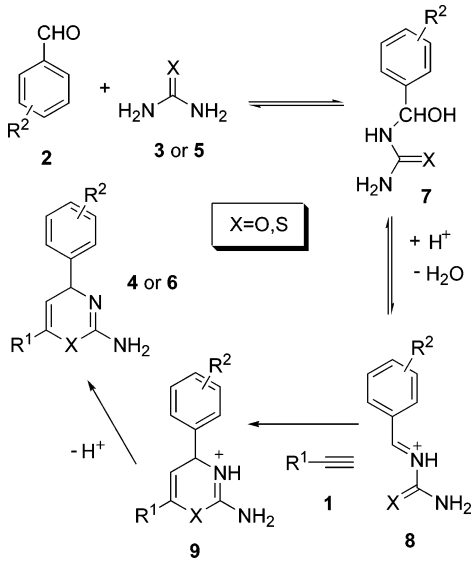
entry	R^1	R^2	yield[b] (%)
6a	C_6H_5	H	73
6b	C_6H_5	4-Me	67
6c	C_6H_5	4-F	75
6d	C_6H_5	4-MeO	72
6e	C_6H_5	4-Cl	69
6f	C_6H_5	4-NO_2	74
6g	C_6H_5	3-NO_2	73
6h	4-FC_6H_5	4-Me	50

[a] Reaction conditions: **1** (2 mmol), **2** (2 mmol), and **5** (3 mmol), reflux, 10 h. [b] Isolated yields.

For aromatic aldehydes, the presence of electron-withdrawing groups and electron-releasing groups on the aromatic rings did not exhibit significant effects on yields. However, for aryl alkynes, those carrying electon-withdrawing groups led to attenuated yields, presumably due to the lower electron density of the alkyne groups (Table 2, entries **4k** and **4l**, and Table 3, entry **6h**).

A proposed reaction mechanism that accounts for the novel multicomponent reaction is shown in Scheme 1. Thus, as in numerous classical multicomponent reaction classics,[10] the initial event in this reaction is the condensation of aldehyde **2** and urea **3** or thiourea **5** to give reactive intermediate **8**. Subsequently, the resulting intermediate **8** undergoes a hetero Diels−Alder cycloaddition[11] with alkyne **1**, affording 2-amino-4*H*-1,3-oxazinium salts or 2-amino-4*H*-1,3-thiazinium salts **9**. Finally, the 2-amino-4*H*-1,3-oxazinium salts or 2-amino-4*H*-1,3-thiazinium salts **9** are deprotonated to furnish 2-amino-4*H*-1,3-oxazine **4** or 2-amino-4*H*-1,3-thiazine **6**.

Scheme 1. Proposed Mechanism



In conclusion, a novel three-component reaction yielding 2-amino-4*H*-1,3-oxazines or 2-amino-4*H*-1,3-thiazines in a one-pot procedure has been developed. This approach allows for considerable flexibility in the nature of both the alkyne R^1 group and the aldehyde R^2 group, facilitating the preparation of a diverse array of 2-amino-4*H*-1,3-oxazines and 2-amino-4*H*-1,3-thiazines. The further determination of the scope and limitations is still under investigation.

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Supporting Information Available: Experimental procedures and spectral data for all compounds and crystallographic information files (CIF) for **4c** and **4n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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