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ARTICLE TYPE www.rsc.org/xxxxxx | XXXXXXXX

Intramolecular C-O/C-S bond insertion of α-diazoesters for the synthesis of 2-aryl-4*H*-benzo[d][1,3]oxazine and 2-aryl-4*H*-benzo[d][1,3]thiazine derivatives

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
First published on the web Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

An intramolecular C-O insertion of 2-(2-arylamidophenyl)-2-diazoacetate has been achieved using a catalytic amount of copper triflate under mild conditions to produce the 2-aryl-4*H*-benzo[*d*][1,3]oxazine-4-carboxylate in good yields. In addition, 2-diazo-2-(2-arylthioamidophenyl)acetate affords the corresponding 2-aryl-4*H*-benzo[*d*][1,3]thiazine derivatives under similar conditions. This is the first example on the synthesis of benzoxazines and benzothiazines from *ortho*-amidophenyl diazoacetate and *ortho*-thioamidophenyl diazoacetate, respectively.

The benzo[*d*][1,3]oxazine and benzothiazine ring systems are the core structures of many biologically active molecules.[1] They are used as fungicidal, anti-inflammatory,[2] anticonvulsant,[3] DNA-binding agents,[4] HSV-1 protease inhibitors (**III**)[5] and inhibitors of human leukocyte elastase (**IV**).[6] In particular, 2-substituted-4*H*-3,1-benzoxazin-4-one (**II**) has the ability to lower the level of plasma cholesterol and triglyceride.[7] Furthermore, 2,4-substituted- 4*H*-3,1-benzoxazines are often found in various natural products and drugs. For example, etifoxine (**I**), a nonbenzodiazepine anticonvulsant drug, is used for the treatment of psychiatric illnesses with great therapeutic efficiency and less toxicity.[8] On the other hand, 2-substituted benzothiazines are used for the preparation of photographic materials.[9] As a result, numerous methods have been developed for the synthesis of benzo[*d*][1,3]oxazines and benzothiazines.[10] Among them, thermolysis of benzo[*d*][1,2,3]triazin-4(3*H*)-one or isatoic anhydride,[11] electrochemical cyclization of *o*-trichloroacetylanilide,[12] palladium-catalyzed cyclization of azidoalkyne,[13] cycloaddition of ketenimine with thione[14] and sulfurization of aryl substituted benzoxazine with P_2S_5.[15] However, many of these methods suffer from several drawbacks such as the use of hazardous materials, expensive metal catalysts and harsh reaction conditions and also the yields are far from satisfactory. Therefore, the development of simple and expedient approaches still remains scarce for the synthesis of this class of *N*-heterocycles.

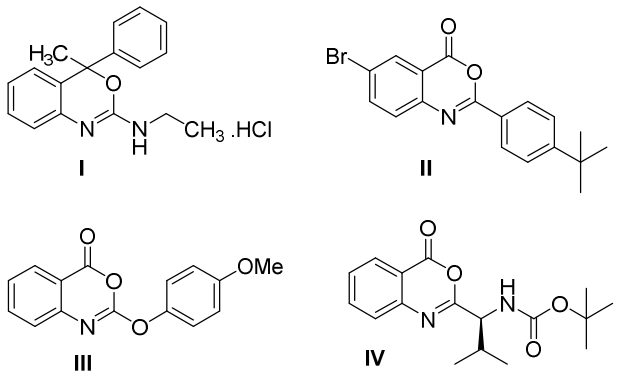

Figure 1. Biologically active natural products

The relative stability and facile decomposition of *α*-diazocarbonyl compounds under thermal, photochemical, Lewis acidic and transition metal catalysis conditions makes them useful intermediates in organic synthesis.[16] Recently, we explored the synthetic potential of α-diazoketones and esters for the synthesis of biologically active heterocycles such as imidazo[1,2-*a*]pyridines, 2-aminothiozoles, quinoxalines and trisubstituted pyrroles and indoles.[17]

Following our research on *α*-diazocarbonyl compounds, we herein report a novel approach for the synthesis of biologically active 2,4-substituted benzoxazines and benzothiazines through a copper-catalyzed intramolecular C-O insertion of *α*-diazocarbonyl compounds.

The starting material, 2-(2-arylamidophenyl)-2-diazoacetate (**2**) was prepared by the reaction of 2-arylamidophenyl acetate (**1**) with *p*-methylbenzenesulfonylazide (PMBSA) in the presence of base. Further the amide derivative (**1**) was prepared from methyl *o*- aminophenyl acetate and acid chloride (Scheme 1). Similarly,

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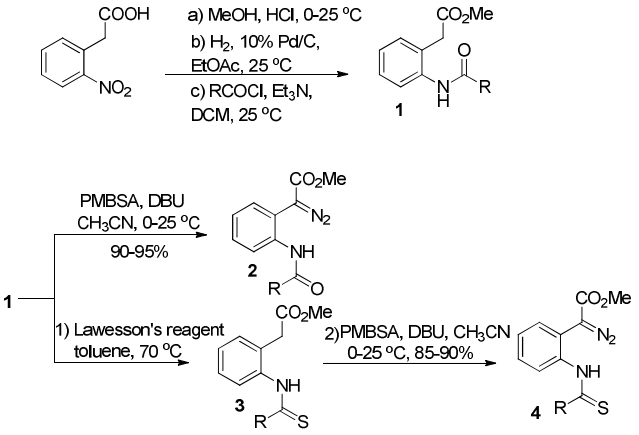
#Electronic Supplementary Information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectrum of products. see DOI: 10.1039/b000000x/

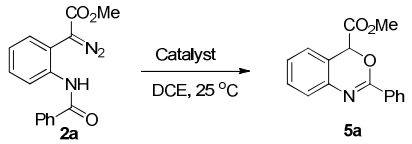
methyl 2-arylthioamidophenyl-2-diazoacetate (**4**) was prepared from the corresponding 2-arylthioamidophenylacetate (**3**) which was prepared by the reaction of 2-arylamidophenyl acetate (**1**) with equimolar amount of Lawesson's reagent,[18] as shown in Scheme 1.

Scheme 1. Synthesis of 2-(2-arylamidophenyl)-2-diazoacetate



As a model reaction, we first attempted the intramolecular cyclization of methyl 2-(2-benzamidophenyl)-2-diazoacetate (**2a**) in the presence of 10 mol% $Cu(OTf)_2$ in dichloroethane. The reaction proceeded smoothly at room temperature to furnish the respective 4*H*-benzo[*d*][1,3]oxazine **5a** as a sole product in 90% yield.

Table 1. Screening of various catalysts in the formation of **5a**

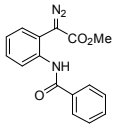
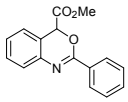
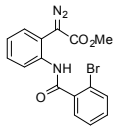
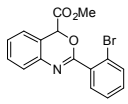
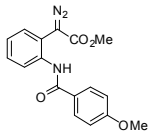
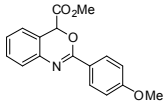
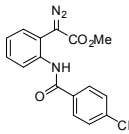
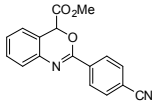
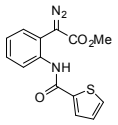
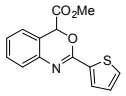
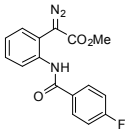
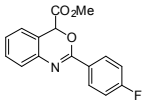
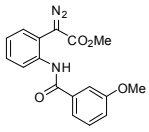
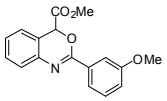
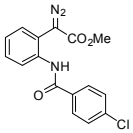
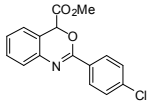


Entry	Lewis acid	Mol%	Solvent[a]	Time (min)	Yield (%)[b] (**5a**)
a	$Cu(OTf)_2$	10	$ClCH_2CH_2Cl$	20	90
b	$Cu(hfacac)_2$	10	,,	30	70
c	$Cu(acac)_2$	10	,,	30	65
d	$Rh_2(OAc)_4$	5	$ClCH_2CH_2Cl$	25	93
e	CuOTf	10	,,	40	75
f	$Cu(OAc)_2$	10	,,	50	40
g	CuI	10	,,	50	45
h	$CuSO_4$	10	,,	40	40
i	$Sc(OTf)_3$	10	,,	30	65
j	$In(OTf)_3$	10	,,	40	70
k	$Bi(OTf)_3$	10	,,	50	45
l	$Cu(OTf)_2$	10	THF	40	70
m	$Cu(OTf)_2$	10	Toluene	40	75

[a]Reaction was performed at 0.5 mmol scale. [b]Isolated yield.

To optimize the reaction conditions, several Lewis acids such as $Cu(OTf)_2$, CuOTf, $Sc(OTf)_3$, $In(OTf)_3$, $Bi(OTf)_3$, $Cu(hfacac)_2$, $Cu(OAc)_2$, and $Cu(acac)_2$ were screened. Among them, $Cu(OTf)_2$ gave the best results in terms of reaction time and conversion (entry a, Table 1). Other copper salts such as $Cu(hfacac)_2$, $Cu(OAc)_2$, $Cu(acac)_2$, $CuSO_4$ and CuI were found be less effective. Similarly, Lewis acids like $Sc(OTf)_3$, $In(OTf)_3$, $Bi(OTf)_3$ were also not effective for this conversion. Indeed, 5 mol% $Rh_2(OAc)_4$ was found to be more effective (entry d, Table 1). However, no cyclization was observed in the absence of catalyst. Next, we examined the effect of solvents such as dichloroethane, toluene, and tetrahydrofuran. Of these, dichloroethane gave the best results in terms of conversion.

Table 2. Synthesis of benzo[*d*][1,3]oxazine derivatives from (arylamidophenyl)diazoacetate

Entry	Phenyldiazoacetate (**2**)	Product (**5**)[a]	Time (min)	Yield (%)[b]
a			20	90
b			35	87
c			30	80
d			25	85
e			30	85
f			40	80
g			35	70
h			30	75

[a]All the products were characterized by NMR, IR and mass spectroscopy.
[b]Yield refers to pure products after chromatography.

The scope of this process is further illustrated with respect to various amides and the results are summarized in Tables 2. In the presence of either electron-rich (entries c and g, Table 2) or electron-deficient substituents (entry d, Table 2) on aromatic ring, the amides gave the desired products in good yields. Similarly,

halogen substituted amides also afforded the respective benzo[*d*][1,3]oxazine derivatives in good yields (entries b, f and h, Table 2). In all cases, the reactions proceeded efficiently in the presence of 10 mol% of $Cu(OTf)_2$ in dichloroethane. All products were characterized by IR, ^1H and ^{13}C NMR and mass spectrometry. It is entirely a new approach for the direct conversion of methyl 2--(2-arylamidophenyl)-2-diazoacetates (**2**) into benzoxazine derivatives. The structure and stereochemistry of **5c** were confirmed by X-ray crystallography (Fig. 2).[19]

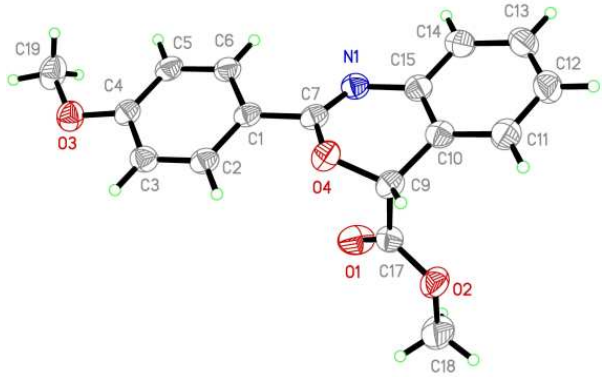
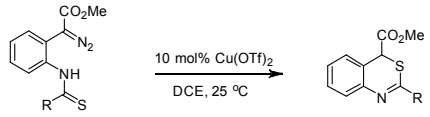
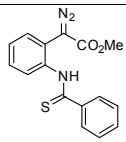
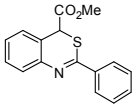
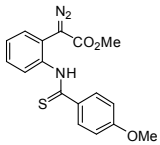
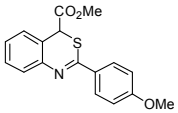
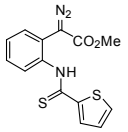
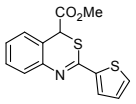
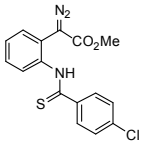
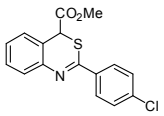


Figure 2. ORTEP diagram of **5c**

Table 3. Synthesis of benzo[*d*][1,3]thiazines *via* an intramolecular C-S bond insertion

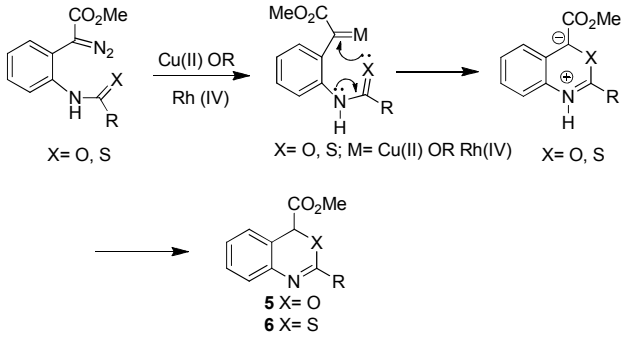


Entry	Phenyldiazoacetate (**4**)	Product (**6**)[a]	Time (min)	Yield (%)[b]
a			30	80
b			40	76
c			45	75
d			35	78

[a]All the products were characterized by NMR, IR and mass spectroscopy.
[b]Yield refers to pure products after chromatography.

Encouraged by the results obtained with methyl 2-(2-arylamidophenyl)-2-diazoacetate (**2**), we extended this method to the synthesis of 2,4-disubstituted benzothiazines. Accordingly, the 2-(2-phenylthioamidophenyl)-2-diazoacetate (**4a**) was treated with $Cu(OTf)_2$ (10 mol%) in dichloroethane (5 mL) at room temperature to afford the respective benzothiazine **6a** as a sole product in 85% yield (Table 3). Similarly, halogen substituted aromatic thioamides gave the corresponding benzothiazines in good yields(Table 3).

Mechanistically, we assume that the metal is expected to activate the diazo functionality to generate the metal carbenoid which facilitates the intramolecular O/S atom insertion leading to the formation of 1,3-benzofused heterocycles (5 & 6) (Scheme 2).



Scheme 2. A plausible reaction pathway

In summary, we have developed a novel method for the synthesis of benzoxazine derivatives from easily accessible 2-(2-arylamidophenyl)-2-diazoacetate. It also provides a direct access to produce a new series of benzothiazine derivatives in a single-step process.

Experimental

General. All reactions were carried out under nitrogen atmosphere. Commercial reagents were used as received, unless otherwise stated. ^1H NMR spectra were recorded on 300 MHz or 500 MHz spectrometer using $CDCl_3$ as a solvent. ^{13}C NMR were recorded on 75 MHz and 125 MHz spectrometer using $CDCl_3$. TMS was used as an internal reference for ^1H NMR analysis. All the compounds were purified by column chromatography on silica gel (60-120 mesh) using hexane-ethyl acetate mixture as eluent. Mass analysis was carried out using *APCI* mass spectrometer.

General procedure for the synthesis of 2-(2-aryl thioamidophenyl)acetate (3):

A solution of methyl 2-(2-arylamidophenyl)acetate (**1**) (1 mmol) and Lawesson's reagent (1 mmol) in toluene (10 mL) was heated at reflux conditions under argon atmosphere for 15 min. After removal of the solvent, the residue was purified by column chromatography on silica gel using hexane-ethyl acetate as eluent to give the thioamidophenyl acetate (**3**).

General procedure for the synthesis of diazoesters (2 & 4):

To a stirred solution of **1** or **3** (1 mmol) and *p*-methylbenzenesulfonylazide (PMBSA) (1.5 mmol) in acetonitrile (5 mL) was added 1,8-Diazabicycloundec-7-ene (DBU) (1.5

mmol) at 0 °C. The mixture was then allowed to warm to room temperature. After stirring for 1 h, the mixture was quenched with aqueous NH_4Cl, extracted with diethyl ether, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purified by flash column chromatography on silica gel to give the corresponding diazo compound **2** or **4**.

General procedure for the synthesis of benzo[*d*][1,3]oxazine and benzo[*d*][1,3]thiazine (5 & 6):

To a stirred solution of **2** or **4** (1 mmol) in dichloroethane (5 mL) was added $Cu(OTf)_2$ (10 mol%). The resulting mixture was stirred at 25 °C under nitrogen atmosphere. The yellow colour mixture was allowed to stir until it turns pale red colour (10-30 min). The mixture was quenched with sat. $NaHCO_3$ solution (1.0 mL) and extracted with dichloromethane (2-5 mL). The combined organic layers were washed with brine solution (3-5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (100–200 mesh) using ethyl acetate/hexane as eluent to afford the pure product.

Supporting Information Available:

Detailed procedures and spectroscopic data for novel compounds, Copies of ^{1}H NMR, ^{13}C NMR of novel compounds prepared are available.

Acknowledgements

B. V. S thanks CSIR, New Delhi for the financial support as a part of XII five year plan program under title ORIGIN (CSC-0108).

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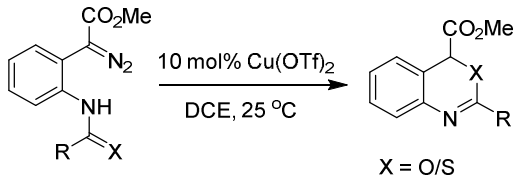
19. CCDC 994907 contains supplementary Crystallographic data for the structure **5c**.

Graphical contents



An intramolecular C-O/C-S insertion of 2-(2-arylamidophenyl)-2-diazoacetate/2-diazo-2-(2-arylthioamidophenyl)acetate is achieved using 10 mol% $Cu(OTf)_2$ to generate benzoxazines/benzothiazines.