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COPPER-CATALYZED DOMINO REACTION OF HETEROALLENES TOWARDS BENZO-HETEROCYCLE COMPOUNDS

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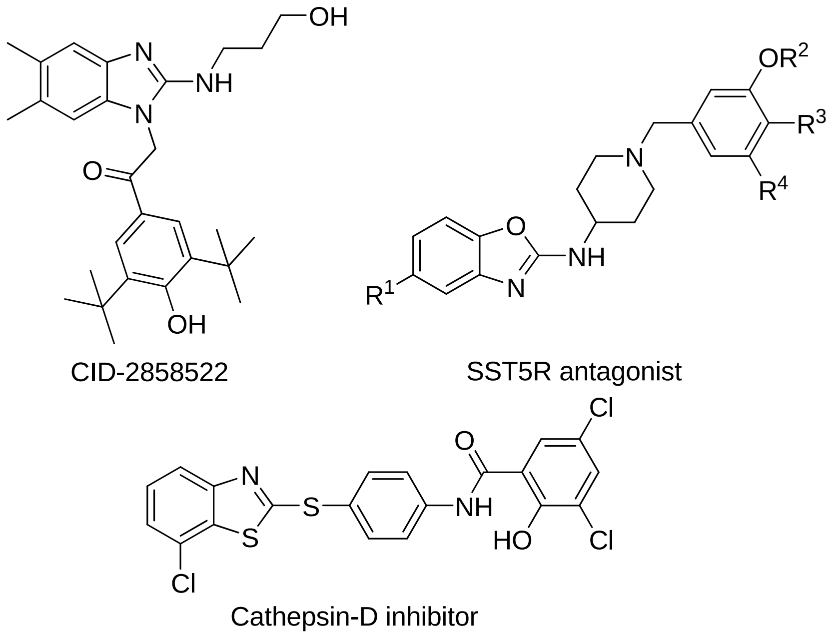
Dedicated to Professor Albert Padwa on the occasion of his 75th birthday

Abstract – The present review summarizes information on the copper-catalyzed reaction of heteroallenes, including carbodiimides, isothiocyanates, and carbon disulfide, with *o*-halobenzenamines or *o*-halophenols or *o*-halobenzamides for constructing benzo-heterocycle compounds *via* domino nucleophilic addition/cyclization reactions.

CONTENTS

I. INTRODUCTION

Benzo-heterocycle compounds are worth attention for many reasons: chief among them are their biological activities and as medicaments, examples are shown in Figure 1.[1] Therefore, organic chemists have been making extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations. Among a variety of new synthetic transformations, domino reactions are some of the most attractive methodologies for synthesizing benzo-heterocycle compounds, since a domino reaction can directly construct such compounds in one-pot under identical reaction conditions from readily accessible starting materials.[2] Particularly, transition-metal-catalyzed domino reactions opened a new route to benzo-heterocycle compounds.[3]



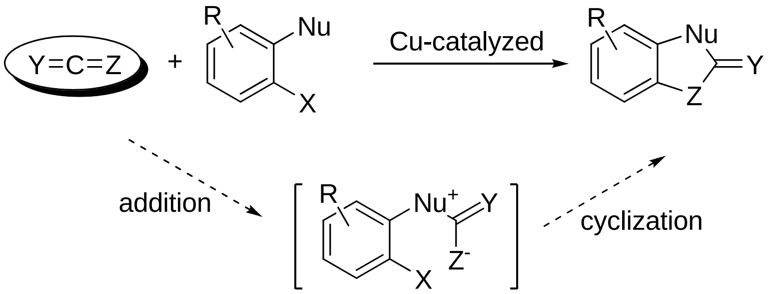
CID-2858522

SST5R antagonist

Cathepsin-D inhibitor

Figure 1. Examples of Some Biologically Active Compounds

Heteroallene is a moiety with two cumulated double bonds between three atoms (Y=C=Z) in which Y as well as Z is a heteroatom. Characteristic of the heteroallene supplied the qualifications to the domino reaction for the synthesis of heterocycles. In this review, we mainly focus on the copper-catalyzed the reaction of heteroallenes, including isothiocyanates, carbodiimides, and carbon disulfide, with *o*-halobenzenamines or *o*-halophenols or *o*-halobenzamides for constructing benzo-heterocycle compounds *via* nucleophilic addition/cyclization reaction (Scheme 1).

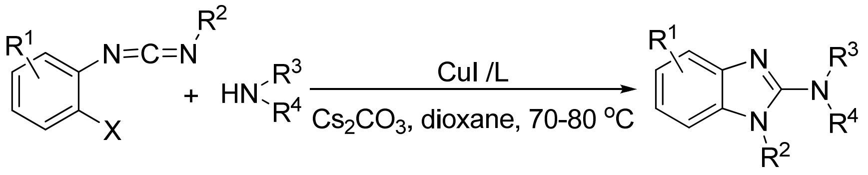


Scheme 1

II. DOMINO REACTION OF CARBODIIMIDES TOWARDS 2-AMINOBENZIMIDAZOLES AND 2-AMINOBENZOXAZOLES

2-Aminobenzimidazoles have attracted much attention due to their varied biological activities toward numerous diseases.[4] Many methods for syntheses of 2-aminobenzimidazole derivatives have been developed thus far.[5] Although these protocols provided access to 2-aminobenzimidazoles, they suffered limitations in scope and generality. Furthermore, some protocols proceeded in harsh reaction conditions or low yields. Recently, copper-catalyzed one-pot strategy for the synthesis of such compounds provided a straightforward protocol based on the metal-catalyzed C-N bond formation.

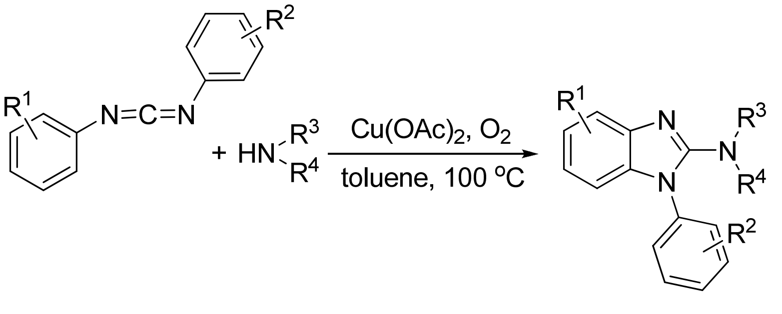
Bao and co-workers reported a novel copper-catalyzed one-pot protocol to synthesize 2-aminobenzimidazoles from *o*-haloarylcarbodiimides and amines (Scheme 2).[6] A number of 2-aminobenzimidazoles were smoothly synthesized in high yields with L-proline or 1,10-phenanthroline as ligand.



X= I, R^1 = 4-Me, R^2 = Ph, R^3 = Bn, R^4 = Me, yield = 90%
X= Br, R^1 = 4-Cl, R^2 = Ph, R^3 = R^4 = -HN(CH_2)$_5$-, yield = 88%
X= I, R^1 = H, R^2 = Bn, R^3 = R^4 = -HN(CH_2)$_5$-, yield = 72%

Scheme 2

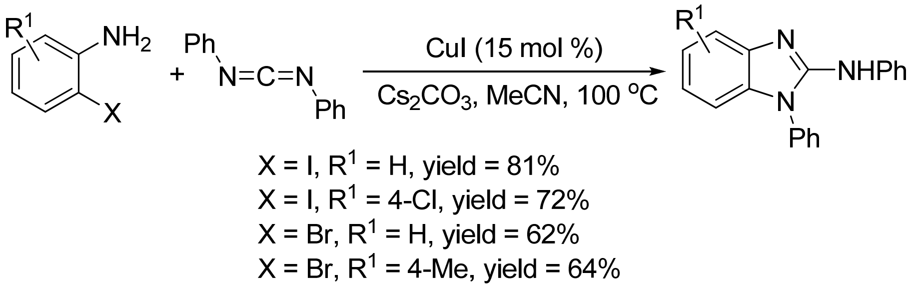
More recently, Bao and co-workers disclosed an efficient $Cu(OAc)_2/O_2$-catalyzed C-H activation/C-N bond-forming approach to benzimidazoles in moderate to good yields directly from arylcarbodiimides and amines (Scheme 3).[7] A number of 2-aminobenzimidazoles were smoothly synthesized *via* this process.



R^1 = 4-Me, R^2 = H, R^3 - R^4 = -HN(CH_2)$_5$-, yield = 69%
R^1 = 4-Cl, R^2 = H, R^3 - R^4 = -HN(CH_2)$_5$-, yield = 53%
R^1 = 4-Me, R^2 = H, R^3 = R^4 = Et, yield = 78%

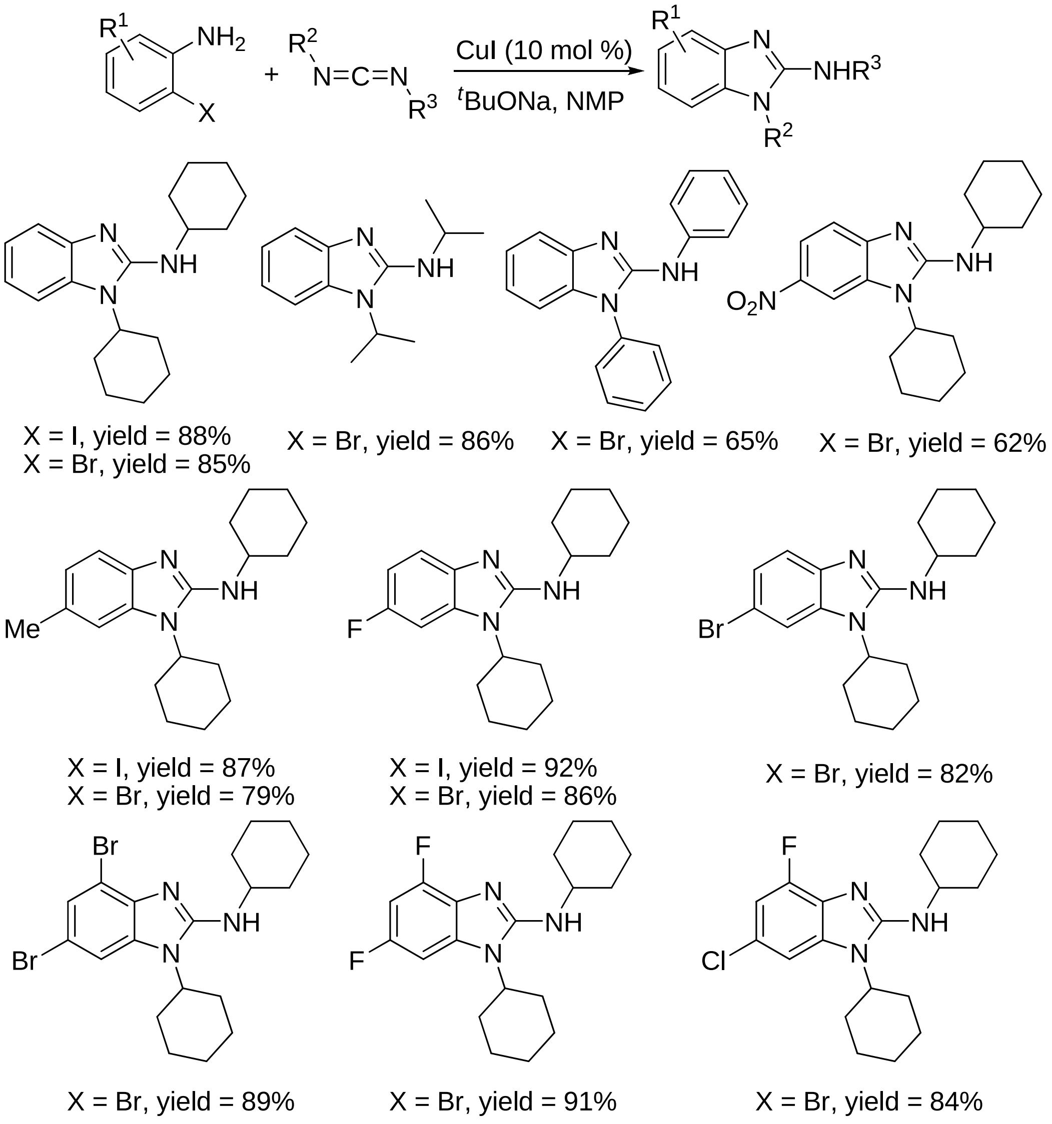
Scheme 3

Copper-catalyzed methods enabled the coupling of *o*-haloanilines with carbodiimides, which provided a straightforward method to 2-aminobenzimidazoles. Bao and co-workers again reported that reaction of diphenylcarbodiimide with *o*-haloanilines afforded 2-aminobenzimidazole derivatives (Scheme 4).[8]



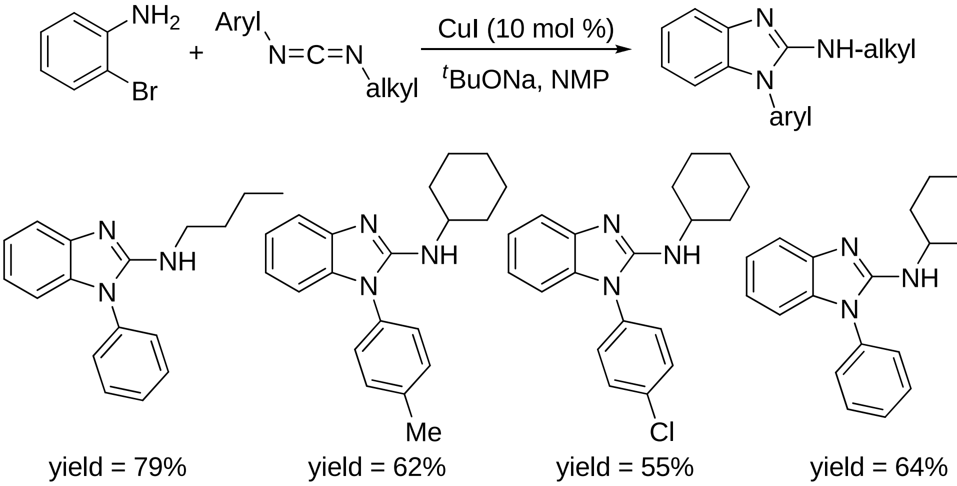
Scheme 4

Our group developed one general protocol to 2-aminobenzimidazoles from carbodiimides and haloanilines using CuI as catalyst under ligand-free conditions, in which both aryl and alkyl carbodiimides were employed with high yields (Scheme 5).[9]



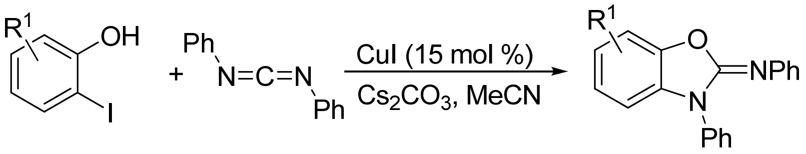
Scheme 5

Carbodiimides possessing a combination of aliphatic and aromatic substituent groups such as *N*-cyclohexyl-*N'*-phenyl-carbodiimide, *N*-butyl-*N'*-phenyl-carbodiimide, *N*-cyclohexyl-*N'*-*p*-tolyl-carbodiimide, and *N*-cyclohexyl-*N'*-*p*-chlorophenyl-carbodiimide were employed, only *N*-alkyl-1-aryl-2-aminobenzimidazoles were afforded in satisfying yields, indicating a high regioselectivity for the reaction (Scheme 6).[9]



Scheme 6

Benzoxazoles are important classes of molecules and the scaffolds widely occur in biologically active and natural products.[10] They are also found in a variety of medicinally significant compounds and are important targets in drug discovery.[11] Based on the same strategy, copper-catalyzed reaction of carbodiimides with *o*-iodophenols was also achieved and 2-aminobenzoxazole derivatives afforded in satisfying yields (Scheme 7).[8] It is noteworthy that the reaction proceeded under ligand-free conditions.

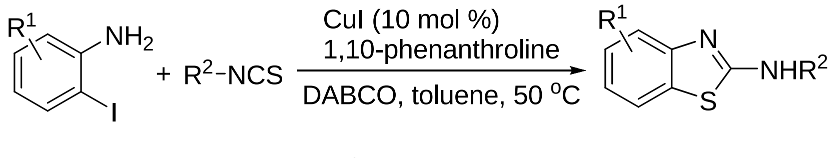


R^1 = H, yield = 93%
R^1 = 4-Me, yield = 92%
R^1 = 4-^{t}Bu, yield = 85%
R^1 = Cl, yield = 86%

Scheme 7

III. DOMINO REACTION OF ISOTHIOCYANATES TOWARDS 2-AMINOBENZOTHIAZOLES AND 2-THIOXO-2,3-DIHYDRO-1*H*- QUINAZOLIN-4-ONES

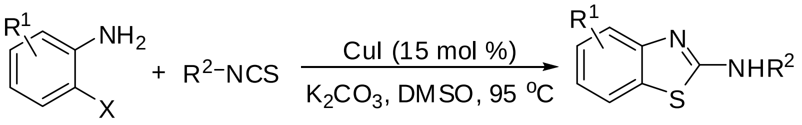
2-Aminobenzothiazoles are important intermediates and broadly found in biological chemistry and medicinal areas.[12] There are several methods to synthesize 2-aminobenzothiazoles. Although these reactions might proceed efficiently, they usually suffered from the use of highly toxic and corrosive reagents, high-costing metal catalysts, and specific ligands. Wu and co-workers developed a new copper-catalyzed tandem route to the construction of 2-aminobenzothiazole core (Scheme 8).[13] In the presence of CuI, 1,10-phenanthroline, and DABCO, 2-iodobenzenamines underwent the reaction with isothiocyanates in moderate to excellent yields.



R^1 = H, R^2 = Ph, yield = 88%
R^1 = 4-F, R^2 = Ph, yield = 51%
R^1 = 4-CF_3, R^2 = Ph, yield = 82%
R^1 = 4-F, R^2 = *c*-Hex, yield = 60%
R^1 = 4-Me, R^2 = Et, yield = 83%

Scheme 8

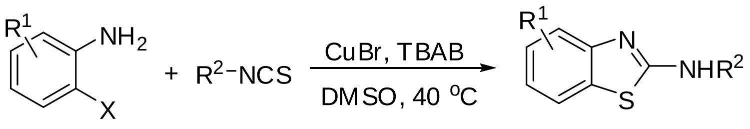
Bao and co-worker reported a novel and efficient formation of 2-aminobenzothiazoles from 2-iodoanilines or 2-bromoanilines and isothiocyanates *via* a ligand-free copper(I)-catalyzed one-pot cascade process (Scheme 9).[14]



X = I, R^1 = 4-Me, R^2 = 2-MeC_6H_4, yield = 84%
X = I, R^1 = 4-Me, R^2 = 4-$MeOC_6H_4$, yield = 92%
X = I, R^1 = 4-Me, R^2 = Bn, yield = 78%
X = I, R^1 = H, R^2 = Ph, yield = 91%

Scheme 9

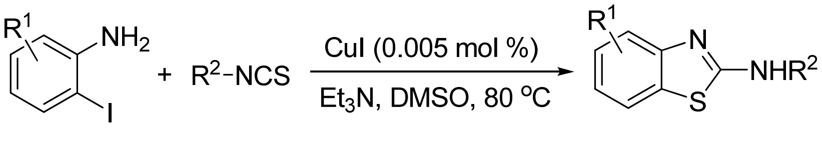
Li and co-workers developed a ligand- and base-free copper-catalyzed reaction of 2-halobenzenamines with isothiocyanates using tetrabutylammonium bromide (TBAB) as a promoter. Moreover, the reaction was conducted smoothly at 1 mol % loading of CuBr under mild conditions (Scheme 10).[15]



X = I, R^1 = H, R^2 = 4-MeC_6H_4, yield = 91%
X = I, R^1 = F, R^2 = Ph, yield = 90%
X = Br, R^1 = H, R^2 = Ph, yield = 66%
X = Cl, R^1 = H, R^2 = Ph, yield = 67%

Scheme 10

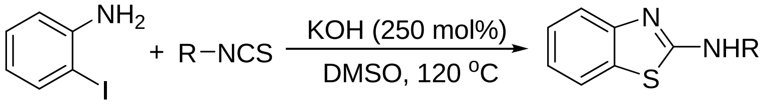
Wang and co-workers reported a CuI/Et$_3$N catalytic system for the efficient preparation of 2-aminobenzothiazoles with very low catalyst loadings (at ca. 50 ppm level) under mild reaction conditions (80 °C for 24 h under air) (Scheme 11).[16] A variety of 2-iodoanilines could be cross-coupled with isothiocyanates to produce 2-aminobenzothiazoles in moderate to good yields (49-93%) under the given conditions without any additional ligands. The TON of this reaction could reach 67,000 and the reaction could be scaled up.



R^1 = 4-Me, R^2 = Ph, yield = 71%
R^1 = F, R^2 = Ph, yield = 80%
R^1 = 4-CF$_3$, R^2 = Ph, yield = 58%
R^1 = 4-Me, R^2 = 3-CF$_3$C$_6$H$_4$, yield = 78%

Scheme 11

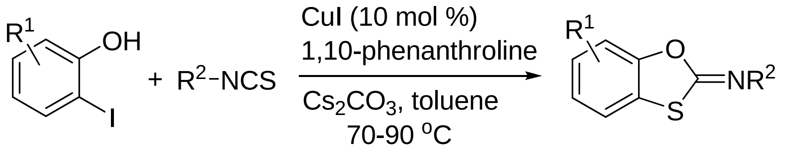
More recently, Ramón and co-workers reported copper-free type reaction in the synthesis of 2-aminobenzothiazoles from isothiocyanates and 2-iodoanilines (Scheme 12).[17] The reaction proceeded well with 250 mol% of KOH.



R = Ph, yield = 80%
R = 3,5-(CF$_3$)$_2$C$_6$H$_3$, yield = 77%
R = ^{t}Bu, yield = 74%

Scheme 12

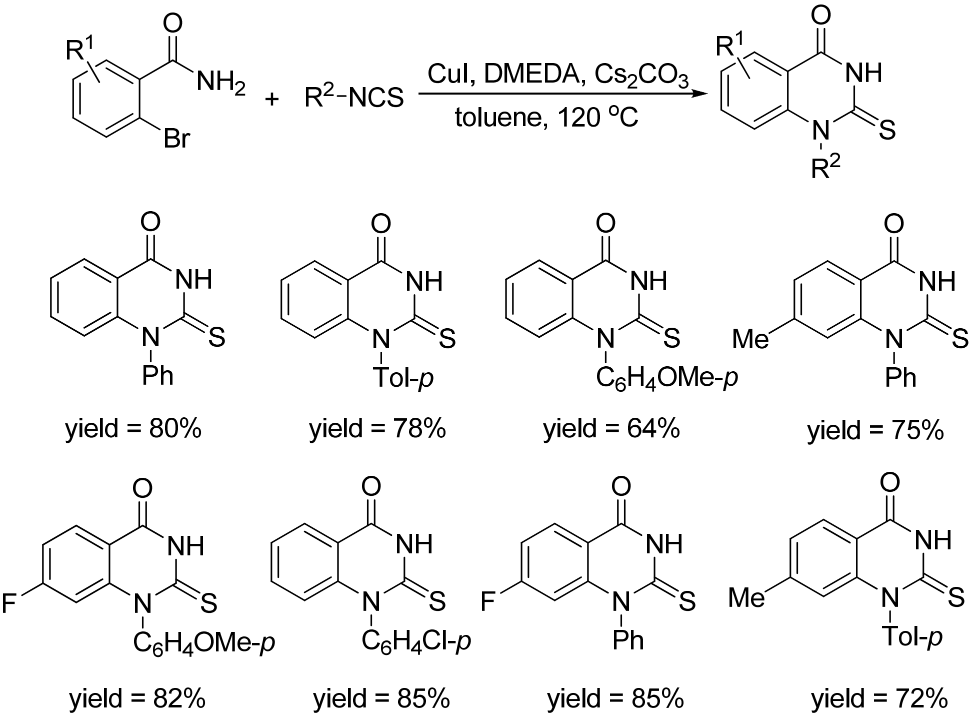
In addition, isothiocyanates underwent the intermolecular addition/intramolecular C-S coupling reaction with *ortho*-iodophenols under catalysis of Cu(I)–ligand–base to give 2-iminobenzo-1,3-oxathioles (Scheme 13).[18] This reaction provides a novel and efficient method for the formation of 2-iminobenzo-1,3-oxathioles from readily available precursors *via* a copper(I)-catalyzed one-pot cascade process.



R^1 = H, R^2 = Ph, yield = 97%
R^1 = 4-Me, R^2 = Ph, yield = 96%
R^1 = ^{t}Bu, R^2 = Ph, yield = 94%
R^1 = Cl, R^2 = Ph, yield = 52%

Scheme 13

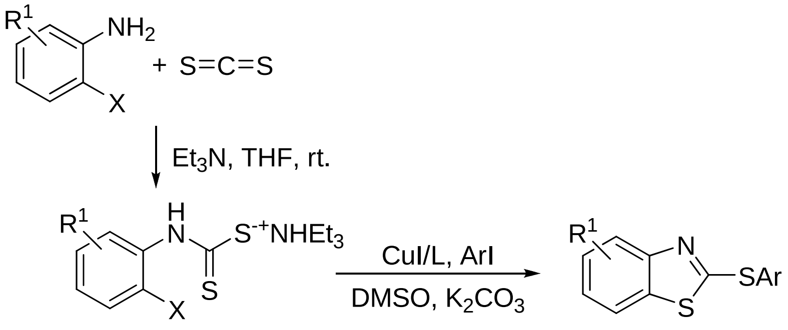
2-Thioxo-2,3-dihydro-1*H*-quinazolin-4-one is an important subclass of quinazolinones found to possess a variety of bioactivities.[19] New and efficient methodologies for construction of 1-aryl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-ones are still desirable, although a number of methods have been reported. Our group reported an efficient one-pot domino reaction to synthesize 2-thioxo-2,3-dihydro-1*H*-quinazolin-4-ones from isothiocyanates and *o*-bromobenzamide *via* intermolecular addition/intramolecular C-N coupling process in the Cu(I)-ligand-base system (Scheme 14).[20] In order to investigate the scope and the generality of this method, various isothiocyanate and *o*-bromobenzamide derivatives were subjected in this reaction. In most cases the reaction proceeded well and the desired products obtained in high yields. Moreover, this reaction provided thioxoquinazolines with the substituent bonded to the N-1 substituted structures, which were rarely reported.[21]



Scheme 14

IV. DOMINO REACTION OF CARBON DISULFIDE TOWARDS 2-MERCAPTOBENZOTHIAZOLE

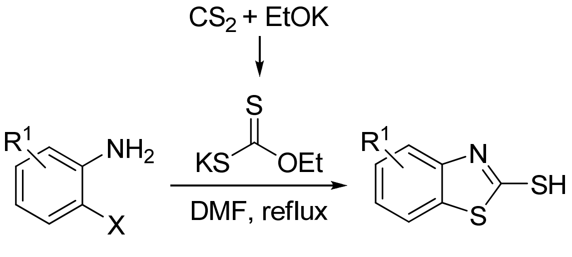
2-Mercaptobenzothiazoles (MBTs) categorized as significant derivatives of benzothiazoles have frequently been used as core structures for development of pharmaceutical agents.[22] Many approaches to the 2-mercaptobenzothiazole derivatives have been developed, however, some methods often suffer from harsh reaction conditions, limited substrates, poor substituent tolerance, and low yields. Accordingly, development of a facile and scalable route to construct MBTs scaffold is still desirable. Patel and co-workers reported copper-catalyzed an indirect synthesis of 2-arylthiobenzothiazoles from carbon disulfide and triethylamine (Scheme 15).[23] The 2-halophenylcarbamodithioate salts were prepared by treating 2-haloaniline with carbon disulfide and triethylamine.



X = I, R^1 = H, yield = 86%
X = I, R^1 = 4-Cl, yield = 66%
X = Br, R^1 = H, yield = 82%
X = Br, R^1 = 4-Br, yield = 68%

Scheme 15

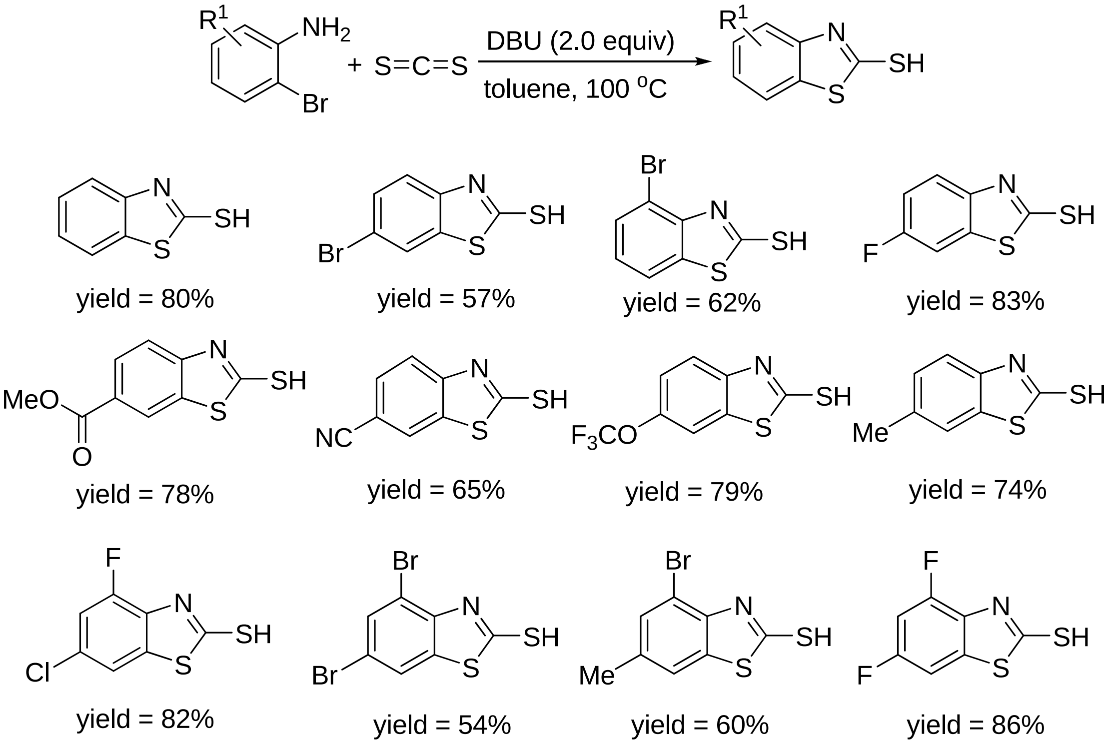
Zhang's and other group reported a strategy for the preparation of 2-mercaptobenzothiazoles from a potassium/sodium *o*-ethyl dithiocarbonate and *o*-haloaniline (Scheme 16),[24] in which the potassium/sodium *o*-ethyl dithiocarbonate was prepared by treating carbon disulfide with potassium/sodium ethanolate.



X = Br, R^1 = 4-F, yield = 99%
X = Cl, R^1 = 3-Cl, yield = 88%
X = F, R^1 = 3-F, yield = 96%

Scheme 16

Recently, our group developed a direct reaction between carbon disulfide and *o*-bromoanilines to afford 2-mercaptobenzothiazole derivatives in satisfied yields (Scheme 17).[25] Notablely, the reaction avoids utilization of copper as catalyst.



Scheme 17

V. CONCLUSION

The reactions of heteroallenes, including carbodiimides, isothiocyanates, and carbon disulfide, with *o*-halobenzenamines or *o*-halophenols or *o*-halobenzamides for constructing benzo-heterocycle compounds *via* domino nucleophilic addition/cyclization reaction could be successfully performed dependent on the choice of reaction conditions. The reaction could be performed with a broad range of substrates, keeping the high level of the results, and permission the easy entry to the synthesis of interesting benzo-heterocycles. Several facile and practical synthetic methodologies to access a variety of benzo-heterocycles using carbodiimides, isothiocyanates, and carbon disulfide were developed. So far, the employment of other heteroallenes, such as isocyanates, carbon dioxide, and *o*-halothiophenols has not yet exploited and many new, interesting and useful reactions for construction of such heterocycles are expected to be discovered. We believe that these important findings will pave the way to apply in the biological activities and drugs.

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