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ARTICLE

Novel Ferrocene-labeled Propargyl amines via CuI Multicomponent Amination/Alkynylation

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An efficient synthesis of Ferrocene-tagged Propargyl Amine derivatives via one-pot three-component domino amination/alkynylation in water is reported. The synthesis involves single Cu(I) catalyst without the addition of ligand with broad substrate applicability and excellent yields.

The Multicomponent diversity oriented reactions (MCRs) are of great interest to organic chemists due to their use in medicinal chemistry as fast and selective methods for the synthesis of large libraries of organic molecules.[1] In these reactions the products are formed in a single step by simultaneous reaction of several reagents and the molecular diversity required for such combinatorial libraries can be achieved by simply varying each component through a chain of consecutive elementary transformations.

Propargyl amines[2] are versatile structural units present in various important natural products which exhibit interesting biological activities. For example Pargyline,[3] Rasagyline,[4] and Selegiline[5] have found direct application in the treatment of neurodegenerative diseases, such as Parkinson's[6] and Alzheimer's diseases (Figure 1).[7] Several methods have been developed for the preparation of Propargyl amines, among which simplest and most straightforward method involves the addition of alkynyl metal reagents to imines. [8]

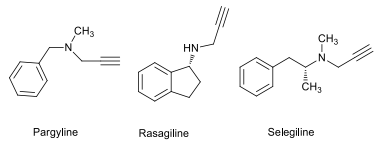
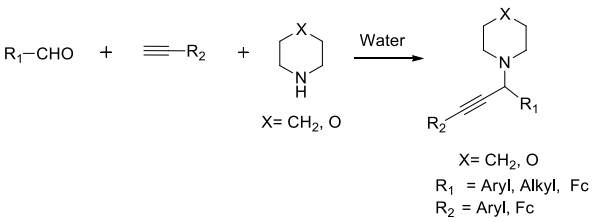


Figure1. Bioactive Propargyl amines

In last past years there has been an increasing interest in the design of new compounds incorporating the Ferrocene skeleton[9], due to its easy chemical modification, small size, relative lipophilicity, and stability in aqueous and aerobic media. Several examples of Ferrocene derivatives of drug moiety such as antibiotics (penicillin or cephalosporins)[10] and cancer drugs (tamoxifen)[11] have also been synthesized. In this context, heterocycles containing a Ferrocene moiety show interesting features that make them attractive for use as biologically active compounds. Recently, we have reported some procedures for the synthesis of Ferrocene based thiopropanone[12] and furan[13] derivatives. Considering the above reports, and as part of our program aimed at developing new ecofriendly and green methodologies for the preparation of bioactive heterocyclic compounds,[14] We are currently investigating the Copper(I) catalysed synthesis of various ferrocene tagged Propargyl amine via a facile, atom-economical, diversity oriented one pot three-component reaction in water.



Scheme 1. Propargyl amine synthesis in water

Despite the extensive use of Propargyl amines in organic synthesis, to the best of our knowledge, no report describing the synthesis of Ferrocene tagged propargyl amine has been reported in the literature so far.

The catalytic activity of various copper salts such as CuI, CuBr, CuCl was examined for the coupling of Ferrocene carboxaldehyde, piperidine and Phenylacetylene because they are readily available and much cheaper than silver, gold, ruthenium, or other additives. Initially, a mixture of Ferrocene carboxaldehyde, Piperidine and Phenylacetylene in acetonitrile was stirred in the presence of 20 mol% of CuX (I, Br, and Cl) at room temperature for 24 h and the product was not observed and reaction stopped after the formation of iminium intermediate (Table 1, Entry 2), leading to the assumption that more temp may be needed. To focus on the effect of temperature, the reaction was carried out at 80°C in

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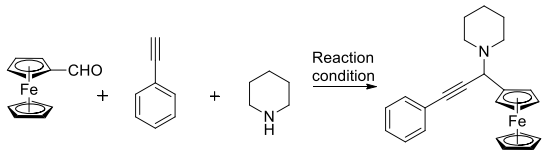
acetonitrile as solvent, which allowed the product to form with a 22, 35, and 75% yield for CuCl CuBr, and CuI respectively (Table 1, Entry 3, 4 and 5). The coupling process proceeded well in the presence of 20 mol% of CuI to give Ferrocene tagged Propargylamines in 75% conversion (Table 1, Entry 5). By reducing the catalyst amount by 20 to 10 % yield remains almost same (Table 1, Entry 6). No reaction occurred in the absence of catalyst (Table 1, Entry 1). In addition, no other additive was needed for this system, and the experimental process was quite simple and easy.

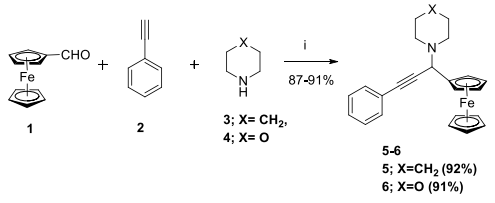
Table 1: Optimisation of reaction condition[a]



S.no	Reaction condition[a]	Mol (%)	(yield)[b]%
1	No catalyst, 80˚C, CH_3CN	-	-
2	CuX, Rt, CH_3CN, 24h	20	-
3	CuCl, 80˚C, CH_3CN, 24h	20	22
4	CuBr, 80˚C, CH_3CN, 24h	20	35
5	CuI, 80˚C, CH_3CN, 6h	20	75
6	CuI, 80˚C, CH_3CN, 6h	10	78
7	CuI, Water, 100˚C, 4h	10	92

[a]Reaction Conditions: Ferrocene caboxaldehyde, (1.0 mmol)), Piperidine (1.5mmol) and Phenylacetylene (1.2 mmol), [b]Isolated yield, CuX (X=Br, Cl, I)

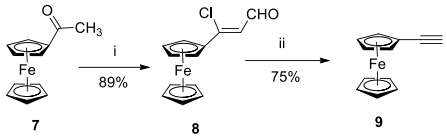
After optimisation of temperature and catalyst, the establishment of the reaction conditions was undertaken by investigating the effect of different solvents, and reaction times. The choice of an appropriate reaction media is also of crucial importance for successful synthesis. Our attention then moved on to investigate the effect of solvents on the product yields, and acetonitrile was replaced by water. Water produced the desired Propargyl amine in a significantly higher yield (92%) in less time (Table 1, Entry 7).



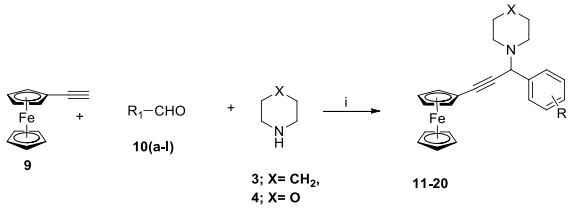
Scheme 2. Reagent and Conditions: (i) CuI (10mol %), refluxed in water

Having successfully optimized the reaction conditions for preparation of Propargyl amine using Ferrocene carboxaldehyde (Table 2, entry 1,2) Next to expand the structural diversity, propargyl amine using Ethynyl ferrocene was synthesized.

Towards this objective initially the Ethynyl ferrocene[15] was synthesized from Acetyl ferrocene (Scheme 3). In the next stage of the study the attention was focused towards synthesis of Propargyl amine, employing Ethynyl ferrocene.

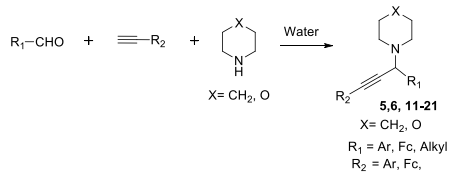


Scheme 3. Reagents and conditions: (i) $POCl_3$, DMF, CH_3COONa, 0°C to rt, 3h; (ii) aqueous NaOH, dioxane, reflux, 10 min.



Scheme 4. Reagent and Conditions: (i) CuI (10mol %), refluxed in water.

Table 2. Substrate scope of ferrocene tagged propargyl amine[a]

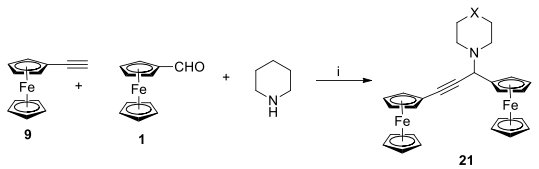


Entry	product	R_1(a-l)	R_2	Amine	Time (h)	Yield[b] (%)
1	**5**	Fc	Ph	Piperidine	4	92
2	**6**	Fc	Ph	Morpholine	4	91
3	**11**	Ph	Fc	Piperidine	2	87
4	**12**	2,5-$OCH_3C_6H_4$	Fc	Morpholine	2.5	76
5	**13**	4-$OCH_3C_6H_5$	Fc	Piperidine	2.5	78
6	**14**	2,5-$OCH_3C_6H_4$	Fc	Piperidine	2.5	75
7	**15**	4-$NO_2C_6H_5$	Fc	Morpholine	2	90
8	**16**	4-$NO_2C_6H_5$	Fc	Piperidine	2.5	92
9	**17**	Napthyl	Fc	Morpholine	1.5	82
10	**18**	4-FC_6H_5	Fc	Piperidine	2.5	89
11	**19**	4-$OCH_3C_6H_5$	Fc	Morpholine	2	79
12	**20**	Butyraldehyde	Fc	Morpholine	1.0	92
13	**21**	Fc	Fc	Piperidine	2.5	84

[a]**Reaction Conditions**: Substituted aldehyde (Aromatic, Aliphatic and Ferrocene carboxaldehyde, 1.0 mmol)), Piperidine/Morpholine (1.5mmol) and Phenylacetylene/ Ethynyl ferrocene (1.2 mmol), CuI (10 mol%), [b]Isolated yield.

The same standardized protocol was used by refluxing Piperidine, Benzaldehyde, with Ethynyl Ferrocene in the presence

of CuI in water (Scheme 4). As compared to the scheme 2, it was observed that the reaction between Piperidine, Ethynyl ferrocene and Benzaldehyde completed within 2h (Table 2, entry 3).



Scheme5. Reagent and Conditions: (i) CuI (10mol %), refluxed in water

Subsequently, various Aldehydes, Alkynes, and Amines were coupled and the results were summarized in Table 2. Aromatic aldehydes carrying both electron-withdrawing and electron-releasing substituents were also converted to their corresponding Propargyl amine derivatives in relatively similar times and yields (Table 2, entries 3-11). Aliphatic aldehyde also gave excellent yield in less time as compared to aromatic aldehyde (Table 2, entry 12). The Ferrocene carboxaldehyde, was used for this transformation and gave very good yields (Table 2, entry 13).

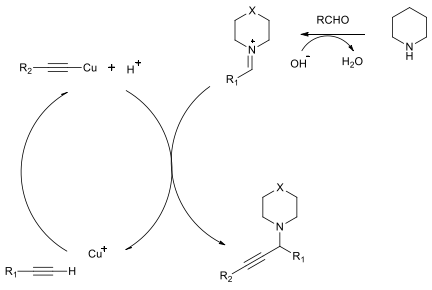


Figure 2: Proposed Mechanistic pathway

A plausible mechanism is also proposed. The generated Copper acetylide intermediate can react with the iminium ion prepared in-situ from the Aldehyde and the Secondary amines, to form the corresponding Propargylamine.

An efficient synthesis of Ferrocenyl tagged Propargylamines through three-component coupling of Aldehydes, Secondary amines and Alkynes in water is described by using copper iodide as catalyst and to the best of our knowledge this is the first report of the CH activation on Ethynyl ferrocene. This new method offers the following competitive advantages: (i) Use of readily available, cheap copper iodide as catalyst; (ii) Broad substrate applicability; (v) high yields attained in short reaction times; (vi) simple and easy operation. The protocol may find application in the diversity oriented synthesis of chemoprobes with structural complexity. Further the biological activity is underway.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

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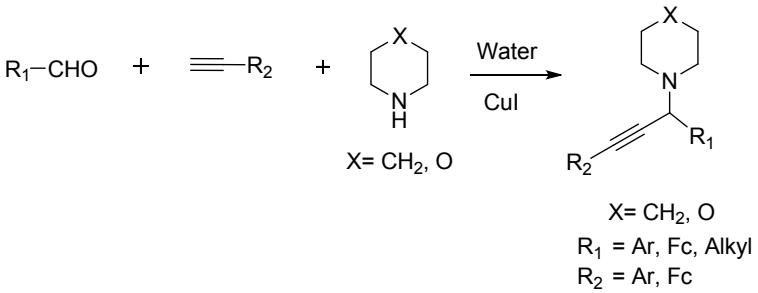

X= CH_2, O
R_1 = Ar, Fc, Alkyl
R_2 = Ar, Fc