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BISMUTH (III) BROMIDE AS AN EFFICIENT CATALYST FOR THE MULTI-COMPONENT SYNTHESIS OF DIHYDRO-2-OXYPYRROLES

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ABSTRACT

A simple and efficient protocol has been developed for the synthesis of dihydro-2-oxypyrroles *via* multi-component reaction of amines, dialkyl acetylene dicarboxylates and formaldehyde amines in the presence of Bismuth (III) bromide as a promoter stirred at 75°C for 3 hrs has been investigated. The significant advantages of this protocol are mild reaction conditions, low toxicity bismuth compound, inexpensive material, short reaction times, good yields, simple work-up.

KEYWORDS: Bismuth (III) bromide ($BiBr_3$), dihydro-2-oxypyrroles, dialkyl acetylene dicarboxylates, formaldehyde and amines.

INTRODUCTION

Dihydro-2-oxypyrroles constitutes and their derivatives have been reported to possess varied biological, medicinal, physiological and pharmacologically active compounds.[1–2] These analogues are valuable heterocyclic molecules are present in many naturally occurring biologically active agents such as antitumor,[3] anticancer,[4] antibiotics,[5] pesticides,[6] herbicidal,[7] Oteromycin[8] and HIV integrase.[9] Additionally, dihydro-2-oxypyrroles derivatives are attractive inhibitors for example anneexin A2-S100A10 protein interaction,[10] it has been used as Pl-091,[11] cardiac cAMPphosphodiestrase[12] and some of alkaloids used as optoelectronic materials.[13] These facts reflect in the field of pharmacological and medicinal potential of dihydro-2-oxypyrroles derivatives as drug candidates of therapeutic significance and as intermediates in organic synthesis shown in Figure 1. Thus the synthesis of these heterocyclic molecules has become an area of great interest.

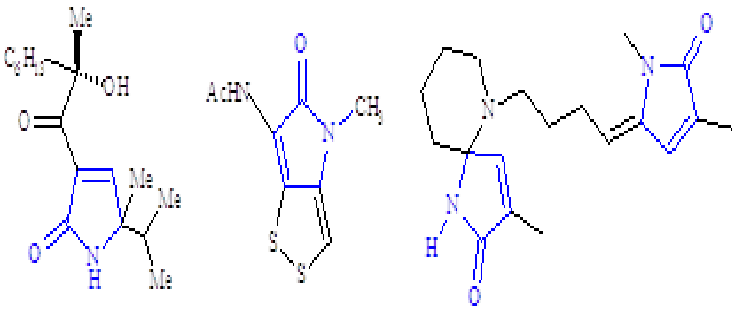
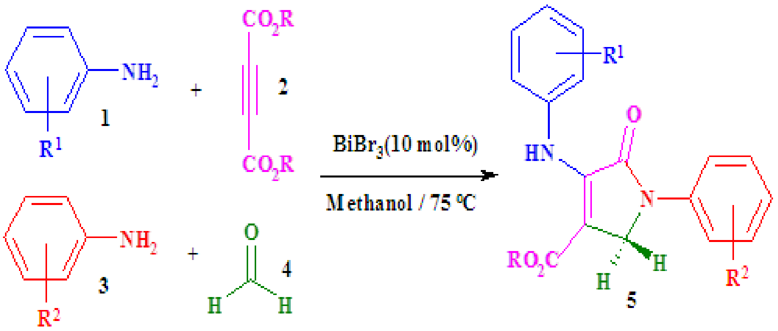


Figure 1. Biologically active compounds containing dihydro-2-oxypyrroles core unit.

Recently, Mirjalili *et al*. recommended procedure of synthesizing dihydro-2-oxypyrroles derivatives, where direct condensation of dialkyl acetylene dicarboxylates, formaldehyde and amines in presence of BF_3/nano-sawdust as a catalyst and reported good yield at thermal condition.[14] Numerous existing reports are using bronsted or lewis acid catalysts such as $Al(H_2PO_4)_3$,[15] $InCl_3$,[16] molecular I_2,[17] $[n\text{-}Bu_4N][HSO_4]$,[18] trichloroacetic acid (Cl_3CCO_2H),[19] nano–Zno,[20] acetic acid,[21] trityl chloride, [22] Cu(OAc)2·H_2O,[23] nano–TiO_2[24] and $MnCl_2 \cdot 4H_2O$[25] have been employed to accomplish these reactions. Although, atop described protocols are valuable, yet some of the procedure use high temperature, lavish metal precursors and accession takes long time period.

Recently, we are reported biological active molecule like 2,3-dihydroquinazolin-4(1*H*)-ones and 1, 2, 4, 5-tetrasubstituted imidazoles using $BiBr_3$ as a promoter.[26-27] Nowadays, wildly using non-transition-metal bismuth (III) compounds such as $BiCl_3$, $BiBr_3$, $Bi(OTf)_3$ and $Bi(NO_3)_3$[28] *etc*., have attracted growing interests as versatile catalysts in manifold organic synthesis attributed to their remarkable transformation relating to C-C, C-N, C-S bonds formation, in oxidation reaction, protection/deprotection of alcohols and carbonyl compounds furthermore extendable applications of organic reactions in aqueous media. $BiBr_3$ have attracted growing interests as versatile catalysts in diverse organic synthesis owing to their remarkable chemical and physical properties such as relevant stability, air- and moisture-tolerance, low toxicity compare to sodium chloride.[29-30]

In continuation of our research work to syntheses of biologically active compound via multicomponent reaction have emerged as a versatile approach in organic synthesis due to their advantages over the conventional multi-step synthesis. We have previously reported various heterocyclic molecules using readily available catalyst.[31–35] Herein, we would like to report a practical synthesis of dihydro-2-oxypyrroles derivatives **5** & **6** through a one-pot four component reaction between substituted aryl amine, dialkyl acetylene dicarboxylate, formaldehyde in the presence of $BiBr_3$ catalyst as an efficient and mild catalyst stirred at temperature (75°C) in methanol, to get **5a-l** & **6a-e** desired compound in good to excellent yield it shown in **Table II** & **Table III**, **Scheme I**.



Scheme I.

MATERIALS AND METHODS

Experimental and characterization

Melting points were determined on a Buchi melting point apparatus and are uncorrected. IR, ^{1}H and ^{13}C NMR and LCMS were recorded on Nicolet 400DFT-IR spectrophotometer, 300 MHz Brucker spectrometer and Shimadzu LC-MS respectively. aryl amine, dialkyl acetylene dicarboxylate, formaldehyde and $BiBr_3$ were all commercial products and were used without further purification.

General procedure for the synthesis of 5a–l

A mixture of arylamine **1** (10 mmol), dialkyl acetylenedicarboxylate **2** (10 mmol) in methanol (20 ml) was stirred for 30 min, then charged arylamine **1** (10 mmol), formaldehyde (35% solution, 20 mmol) and charged catalyst $BiBr_3$ (10 mol %) and stirred at 75°C for a 3hrs. The progress of the reaction was monitored by TLC (Petether: EtOAc, 7:3). After completion of the reaction, minimizes the methanol from reaction mass using rotary evaporator, the solid precipitate out, which was filtered through a Büchner funnel. The product was washed with 2 mL of ethanol to remove un-reacted starting materials. The pure product was obtained after recrystallization from ethanol. After remove the solvent we got ***Methyl 2,5-dihydro-5-oxo-1-phenyl-4-(phenylamino)-1H-pyrrole-3-carboxylate*** (**Table II**, entry 1, **5a**). White solid: IR (KBr): ν_{max}= 3278, 1688, 1652 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.73 (s, 3H), 4.54 (s, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.19 (t, J = 7.6 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 8.01 (s, 1H); ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 48.36, 51.39, 103.03, 119.30, 122.86, 124.71, 125.16, 128.43, 129.24, 138.78, 142.98, 163.91, 164.85.; MS m/z: 308.33; All known products reported previously in the literature were characterized by comparison of m.p., IR & ^{1}HNMR spectra with those of authentic samples.[17]

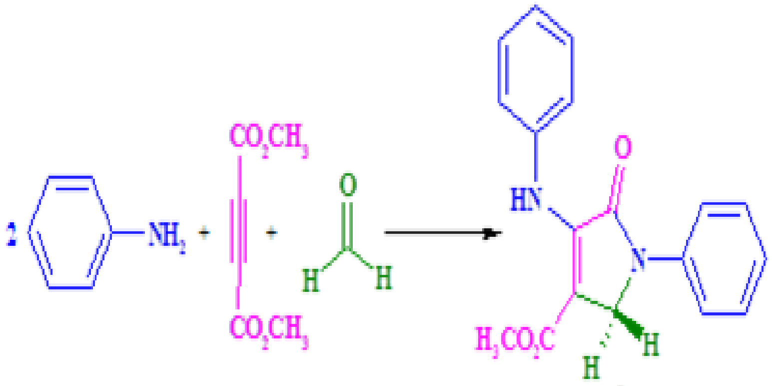
General procedure for the synthesis of 6a–e:

A mixture of cyclohexylamine **7** (10 mmol), dialkyl acetylenedicarboxylate **2** (10 mmol) in methanol (20 ml) was stirred for 30 min, then charged 4-Bromo aniline **3** (10 mmol), formaldehyde (35% solution, 20 mmol), and charged catalyst $BiBr_3$ (10 mol %) and stirred at 75°C for a 3hrs. The progress of the reaction was monitored by TLC (Petether: EtOAc, 7:3). After completion of the reaction, minimizes the methanol from reaction mass using rotary evaporator, the solid precipitate out, which was filtered through a Büchner funnel. The product was washed with 2 mL of ethanol to remove un-reacted starting materials. The pure product was obtained after recrystallization from ethanol. After remove the solvent we got ***Methyl 1-(4-bromophenyl)-4-(cyclohexylamino)-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate*** (**Table III**, entry 5, **6e**). Yellow solid: IR (KBr): ν_{max}= 3309, 1700, 1631 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.27 (m, 3H), 1.37–1.46 (m, 3H), 1.61–1.68 (m, 1H), 1.73–1.77 (m, 2H),1.99–2.02 (m, 2H), 3.79 (s, 3H), 4.37 (s, 2H), 4.57 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 2H),7.67 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.81, 25.62, 34.89,47.95, 51.14, 95.92, 117.89, 120.73, 132.17, 138.02, 164.51, 165.62; MS m/z: 392.0; All known products reported previously in the literature were characterized by comparison of m.p., IR & ^{1}HNMR spectra with those of authentic samples.[17]

RESULTS AND DISCUSSION

Initially we selected aniline **1** (10 mmol), dialkyl acetylene dicarboxylate **2** (10 mmol), in methanol (20 ml) was stirred for 30 min, then charged arylamine **1** (10 mmol), formaldehyde (35% solution, 20 mmol), as a model substrate to optimize the amount of catalysts. First we conducted the reaction without catalyst stirred for 6 hrs at temperature 75°C; result is there is no desired compound **5a**. Next run we tried with 10 mol % $BiBr_3$ with same solvent after 3 hrs stirring we got 76% of desired compound. Observed 5 mol % $BiBr_3$ in the presence methanol stirred for 3 hrs got same 80% yield. We carried out the reaction without solvent, after 6hrs got 35% desired compound and also we monitored the reaction using different solvent like acetonitrile, ethanol and dichloro methane among these, methanol is the best solvent, is sufficient for the this method to reduce the time duration of this protocol, additional we have run the reaction without catalyst but could not isolated the desired compound. **Table I**. These results encouraged us to extend this protocol to preparation of other dihydro-2-oxypyrroles derivatives. Results were discussed in Table II & III using different substituted aniline reacted with dialkyl acetylene dicarboxylate and formaldehyde. Anilines bearing either electron-withdrawing functional groups (Cl, Br, F), or electron-donating ones (CH_3, OCH_3), benzylamine, cyclohexylamine substitutes affords good yields of products with purity in short reaction time. Consequently, we developed a new protocol for the synthesis of dihydro-2-oxypyrroles derivatives using $BiBr_3$ as a catalyst.

Table I Optimization for the highly functionalized dihydro-2-oxypyrroles[a]

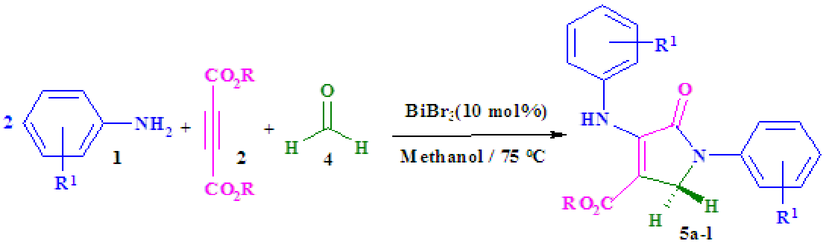


5a

Entry	$BiBr_3$ mol %	Time (hrs)	Yield[b] (%)	Solvent
1[c]	No catalyst	6	00	Neat
2	10	3	76	Methanol
3	5	3	80	Methanol
4	2.5	5	62	Methanol
5	5	3	75	Ethanol
6	5	4	60	Acetonitrile
7[d]	5	4	43	Dichloromethane
9	5	6	35	Neat

[a] aniline **1** (20 mmol), dialkyl acetylene dicarboxylate **2** (10 mmol) and formaldehyde (35% solution, 20 mmol) were taken in presence of various $BiBr_3$ mol % at 75°C; [b]Isolated yields; [c]Reaction was carried out at 100°C and 55°C[d]

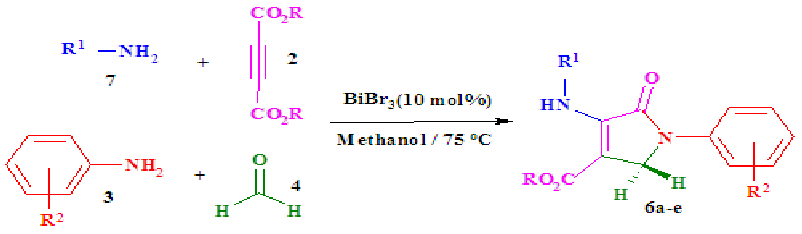
Table II Synthesis of highly functionalized dihydro-2-oxypyrroles (5a-l) catalyzed by $BiBr_3$ (10 mol %).



Entry	R^1	R	Product^{a}	Yield (%)^{b}	mp(^{o}C) Observed	mp(^{o}C) Literature[ref.]
1	H	CH_3	**5a**	80	156–158	155–156[17]
2	4-OCH_3	CH_3	**5b**	83	173–175	172–175[19]
3	4-Cl	CH_3	**5c**	81	170–172	171–173[17]
4	4-CH_3	CH_3	**5d**	79	177–178	177–178[17]
5	4-F	CH_3	**5e**	78	164–166	163–165[19]
6	4-Br	CH_3	**5f**	80	162–166	161–164[17]
2	H	CH_2CH_3	**5g**	82	139–141	138–140[17]
2	4-OCH_3	CH_3CH_3	**5h**	83	153–155	152–154[19]
3	4-Cl	CH_3CH_3	**5i**	84	169–171	168–170[19]
4	4-CH_3	CH_3CH_3	**5j**	85	179–180	177–178[19]
5	4-F	CH_3CH_3	**5k**	76	173–175	172–174[19]
5	4-Br	CH_3CH_3	**5l**	83	170–172	169–171[19]

[a] All the products are known, characterized by m.p., IR, LCMS and NMR spectral analysis and compared with the authentic samples. [b] Isolated yields

Table III Synthesis of highly functionalized dihydro-2-oxypyrroles (6a-e) catalyzed by $BiBr_3$ (10 mol %).



Entry	R^1	R	R^2	Product^{a}	Yield^{b} (%)	mp(^{o}C) Observed	mp(^{o}C) Literature[ref.]
1	$C_6H_5CH_2$	CH_3	H	**6a**	75	141–143	140–141[19]
2	$C_6H_5CH_2$	CH_3	4-Cl	**6b**	80	142–144	144–147[19]
3	$C_6H_5CH_2$	CH_3	4-Br	**6c**	78	127–129	126–128[19]
4	$C_6H_5CH_2$	CH_2CH_3	H	**6d**	76	128–130	130–132[19]
5	Cyclohexyl	CH_3	4-Br	**6e**	75	125–126	123–124[17]

[a]All the products are known, characterized by m.p., IR, LCMS and NMR spectral analysis and compared with the authentic samples. [b]Isolated yields

CONCLUSION

In conclusion, we have reported novel route for the synthesis of dihydro-2-oxypyrroles via multicomponent reaction using aniline/benzyl amine and dialkyl acetylene dicarboxylate with formaldehyde in methanol using $BiBr_3$ as catalyst. This protocol offers several advantages including good to excellent yield, simple work-up procedure, and inexpensive, environmental friendly catalyst.

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