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Terminal alkynes as keto-methyl equivalent toward one pot synthesis of 1,5-benzodiazepine derivatives under catalysis of $Hg(OTf)_2$

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ABSTRACT

Mercuric triflate catalyzes the reaction between 1,2-diaminobenzene and terminal alkynes to afford 2,4-disubstituted 2-methyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine in an excellent yield. The terminal alkynes function as a source of keto-methyl equivalent.

Benzodiazepines and its derivatives constitute an important class of heterocyclic compounds, which possess a wide range of therapeutic and pharmacological properties. Benzodiazepines enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA), which results in sedative, hypnotic, anxiolytic, anticonvulsant, muscle-relaxant, and amnesic action.[1] These properties make benzodiazepines useful in treating anxiety, insomnia, agitation, seizures, muscle spasms, alcohol withdrawal, and as a premedication for medical or dental procedures.[2] Depending on the substitution pattern and nature of substituents, benzodiazepines can have a wide range of half life. Short- and intermediate-acting benzodiazepines are preferred for the treatment of insomnia whereas longer-acting benzodiazepines are recommended for the treatment of anxiety.[3] Although the benzodiazepine was first introduced as a drug candidate nearly 40 years ago, the research in this area is very active and is directed toward the synthesis of compounds of enhanced pharmacological activity. In the last decade, the area of biological interest of 1,5-benzodiazepines has been extended to several diseases such as cancer, viral infection, and cardiovascular disorders.[4] Moreover, 1,5-benzodiazepines are key intermediates for the synthesis of various fused ring systems such as triazolo-, oxadiazolo-, oxazino-, or furanobenzodiazepines.[5] In addition, benzodiazepine derivatives also have also of commercial their importance as dyes for acrylic fibers in photography.[6] Owing to versatile applications, several methods for the synthesis of benzodiazepines have been reported in the literature.

Most of the methods reported in the literature either involve (i) condensation of *o*-phenylenediamines with α,β-unsaturated ketones[7a,b] or (ii) the reaction of *o*-phenylenediamines with various ketones using varieties of reagents and catalysts. These include $BF_3{\cdot}Et_2O$,[8a] $NaBH_4$,[8b] polyphosphoric acid,[8c] CAN,[8d] TCT,[8e] and also under solvent-free conditions using MgO and $POCl_3$,[9a] $Yb(OTf)_3$,[9b] $CeCl_3{\cdot}7H_2O$/NaI supported on silica gel,[9c] $Sc(OTf)_3$,[9d] $InBr_3$,[9e] sulfated zirconia,[9f] $ZnCl_2$,[9g] and $SiO_2/ZnCl_2$.[9h] Al_2O_3/P_2O_5[10a] or AcOH[10b] under microwave conditions, Amberlyst-15 in ionic liquids[10c] and 1,3-di-*n*-butylimidazolium bromide[10d] as solvent without any catalyst have also been reported for this reaction. Apart from these, various other catalysts have also been explored under solvent-free conditions.[11a–d]

Recently, there is a report of [4+2+1] cycloaddition of *o*-phenylene diamines with 2 equiv of alkynoate ester under solvent-free ultrasonic irradiation conditions which afforded the 3,4-disubstituted 1,5-benzodiazepines in a good yield.[12] Srinivasan and coworkers disclosed a multicomponent reaction involving an acyl chloride, aryl acetylene, and phenylenediamine to obtain 2,4-disubstituted-3*H*-benzo[*b*][1,4]diazepines.[13] However, to the best of our knowledge there is no report of employing aryl or alkyl substituted terminal acetylenes directly as keto-methyl equivalent for this transformations. We were interested to develop new synthetic route to benzodiazepines from *o*-phenylenediamines and terminal alkynes as delineated in Scheme 1.

Multicomponent reactions (MCRs) offer the elegance of one-pot reaction, atom-economy, and the possibility of introducing maximum diversity in the product in one chemical operation and have become an integral part of drug discovery program.[14] As a part of our continuing program[15] we were interested to explore the MCR

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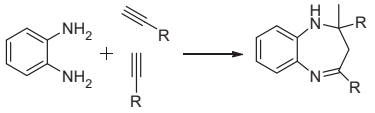


Scheme 1. Route to benzodiazepines.

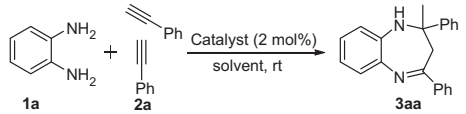
methods toward the synthesis of biologically relevant heterocycles. Herein, we wish to report a new synthetic route to 2-methyl-2,4-disubstituted-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine starting from various phenylenediamines and terminal alkyne derivatives in the presence of $Hg(OTf)_2$ at room temperature in dry ethanol solution in an excellent yield.

We began our investigation by the reactions of *o*-phenylenediamine **1a** and phenyl acetylene **2a** as model substrate to optimize the reaction conditions by using various Lewis acid catalysts, solvents, and catalyst-solvent combination. We put a special emphasis on Au(III) and Hg(II) salts as catalysts in an effort to standardize the reaction due to their ability to polarize the carbon–carbon triple bonds making them more susceptible to nucleophilic attack. Moreover, in recent times there had been a trend to explore the catalytic properties of Hg(II) triflate.[16] The results are summarized in Table 1.

From the Table 1, it is evident that mercuric triflate and ethanol were found to be the most effective catalyst and solvent respectively both in terms of reaction time and yield. The optimum quantity of catalyst was screened and it was found that on increasing the amount of catalyst from 0.5 to 2 mol %, yield of the reaction increases gradually but beyond 2 mol %, there is no significant improvement of the rate as well as yield of the reaction. Employing $HAuCl_4$ as catalyst, a product of polymeric nature was obtained which could not be characterized.

Encouraged by these results, we tried to generalize the scope and versatility of this methodology. Various 1,2-diamines and differently substituted terminal aryl- and alkyl acetylenes were used for the synthesis of substituted 1,5-benzodiazepines.[17] In case of internal alkynes such as methyl phenyl acetylene the reaction did not proceed at all under similar reaction condition. The outcome of our endeavors is summarized in Table 2.

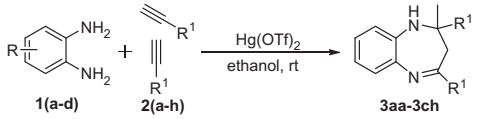
Table 1
Screening of reaction conditions for the synthesis of 1,5-benzodiazepines with **1a** and **2a**[a]

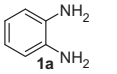
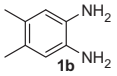
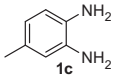
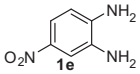


Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	$HAuCl_4$	DCM	12	[c]
2	$HAuCl_4$	THF	12	[c]
3	$HAuCl_4$	Ethanol	12	[c]
4	$Hg(OTf)_2$	THF	24	65
5	$Hg(OTf)_2$	Ethanol	6.5	90
6	$Hg(OTf)_2$	DCM	24	46
7	$HgCl_2$	THF	12	54
8	$HgCl_2$	Ethanol	10	82
9	$FeCl_3$	Ethanol	24	3
10	$Yb(OTf)_3$	Ethanol	24	[c]
11	$Cu(OTf)_2$	Ethanol	24	[c]
12	$Cu(OTf)_2$	THF	24	[c]
13	TfOH	Ethanol	24	[c]

[a] Reaction condition: *o*-phenylenediamine (1.0 mmol), phenylacetylene (2.2 mmol) in 3 mL solvent, catalyst (0.02 mmol), rt.
[b] Pure, isolated yield after column chromatography.
[c] Product not formed.

Table 2
Synthesis of benzodiazepines[a]



Entry	1,2-Diamine	R^1=	Time (h)	Yield[b] (%)	Product[c]
1		Phenyl **2a**	6.5	90	**3aa**
2	**1a**	4-Bromophenyl **2b**	8.0	89	**3ab**
3	**1a**	4-Chlorophenyl **2c**	6.0	80	**3ac**
4	**1a**	4-Methoxyphenyl **2d**	24	49	**3ad**
5	**1a**	3-Nitrophenyl **2e**	24	43	**3ae**
6	**1a**	*n*-Hexyl **2f**	8.5	84	**3af**
7	**1a**	*n*-Butyl **2g**	5.0	84	**3ag**
8		**2a**	1.0	97	**3ba**
9	**1b**	**2b**	1.5	92	**3bb**
10	**1b**	**2e**	24	51	**3be**
11	**1b**	**2d**	2.5	62	**3bd**
12	**1b**	**2c**	2.5	83	**3bc**
13	**1b**	**2g**	5.5	87	**3bg**
14	**1b**	**2h** 4-Methylphenyl	1.0	93	**3bh**
15[d]		**2a**	4.5	84	**3ca**
16[d]	**1c**	**2b**	2.0	97	**3cb**
17[d]	**1c**	**2e**	2.0	45	**3ce**
18[d]	**1c**	**2h**	3.5	81	**3ch**
19		**2a**	24	00	NR[e]
20		**2a**	24	00	NR[e]

[a] Reaction condition: *o*-phenylenediamine (1.0 mmol), terminal acetylene (2.2 mmol) in 3 mL ethanol, mercuric triflate (0.02 mmol), rt.
[b] Pure, isolated yield after column chromatography.
[c] All products were characterized by IR, ^1H NMR, ^{13}C NMR.
[d] Mixture of regioisomers are formed in the ratio of approximately 2:3.
[e] No reaction.

From Table 2, it is evident that the reaction proceeds smoothly with the terminal alkynes. Electronic nature of functional groups on aryl rings of both diamine and terminal acetylene had a marked effect on the rate as well as yield of the reaction. 4-Methoxyphenylacetylene (Table 2, entry 4) reacted much slower compared to phenyl acetylene (Table 2, entry 1) itself and yield was also lower. These observations may be explained by considering the nucleophilic addition of amino group to the Hg(II)–alkyne complex to be slow in case of 4-methoxyphenylacetylene. The electron donating ability of the aryl ring, which is highest for the methoxyl group and least for the nitro group, may explain this observation. However, under the similar reaction condition, we observed that in case of 3-nitrophenylacetylene, reaction was sluggish and also low yielding. Moreover, along with the desired benzodiazepine, it furnished 3-nitroacetophenone as by product. To account for the above observation and to understand the mechanistic pathway, various aryl acetylenes were subjected to react with wet ethanol in the presence of mercuric triflate. Only in case of 3-nirophenylacetylene we were able to isolate 3-nitroacetophenone in a 25%

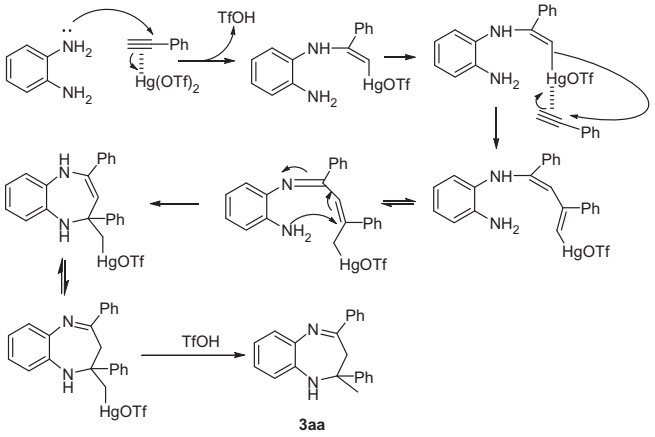


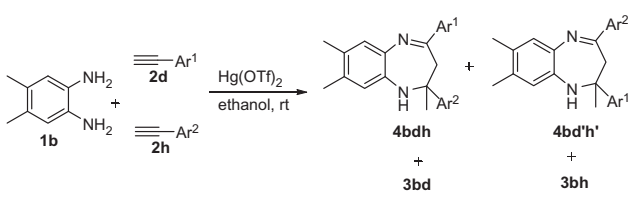
Figure 1. Plausible mechanism of the reaction.

yield but in all other cases only trace amount of acetophenone derivatives were obtained. This observation suggests that for all other aryl acetylenes, the reaction occurs between Hg(II)–alkynes complex and phenylenediamine. However, for 3-nitrophenylacetylene, at least in part, the reaction may proceed through an acetophenone intermediate. This is further supported by the fact that when substituted acetophenones were made to react with *o*-phenylenediamine under similar reaction condition, yields were low even after prolonged stirring at room temperature. On the basis of the above observations we suggest the following major reaction pathway for this transformation (Fig. 1).

1,2-Diamines containing an electron withdrawing group as well as electron deficient aromatic ring such as 4-nitro-*o*-phenylenediamine (Table 2, entry 19) and 2,3-diaminopyridine (Table 2, entry 20) did not react under this reaction condition. On the other hand reactions with 4,5-dimethyl-*o*-phenylenediamine was much faster than the corresponding 1,2-phenylenediamine.

The reaction of various arylacetylene derivatives with 4-methyl-*o*-phenylenediamine furnished the corresponding benzodiazepines as a mixture of two regioisomers, which could not be separated by usual column chromatography. In contrast to the earlier report of regioisomer in equimolecular proportion by Yao and co-workers [8e] in case of 4-methyl-*o*-phenylenediamine, we obtained a mixture of inseparable regioisomers approximately in the ratio of 2:3 and it was almost independent on the substitutions pattern in the aromatic ring of aryl acetylenes (Table 2, entries 15–18). The ratio was determined from the ^{1}H NMR spectrum by comparison of the integrations of C-7 and/or C-10 aromatic proton signals at δ 6.64–6.67 and at δ 7.13–7.16 for the two regioisomers.

In an effort to explore the scope of the reaction using two different alkynes, 4,5-dimethyl-*o*-phenylenediamine (**1b**) was made to react with **2d** and **2h** under $Hg(OTf)_2$ catalysis (Scheme 2). Pure **3bh** (yield 25%) and **3bd** (yield 15%) were formed in 1:1.65 ratio along with regioisomeric mixture (yield 53%) of **4bdh** and **4bd′h′**. The regioisomeric mixture of **4bdh** and **4bd′h′** could not be separated by usual column chromatography. ^{1}H NMR spectrum of the



Scheme 2. Formation of mixed benzodiazepines.

regioisomeric mixture showed the presence of two regioisomers in 1:1.65 ratio, the same proportion in which **3bh** and **3bd** were formed.

In summary, we have developed a mild and efficient reaction between *o*-phenylenediamines and terminal alkynes leading to 2-methyl-2,4-disubstituted-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepines using $Hg(OTf)_2$ catalyst with high atom economy. The notable advantages of this method are operational simplicity, mild reaction conditions, low catalyst loading, ease of isolation of products, and non-toxic ethanol as solvent.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.036.

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17. **Representative experimental procedure**: To a solution of phenylacetylene (225 mg, 2.2 mmol) in 3 mL ethanol, *o*-phenylenediamine (108 mg, 1.0 mmol) and $Hg(OTf)_2$ (10 mg, 0.02 mmol) were added and stirred at room temperature for 6.5 h. Completion of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was quenched with water, extracted with dichloromethane, dried over anhydrous sodium sulphate, and volatiles were removed. The crude residue was purified by short column chromatography over silica-gel (60–120 mesh) using 5% ethylacetate/petroleum ether mixture afforded *2-methyl-2,4-diphenyl-2,3-dihydro-1H-benzo[b][1,4]diazepine* (***3aa***) (281 mg, 90%) as a yellow crystalline solid; mp 148–150 °C (lit.[9e]150–152 °C). R_f = 0.5 (silica: petroleum ether/ethyl acetate, 9:1) ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.77 (s, 3H), 2.99 (d, *J* = 13.1 Hz, 1H), 3.17 (d, *J* = 13.1 Hz, 1H), 3.60 (br s, 1H), 6.86 (dd, *J* = 1.8, 7.5 Hz, 1H), 7.03–7.13 (m, 2H), 7.16–7.20 (m, 1H), 7.20–7.34 (m, 5H), 7.39 (dd, *J* = 1.8, 7.2 Hz, 1H), 7.57–7.63 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.9, 43.2, 73.9, 121.3, 121.6, 125.4, 126.3, 127.0, 128.0, 128.3, 128.6, 129.7, 138.0, 139.4, 140.1, 147.6, 168.0. HRMS calculated for $C_{22}H_{20}N_2Na^+$ 335.1519 found 335.1517.
Spectral data of ***2-methyl-2,4-diphenyl-2,3-dihydro-8-methyl-1H-1,5-benzodiazepine 3ca*** (approximately 2:3 regioisomeric mixture): Yellow crystalline solid. mp 86–88 °C. R_f = 0.5 (silica: petroleum ether/ethyl acetate, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76 (s, 3H, minor regioisomer), 1.77 (s, 3H, major regioisomer), 2.36 (s, 3H, major isomer), 2.37 (s, 3H, minor isomer), 2.97 (d, *J* = 13.2 Hz, 1H, minor isomer), 2.99 (d, *J* = 13.2 Hz, 1H, major isomer), 3.12 (d, *J* = 13.0 Hz, 1H, minor isomer), 3.17 (d, *J* = 13.2 Hz, 1H, major isomer), 3.52 (br s, 2H, major + minor isomers), 6.67 (s, 1H, major isomer), 6.77 (d, *J* = 7.9 Hz, 1H, minor isomer), 6.87 (dd, *J* = 1.2, 8.0 Hz, 1H, major isomer), 6.92 (dd, *J* = 1.5, 7.9 Hz, 1H, minor isomer), 7.16–7.34 (m, 14H, major + minor isomers), 7.57–7.65 (m, 8H, major + minor isomers). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 21.0, 29.7, 30.0, 43.0, 43.3, 72.9, 73.9, 121.5, 122.3, 125.4, 127.0, 127.1, 128.0, 128.3, 128.6, 128.9, 129.6, 129.7, 131.3, 135.5, 136.4, 137.1, 138.0, 139.5, 139.7, 140.3, 147.6, 147.7, 166.8, 167.9. HRMS calculated for $C_{23}H_{22}N_2Na^+$ 349.1681 found 349.1685.
Spectral data of ***2-methyl-2,4-bis(4-bromophenyl)-2,3-dihydro-8-methyl-1H-1,5-benzodiazepine 3cb*** (approximately 2:3 regioisomeric mixture): Yellow crystalline solid. mp 127–129 °C. R_f = 0.4 (silica: petroleum ether/ethyl acetate, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72 (s, 3H, minor isomer), 1.73 (s, 3H, major isomer), 2.34 (s, 3H, major isomer), 2.35 (s, 3H, minor isomer), 2.86 (d, *J* = 13.2 Hz, 1H, minor isomer), 2.88 (d, *J* = 13.2 Hz, 1H, major isomer), 3.03 (d, *J* = 13.2 Hz, 1H, minor isomer), 3.09 (d, *J* = 13.2 Hz, 1H, major isomer), 3.45 (br s, 2H, major + minor isomers), 6.65 (s, 1H, major isomer), 6.75 (d, *J* = 7.9 Hz, 1H, minor isomer), 6.86 (dd, *J* = 1.5, 8.0 Hz, 1H, major isomer), 6.91 (dd, *J* = 1.9, 8.0 Hz, 1H, minor isomer), 7.13 (d, *J* = 1.5 Hz, 1H, minor isomer), 7.22 (d, *J* = 8.0 Hz, 1H, major isomer), 7.34-7.50 (m, 16H, major + minor isomer). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 21.0, 29.5, 29.9, 42.8, 43.1, 72.7, 73.7, 121.1, 121.5, 122.7, 124.4, 124.6, 127.4, 128.4, 128.5 128.6, 128.9, 131.2, 131.3, 131.7, 135.0, 136.7, 136.8, 137.5, 138.0, 138.3, 140.0, 146.3, 146.4, 165.2, 166.3. HRMS calculated for $C_{23}H_{20}Br_2N_2Na^+$ 504.9885 found 504.9890.
Spectral data of ***2-methyl-2,4-bis(4-methylphenyl)-2,3-dihydro-8-methyl-1H-1,5-benzodiazepine 3ch*** (2:3 regioisomeric mixture): Yellow crystalline solid. mp 85–87 °C. R_f = 0.6 (silica: petroleum ether/ethyl acetate, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72 (s, 3H, minor regioisomer), 1.73 (s, 3H, major isomer), 2.32 (br s, 9H, minor isomer), 2.35 (s, 9H, major isomer), 2.96 (d, *J* = 13.1 Hz, 1H, minor isomer), 2.98 (d, *J* = 13.2 Hz, 1H, major isomer), 3.06 (d, *J* = 13.2 Hz, 1H, minor isomer), 3.09 (d, *J* = 13.2 Hz, 1H, major isomer), 3.49 (br s, 2H, major + minor isomers), 6.64 (d, *J* = 1.2 Hz, 1H, major isomer), 6.74 (d, *J* = 7.9 Hz, 1H, minor isomer), 6.83–6.92 (m, 2H, major + minor isomers), 7.07–7.12 (m, 8H, minor + minor isomer), 7.16–7.17 (m, 1H, minor isomer), 7.25 (d, *J* = 7.9 Hz, 1H, major isomer), 7.45–7.52 (m, 4H, major + minor isomers), 7.54–7.60 (m, 4H, major + minor). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 20.9, 21.0, 21.3, 29.7, 29.9, 42.7, 43.1, 72.6, 73.5, 121.4, 121.5, 122.3, 125.2, 125.2, 126.8, 127.1, 127.2, 127.6, 128.5, 128.8, 128.9, 131.2, 135.6, 136.1, 136.4, 136.6, 136.9, 137.1, 137.3, 138.1, 139.8, 140.0, 140.5, 145.1, 166.7, 167.8. HRMS calculated for $C_{25}H_{26}N_2Na^+$ 377.1988 found 377.1984.