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N,N′-alkylidene bisamides: unexpected products in the multi-component reaction of phenyl acetylene/1-Hexyne, aromatic aldehyde and benzamide/acetamide

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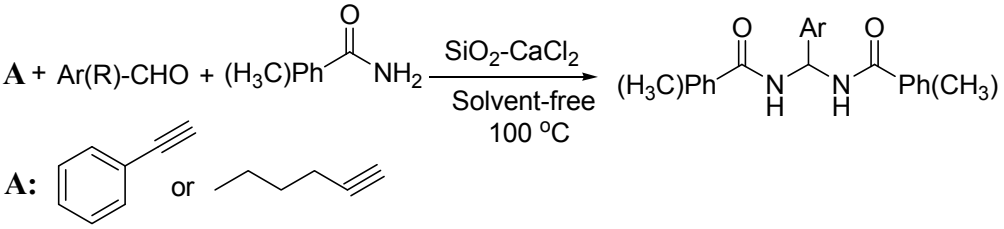
Abstract. An efficient approach for the synthesis of bisamide derivatives is described by Silica supported calcium chloride (SiO_2-$CaCl_2$) mediated the reaction of phenyl acetylene/1-Hexyne, aromatic aldehyde and benzamide/acetamide. The reaction condition is very simple, offers easy isolation, and affords good yields of the products. The contribution of alkyne in the reaction processes has been confirmed by the using of chromatographic study.

Keywords: SiO_2-$CaCl_2$; Heterogeneous Catalyst; *N,N'*-alkylidene bisamides; alkyne

1. Introduction

The carbon-nitrogen bonds creation is an important reaction and demand of organic chemistry and the science of pharmacology. Thus, many approaches for the preparation of compounds containing amino or amido groups have been developed attempting to address their medicinal needs from time to time [1]. Compounds having amido group play a major role in the development and composition of biological and pharmacological systems [2]. For example, they can be easily transformed into other functionalities (such as gem-diaminoalkyl and aminoalkyl groups) and are of considerable interest in the synthesis of pharmacological materials such as peptidomimetic compounds [2]. Common approach on the synthesis of bisamides is the direct reaction of aldehydes with the corresponding carboxamide using a strong acid catalyst, such as sulfuric acid, a sulfonic acid or hydrochloric acid [3]. However, these methods require the presence of corrosive homogeneous liquid acid catalyst (especially in a large amount of acid) and considering the facts that most of the organic reagents involved in fine chemical synthesis are sensitive to harsh conditions, it is desirable to choose catalysts which can catalyze organic transformations under mild conditions.

The chemist interests in utilizing of silica supports in organic synthesis [4] have led us to investigate SiO_2-$CaCl_2$ promoted reactions for the synthesis of *N,N′*-alkylidene bisamide derivatives. Herein we wish to report a mild and convenient methodology for the formation of amide bonds from the reaction of alkyne, aromatic aldehydes and amides in the presence of SiO_2-$CaCl_2$ as catalyst under thermal, solvent-free conditions (Scheme 1).



Scheme 1: preparation of *N,N′*-alkylidene bisamide derivatives

2. Results and discussions

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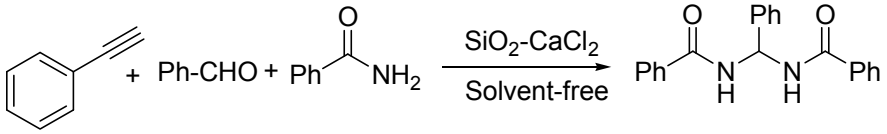
The use of toxic solvents and corrosive homogenous catalysts in the synthesis of organic compounds remain a demand for trying to develop new synthetic methods, reaction conditions, and uses of heterogeneous catalysts that reduce risks to humans and the environment. Thus the reaction of phenyl acetylene, benzaldehydes and benzamide in the presence a catalytic amount of SiO_2-$CaCl_2$ as catalyst under thermal, solvent-free conditions were investigated (Scheme 1).

Within our plan to investigate the structures of bisamide and needing of alkyne for the formation of bisamides, the reaction including benzaldehyde, benzamide, and a catalytic amount of SiO_2-$CaCl_2$ under heating at 100 ^oC failed to give the correlative product in the absence of phenyl acetylene, which indicated that the phenyl acetylene plays an important role in the reaction. Chromatographic studies (TLC indicating) confirm that the alkyne was completely disappearing when the product was formed.

In order to optimize the reaction conditions, the synthesis of *N*-Benzoylamino(phenyl)methyl benzamide was selected as a model reaction (Scheme 2). Therefore, a mixture of phenyl acetylene (1 mmol), benzaldehyde (1 mmol) and benzamide (2.2 mmol) in the presence of SiO_2-$CaCl_2$ as catalyst was heated in an oil bath under various amounts of the catalyst and different temperatures. Initially, the effect of temperature on rate of the reaction was investigated (Table 1). At 80 ^oC, the reaction proceeded smoothly and almost complete conversion of product was observed. Further increase in temperature to 100 ^oC increased the rate of the reaction. Therefore, we kept the reaction temperature as 100 ^oC (giving short reaction time and high yield).



Scheme 2: preparation of *N*-Benzoylamino(phenyl)methyl benzamide using SiO_2-$CaCl_2$ as catalyst

Then we tried to optimize the amount of the catalyst for this reaction. It should be noted that 0.01 g of SiO_2-$CaCl_2$ was efficient enough to catalyze the reaction, and increasing the amount of catalyst did not improve the yield significantly (Table 1). Finally, we achieved an optimized condition using 0.01 g of SiO_2-$CaCl_2$ as the catalyst and 100 °C. The results were summarized in Table 1.

Table 1: Optimization amount of SiO_2-$CaCl_2$ and the reaction temperature

Entry	Catalyst (g)	T (°C)	Time (min)	Yield (%)[a]
1	0.01	rt	300	-
2	0.01	80	300	52
3	0.1	100	220	60
4	0.05	100	210	63
5	0.025	100	190	71
6	0.01	100	180	74

[a]Isolated yield (based on phenyl acetylene (1 mmol), benzaldehyde (1 mmol) and benzamide (2.2 mmol)

Using these optimized reaction conditions, the scope and efficiency of these procedures were explored for the synthesis of a wide variety of substituted bisamides. The results are summarized in Table 2.

All the reactions proceeded smoothly and the desired products were obtained in good to excellent yields. A series of aromatic aldehydes with either electron-donating or electron-withdrawing groups attaching to aromatic ring were investigated (Table 2, Entries 1-9). However, when aromatic aldehydes with electron-withdrawing groups (such as nitro-) are reactants, the reaction time is shorter than that with electron-donating groups (such as methoxy-). Though *meta*- and *para*- substituted aromatic aldehydes gave good results, *ortho*-substituted aromatic aldehydes (such as 2-nitrobenzadehyde) gave lower yields and longer reaction time because of the steric effects. These good results were also obtained in the case of the 1-hexyne (Table 2; Entries 14-19).

As a result the reaction of butyraldehyde with phenyl acetylene and benzamide gave the product in moderate yield (Table 2; Entry 10).

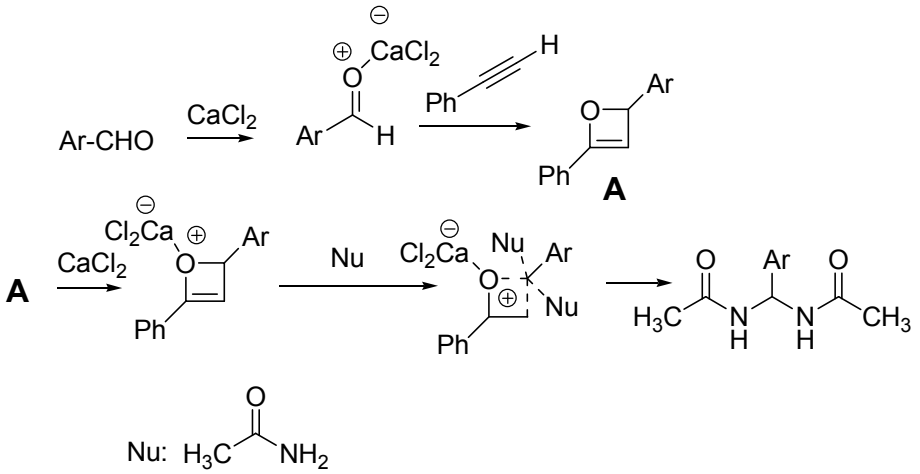
Encouraged by the results obtained with benzamide, we turned our attention to acetamide (Table 2). As shown in Table 2, the reactions of phenyl acetylene and aryl aldehyde with acetamide under the mentioned reaction conditions was progress smoothly but in longer reaction times and the desired products were obtained in good yields. (Table 2, Entries 11-13).

To explain the formation of bisamides via the one-pot multi-component reaction, we have proposed a plausible reaction mechanism, which is illustrated in Scheme 4. Firstly, the activation of aldehyde by empty π orbital of Lewis acid was occurred to form a cation intermediate. In continue the formation of a highly strained oxetene intermediate (**A**) resulting from the cyclo-condensation of activated aldehyde with phenyl acetylene was established [5]. The formation of oxete and oxetane from the cyclo-addition of triple and double bonds is well documented as Paterno-Buchi reaction [6]. The second step is the addition of two molecules of amide to **A** that activated and convert to the bisamide as product by the attack of amide.

Table 2: preparation of *N,N'*-alkylidene bisamide derivatives

Entry	Aldehyde	amide	alkyne	Time (min)	Yield (%)[a]	m.p. (°C)
1	4-Nitrobenzaldehyde	Benzamide	Phenylacetylene	60	85	245-247
2	3-Nitrobenzaldehyde	Benzamide	Phenylacetylene	90	79	236-238
3	2-Nitrobenzaldehyde	Benzamide	Phenylacetylene	300	65	257-259
4	4-Fluorobenzaldehyde	Benzamide	Phenylacetylene	70	81	202-204
5	2,4-Dichlorobenzaldehyde	Benzamide	Phenylacetylene	125	77	235-237
6	2-Chlorobenzaldehyde	Benzamide	Phenylacetylene	180	64	244-246
7	Benzaldehyde	Benzamide	Phenylacetylene	180	74	226-228
8	4-*tert*-butylbenzaldehyde	Benzamide	Phenylacetylene	420	65	212-214
9	4-Methoxybenzaldehyde	Benzamide	Phenylacetylene	450	62	228-230
10	butyraldehyde	Benzamide	Phenylacetylene	360	59	212-214
11	Benzaldehyde	Acetamide	Phenylacetylene	260	66	252-254
12	4-Fluorobenzaldehyde	Acetamide	Phenylacetylene	250	71	258-260
13	4-Nitrobenzaldehyde	Acetamide	Phenylacetylene	135	76	233-235
14	Benzaldehyde	Benzamide	1-Hexyne	270	77	225-227
15	butyraldehyde	Benzamide	1-Hexyne	300	74	210-212
16	4-Nitrobenzaldehyde	Benzamide	1-Hexyne	80	84	246-248
17	4-Nitrobenzaldehyde	Acetamide	1-Hexyne	300	69	233-235
18	3-Nitrobenzaldehyde	Benzamide	1-Hexyne	105	78	236-238
19	4-Fluorobenzaldehyde	Benzamide	1-Hexyne	140	81	203-205

[a]Isolated yields.



Scheme 3: Proposed mechanism for the formation of *N,N'*-alkylidene bisamides

In conclusion, a practical method for the environmentally friendly preparation of *N,N'*-alkylidene bisamides in a one-pot procedure has been developed. The work-up procedure is very clear-cut; that is the products were isolated and purified by simple filtration and crystallization from aqueous ethanol (or diethyl ether). Our protocol avoids the use of SiO_2-$CaCl_2$ as heterogeneous non-toxic Lewis acid catalyst and dry media during the reaction process, making it superior to the reactions that use solvent.

3. Experimental

All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to isolated products after purification. Products were characterized by comparison of spectroscopic data (IR, ^{1}H NMR spectra) and melting points with authentic samples. The NMR spectra were recorded on a Bruker Avance DPX 300 MHz instrument. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). IR spectra were recorded on a PerkineElmer 781 spectrophotometer. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. TLC was performed on silica gel polygram SIL G/UV 254 plates.

3.1. General Procedure for the Synthesis of *N,N'*-alkylidene bisamides

To a mixture of aryl aldehyde (1 mmol), benzamide/acetamide (2.2 mmol) and phenyl acetylene/1-hexyne (1 mmol) was added SiO_2-$CaCl_2$ (0.01 g) and mixture was heated at 100 ^{o}C in an oil bath for the appropriate time (Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, mass was cooled to 25 ^{o}C and the mixture was dissolved in boiling ethanol. The catalyst was removed by simple filtration. Solvent was concentrated and the solid product was purified by recrystallization procedure in appropriate solvent (ethanol 40% or diethyl ether). All the products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra. Selected data:

N-Benzoylamino(4-nitrophenyl)methyl benzamide (Table 2, Entry 1):
^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.08 (t, *J* = 7.3 Hz, 1H), 7.47-7.60 (m, 6H), 7.75 (d, *J* = 8.6 Hz, 2H), 7.93 (d, *J* = 7.1 Hz, 4H), 8.26 (d, *J* = 8.7 Hz, 2H), 9.22 (d, *J* = 7.4 Hz, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ= 59.4, 124.4, 128.5, 128.9, 129.2, 132.6, 134.4, 147.9, 148.4, 166.8 ppm; IR (KBr, cm^{-1}): 3264, 3085, 3028, 2963, 1650, 1633, 1608, 1579, 1548, 1486, 1345, 1295, 1277, 1201, 1143, 1083, 1055, 875, 852, 794, 718, 695; Found: C, 67.36; H, 4.60; N,11.26 $C_{21}H_{17}N_3O_4$ requires C, 67.19; H, 4.56; N, 11.19 %].
N-Benzoylamino(3-nitrophenyl)methyl benzamide (Table 2, Entry 2):
^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.11 (t, *J* = 7.3 Hz, 1H), 7.47-7.60 (m, 6H), 7.71 (t, *J* = 7.9 Hz, 1H), 7.94-7.96 (m, 5H), 8.21 (d, *J* = 8.1 Hz, 2H), 8.36 (s1H), 9.27 (d, *J* = 7.3 Hz, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ= 59.5, 122.3, 123.6, 128.5, 129.2, 130.8, 132.6, 134.4, 134.6, 143.3, 148.7, 166.8 ppm; IR (KBr, cm^{-1}): 3313, 3259, 3086, 2969, 1649, 1602, 1581, 1534, 1505, 1340, 1271, 1211, 1140, 1054, 873, 736, 716; Found: C, 67.32; H, 4.65; N,11.29 $C_{21}H_{17}N_3O_4$ requires C, 67.19; H, 4.56; N, 11.19 %].

4. Acknowledgments

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