Organic LETTERS

Letter

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Aldehyde-Promoted One-Pot Regiospecific Synthesis of Acrylamides Using an in Situ Generated Molybdenum Tetracarbonyl Amine [$Mo(CO)_4(amine)_2$] Complex

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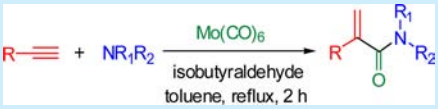
Supporting Information

ABSTRACT: A novel complex system generated in situ from $Mo(CO)_6$ and an amine is described for the regiospecific aminocarbonylation of various terminal alkynes. The $Mo(CO)_6$–amine system played a dual role as complexing agent and as CO donor, thus making this process palladium-free.



Acrylamide and its derivatives play a significant role in a wide range of organic reactions such as nucleophilic additions, cycloaddition reactions, radical reactions, *etc.*[1] They are also extensively used as starting materials in the synthesis of various bioactive and polymeric materials.[2]

Although the most widely used process for the synthesis of acrylamides has been by the hydration of acrylonitriles, the *N*-substituted acrylamides are usually synthesized stepwise from acrylic acid or its esters.[3] In an alternative approach, *N*-substituted acrylamides could be prepared in 35−52% yields by reacting alkylidenecarbenes with isonitriles.[4] Recently, nickel-catalyzed synthesis of acrylamides using α-olefins and isocyanates was reported.[5] However, a commonly applied direct and clean synthesis of substituted acrylamides is by the carbonylation of alkynes in the presence of amines, that is, aminocarbonylation.[6] Indeed, also reported was the synthesis of 2-substituted acrylamides via a palladium-catalyzed aminocarbonylation of terminal alkynes either in a strongly acidic medium[7] or in the presence of organic iodide,[8] and *p*-TsOH.[9]

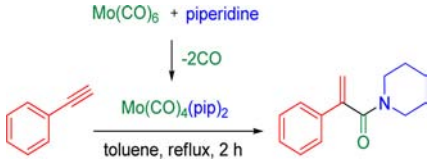
Thus, literature reports on the carbonylative regioselective coupling of alkylamines with terminal alkynes have certainly been relatively few in number.[7] Also, the acid constituents of the aminocarbonylation catalyst, in the cases where they are applied, makes the process corrosive. Hence, developing aminocarbonylation reactions that do not involve the use of corrosive agents would be highly desirable.[10]

Moreover, there are major concerns in the chemical industry regarding the use of reactive gases and their efficient utilization. Specifically, the difficulty in the handling of toxic carbon monoxide in synthesis has created interest in finding alternative sources of CO[11] and has led to the development of modified gas-free aminocarbonylation protocols,[12] especially in the preparation of *N*,*N*-dimethylbenzamides and acrylamides.[13] The commercially available $Mo(CO)_6$ functions as a convenient and solid carbon monoxide source in palladium-catalyzed aminocarbonylations of terminal alkynes.[14]

Molybdenum coordination chemistry is an intriguing research area owing to its numerous potential applications in organic synthesis.[15] Though, $Mo(CO)_6$ is not generally active itself as a complexing agent, in the presence of suitable ligands it is known to become active making the desired reactions possible.[16] To achieve this, substitution of one or more of the CO units in the structure with other ligands is carried out. It is well-known that $Mo(CO)_6$ can easily undergo ligand exchange with amines, and in this process carbon monoxide is released into the reaction mixture usually at elevated temperatures.[17]

In this context, we envisioned the development of an in situ generated complex system using $Mo(CO)_6$ and an amine for the regiospecific aminocarbonylation of terminal alkynes in which the generated complex could play the dual role of the complexing agent as well as the CO donor (Scheme 1).

Scheme 1. Proposed Synthesis of 2-Phenyl-1-(piperidin-1-yl)prop-2-en-1-one



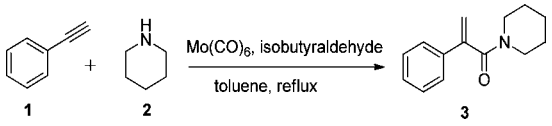
Thus, experiments were carried out using phenylacetylene and piperidine as the substrates in toluene, and the results are summarized in Table 1. Phenylacetylene **1** (1 mmol), piperidine **2** (1.5 mmol), and $Mo(CO)_6$ [1 mmol] were dissolved in toluene, and the solution was stirred at room temperature for 6 h under a nitrogen atmosphere. On the basis of TLC analysis, it was observed that the reaction failed to proceed even at elevated temperatures (Table 1, entry 1). Hence, we assumed that $Mo(CO)_4(pip)_2$ requires an additional activator to promote the reaction.

Phenols (2-fluorophenol/4-chlorophenol) are well-known to assist $Mo(CO)_6$ in catalyzing metathesis reactions.[18] To the best of our knowledge, there are no earlier reports on a

Received: August 11, 2015
Published: September 2, 2015

DOI: 10.1021/acs.orglett.5b02231
Org. Lett. 2015, 17, 4592–4595

Table 1. Optimization of the Reaction Conditions for the Synthesis of Acrylamides[a]



entry	$Mo(CO)_6$/piperidine [mmol]	isobutyraldehyde (mmol)	time (h)	yield[b] (%)
1	1/1.5		48	
2[c]	1/1.5		12	20
3	1/1.5	0.5	6	55
4	1/1.5	1	4	77
5	1/1.5	2	4	72
6	1/2.0	1	2	83
7	1/2.5	1	2	79
8	1.5/2.0	1	2	81

[a]Reaction conditions: Phenylacetylene (1 mmol), piperidine, isobutyraldehyde, $Mo(CO)_6$, toluene, reflux. [b]Isolated yields. [c]Acetaldehyde (0.5 mmol) was added as promoter.

carbonyl compound (aldehyde/ketone) assisting in organometallic reactions. Hence, to explore this area we repeated the same reaction by adding a simple aldehyde such as acetaldehyde (0.5 mmol) (Table 1, entry 2). We observed that the color of the reaction turned from clear light brown to dark brown. Though the anticipated product **3** was formed, the yield was below par; however, when the reaction was performed again using isobutyraldehyde, the yield slightly improved (Table 1, entry 3). When the concentration of isobutyraldehyde was increased to 1 mmol, the product was formed in good yield (Table 1, entry 4). No improvement in the yield was observed with a further increment in the isobutyraldehyde concentration (Table 1, entry 5). Next, we conducted a number of experiments to optimize $Mo(CO)_6$/piperidine concentration. It was observed that $Mo(CO)_6$ [1 mmol] and piperidine (2 mmol) is the optimum concentration for the smooth reaction (Table 1, entries 6–8).

Out of all the aliphatic aldehydes screened, isobutyraldehyde gave the best result as an activator (Table 2).

Surprisingly, reactions with aromatic aldehydes were not productive (Table 2, entries 5–7). Studies were also performed using ketones as a reaction promoter, but no success was achieved (Table 2, entries 8 and 9). Further, solvent studies were performed using different solvents such as tetrahydrofuran, dichloromethane, acetonitrile, and ethanol. Interestingly, the reaction was found to be solvent-specific for toluene.

Table 2. Screening of Carbonyl Compounds as Promoter for the Synthesis of Acrylamides[a]

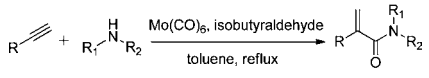
entry	carbonyl compound	time (h)	yield[b] (%)
1	isobutyraldehyde	2	83
2	acetaldehyde	6	45
3	butyraldehyde	2	78
4	hexanal	2	75
5	benzaldehyde	12	
6	2-phenylacetaldehyde	12	
7	2-napthaldehyde	12	
8	acetone	12	
9	2,4-dimethylpentan-3-one	12	

[a]Reaction conditions: Phenylacetylene (1 mmol), piperidine (2 mmol), aldehyde/ketone (1 mmol), $Mo(CO)_6$ (1 mmol), toluene, reflux. [b]Isolated yields.

A variety of substrates bearing a terminal alkyne unit were screened under the optimized reaction conditions, and very good results were obtained (Table 3).

Reactions involving different halogen-substituted phenylacetylenes, such as 4-fluoro- and 3-chloro- derivatives gave good to excellent yields (Table 3, entries 2 and 3). Reaction

Table 3. $Mo(CO)_6$/Amine-Mediated Synthesis of Acrylamides[a]



entry	alkyne (**1**)	amine (**2**)	product (**3/4**)	time (min)	yield[b] (%)
1	Ph—	NH	**3a**	120	83
2	F—	NH	**3b**	135	79
3	Cl	NH	**3c**	115	80
4		NH	**3d**	140	85
5	O_2N O	NH	**3e**	155	78
6[c]	MeO O	NH	**3f+4f**[d] (62:38)	160	79
7	TBDPSO	NH	**4g**[d]	145	75
8	Ph—	O NH	**3h**	130	65
9		O NH	**3i**	140	76
10	Ph—	NH	**3j**	135	85
11	F—	NH	**3k**	150	80
12	Cl	NH	**3l**	145	79
13		NH	**3m**	135	84
14	Ph—	N H	**3n**	145	81
15		N H	**3o**	120	75
16	Ph—	NH	**3p**	135	76
17		NH	**3q**	140	79
18	Ph—	—N NH	**3r**	150	85

[a]Reaction conditions: Alkyne (1 mmol), amine (2 mmol), isobutyraldehyde (1 mmol), $Mo(CO)_6$ (1 mmol), toluene, reflux. [b]Isolated yields. [c]Ratio calculated with the help of UPLC. [d]For structures, please refer to Figure 1.

DOI: 10.1021/acs.orglett.5b02231
Org. Lett. 2015, 17, 4592–4595

using phenylacetylenes substituted with alkyl moieties, such as 4-*tert*-butyl- resulted in an increased product yield (Table 2, entry 4). To explore further the range of substituted terminal alkynes, we tried reactions using *O*-propargylated compounds, such as 1-nitro-3-[(prop-2-yn-1-yloxy)methyl]benzene and 1-methoxy-4-[(prop-2-yn-1-yloxy)methyl]benzene. Compound **3e** was formed without being accompanied by any rearrangement product (Table 3, entry 5), but compounds **3f** and **4f** were formed as an inseparable mixture in a ratio of 62:38 (expected product/rearrangement product) [Table 3, entry 6]. Amused by this observation, we further tried a reaction using an alkyne bearing an acid sensitive protecting group, namely TBDPS. We were surprised to see that the rearrangement product **4g** was formed with absence of the regular anticipated product (Table 3, entry 7). The rearranged product **4g** was formed selectively as the *Z* isomer (confirmed by ^{1}H NMR through ppm shift value of the alkene unit at δ 6.45) with negligible amounts of the *E* isomer. The cause for this unusual rearrangement could not be explained, although this phenomenon was observed only in the case of propargyl ethers (Figure 1).

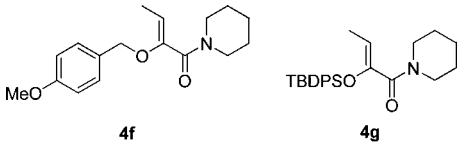


Figure 1. Rearrangement products **4f** and **4g**.

Next, to check the versatility of the protocol, a wide range of amines were screened. We were surprised to see that the reaction proceeded only with secondary aliphatic amines. The reaction involving primary amines, benzylamines, anilines and *N*,*N*-dibenzylamine did not proceed. Reactions with morpholine furnished moderate yields (Table 3, entries 8 and 9), whereas reactions involving 4-methylpiperidine (Table 3, entries 10−13), pyrrolidine (Table 3, entries 14 and 15) and diethylamine (Table 3, entries 16 and 17) provided good yields. Higher yields were observed when the reaction was carried out using 1-methyl piperazine (Table 3, entry 18).

Although the mechanism for this reaction is unclear, our hypothesized mechanism includes the formation of the active neutral species **B** via the coordination of the alkyne to the neutral species **A** (Figure 2).

Insertion of CO forms the intermediate **C**. This step may be promoted by the coordination of the molybdenum nucleus with aldehyde in enol form which facilitates the CO moiety release, followed by the addition of piperidine to the carbonyl carbon forming the product **D**. The added aldehyde was consumed in the reaction, which prompted us to assume that it remains coordinated with the molybdenum forming the complex **E**.

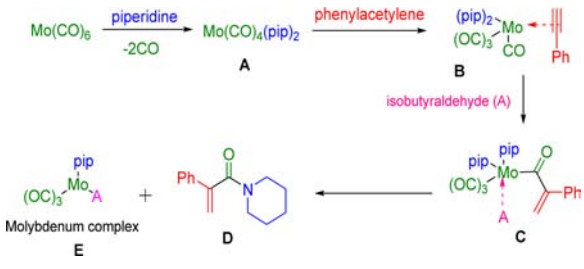


Figure 2. Plausible mechanism for the acrylamide formation.

Even though we have proposed a plausible reaction mechanism, the stepwise details for this aminocarbonylation process are still open to debate and remain an area for further experimental and computational investigations.

In conclusion, the regioselective control in the synthesis of 2-acrylamides **3(a−r)** and **4g** was achieved by the aminocarbonylation of terminal alkynes using an in situ generated complex system $Mo(CO)_4(amine)_2$, along with the assistance of an aliphatic aldehyde as promoter. A wide range of terminal alkynes along with cyclic and acyclic secondary aliphatic amines were well suited. Most importantly, the products were easily separated and purified using conventional column chromatography. Novel, unprecedented, rearrangement products were seen in the case of propargyl ethers. Striking advantages of the present protocol are that it is regiospecific, is compatible with acid sensitive protecting groups such as TBDPS, is palladium-free, utilizes a dual-acting complex system, is of short reaction time, is easy to work up, and provides good yields. A computational study of the suggested mechanistic pathway is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02231.

Experimental procedures and characterization data for acrylamides **3(a−r)** and **4g**(PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Authors are thankful to the Department of Pharmaceuticals (Ministry of Chemicals and Fertilizers, Govt. of India) for providing funds and Prof. K.P.R. Kartha, Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S. A. S. Nagar, Punjab 160062, India, for his valuable suggestions in the manuscript.

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DOI: 10.1021/acs.orglett.5b02231
Org. Lett. 2015, 17, 4592−4595