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Synthesis of Naphthalene Derivatives from *ortho*-Alkynylacetophenone Derivatives via Tandem *in Situ* Incorporation of Acetal and Intramolecular Heteroalkyne Metathesis/Annulation

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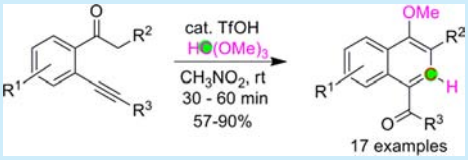
Supporting Information

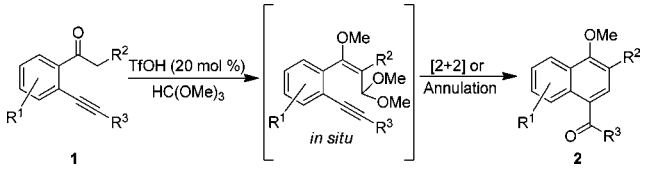
ABSTRACT: An interesting domino reaction for the synthesis of substituted naphthyl ketones has been developed using readily accessible starting materials. This domino reaction proceeds via *in situ* incorporation of an acetal followed by intramolecular heteroalkyne metathesis/annulation in an *ortho*-alkynylacetophenone derivative. A deuterium incorporation experiment has been carried out to understand the mechanism.



The naphthalene core is an important structural motif present in many natural products and bioactive compounds.[1] In addition, it has numerous applications in material science.[2] Hence development of new methods for the efficient synthesis of substituted naphthalenes has always been attractive. Different strategies have been reported for the construction of a naphthalene framework.[3] Very recently, Lee and co-workers have reported regioselective synthesis of naphthalenes by employing Pt-catalyzed selective 6-*endo* hydroarylation of aryl enynes.[4] Wu and co-workers have developed a new method for the construction of substituted naphthalenes via novel rearrangement of benzo[*c*]oxepine.[5]

In contrast to transition metal mediated processes, use of a Brønsted acid for the construction of a naphthalene core is very limited.[6] Brønsted acid catalysts have their own advantage over transition metal catalysts in the pharmaceutical industries since complete removal of the metal based impurities is a significant task.[7] It is known that the carbonyl compounds (aldehyde/ketone) form acetal in the presence of a Lewis/Brønsted acid and trialkyl orthoformate. During our research endeavor in utilizing an *in situ* formed acetal,[8,9] we have found that alkyl ketones can directly be alkylated using diaryl methanols, allyl and propargyl alcohols via *in situ* acetal formation using trimethyl orthoformate and triflic acid.[9] Along these lines, we observed that the reaction of *o*-alkynylacetophenone derivatives with trimethyl orthoformate and catalytic triflic acid generated naphthyl ketones efficiently (Scheme 1). It is expected that the *in situ* formed acetal incorporates an acetal moiety at the α-carbon which undergoes [2 + 2] heteroalkyne metathesis or annulation with an alkyne under the influence of an acid to form the naphthalene core. Hence the additional carbon atom present in the naphthalene core is from the trimethyl orthoformate.

Scheme 1. Incorporation of Acetal and Alkyne-Carbonyl Metathesis/Annulation of *ortho*-Alkynylacetophenone Derivatives 1



Incorporation of an acetal at the α-carbon of ketones is known to occur in the presence of trialkyl orthoformate and Lewis/Brønsted acids. Mukaiyama and co-workers reported the formation of a β-ketoacetal from silyl enol ether and trimethyl orthoformate in the presence of $TiCl_4$.[10] Formation of β-ketoacetals from aliphatic and aromatic ketones was achieved by Mock and Tsou in the presence of *N*,*N*-diisopropylethylamine, triethyl orthoformate, and boron trifluoride etherate.[11] Using perchloric acid, Dusza et al. developed the alkylation of steriod ketones using trialkyl orthoformate.[12] Ghatak and co-workers have utilized such an *in situ* formed β-ketoacetal in the synthesis of polycyclic compounds.[13] Apart from these reports, the potential of such a facile *in situ* acetal incorporation has not been utilized in organic synthesis.

In recent years there has been quite an interest in the alkyne-carbonyl metathesis reaction.[14,15] Different molecular skeletons have been synthesized, utilizing it as the key reaction. The alkyne-carbonyl metathesis has mainly been accomplished by Lewis acid catalysts.[14] Only a few reports exist where such a reaction is carried out using a Brønsted acid.[15] Saá and co-workers have used the Brønsted acid HBF_4 or TFA to carry out the intramolecular metathesis of an alkyne with either an acetal[15a] or aldehyde[15b] functionalities. In the former case they have advantageously utilized the intermediate to undergo subsequent Nazarov cyclization under the reaction conditions.[15a] Yamamoto and co-workers have established that acetal/hemiacetal formed in the TfOH catalyzed reaction of an alkynal in MeOH undergoes the [2 + 2] heteroalkyne metathesis efficiently with an alkyne.[15c] Zhu et al. have used acetals in a

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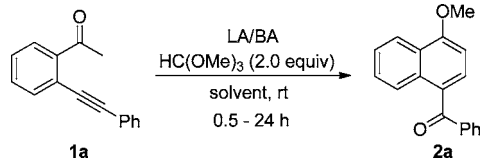
similar metathesis reaction with an alkyne, however using a Lewis acid, to form a Nazarov intermediate for the construction of indanones.[14b] The reaction using an acetal might be more facile because it proceeds through an oxonium ion intermediate. In the reaction presented in this manuscript we have effectively trapped intramolecularly the *in situ* incorporated acetal with an alkyne to make naphthyl ketone derivatives.

Using substrate **1a**, optimization of the reaction conditions was established. This substrate was prepared by Sonogashira coupling of commercially available 2′-iodo acetophenone and phenylacetylene. The results are summarized in Table 1.

Table 1. Optimization of Incorporation of Acetal and Alkyne-Carbonyl Metathesis/Annulation Using Compound 1a



1a **2a**

entry	solvent	catalyst	cat. (mol %)	time (h)	yield (%)[a]
1	CH_2Cl_2	TfOH	50	0.5	84
2	CH_2Cl_2	conc. HCl	50	24	NR
3	CH_2Cl_2	TFA	50	24	NR
4	CH_2Cl_2	PTSA	50	24	NR
5	CH_2Cl_2	$AuCl_3/AgSbF_6$	5	24	–
6	CH_2Cl_2	AgOTf	5	24	–
7	CH_2Cl_2	$Cu(OTf)_2$	5	24	NR
8	DCE	TfOH	50	0.5	76
9	hexane	TfOH	50	0.5	34
10	toluene	TfOH	50	0.5	65
11	dioxane	TfOH	50	0.5	52
12	CH_3CN	TfOH	50	24	NR
13	MeOH	TfOH	50	24	NR
14	CH_3NO_2	TfOH	50	0.5	89
15	CH_3NO_2	TfOH	5	0.5	25
16	CH_3NO_2	TfOH	10	0.5	80
17	CH_3NO_2	TfOH	20	0.5	90
18	CH_3NO_2	TfOH	20	0.5	40[b]

[a]Isolated yield. [b]1.0 equiv of trimethyl orthoformate was used. NR: no reaction.

Initially **1a** was treated with 2.0 equiv of trimethyl orthoformate and 50 mol % of trifluoromethanesulfonic acid (TfOH) in dichloromethane at room temperature. Interestingly, the product **2a** was obtained in 84% yield in 30 min (Table 1, entry 1). The reaction did not work with other Brønsted acids such as conc. HCl, TFA, and PTSA (Table 1, entries 2−4) even after 24 h. Then, the reaction was attempted with Lewis acids and found to be ineffective, as they resulted in either a complex mixture or no reaction (Table 1, entries 5−7). Since TfOH alone worked in effecting the reaction, further optimization was carried out using TfOH only by changing other parameters such as solvent and catalyst loading. In dichloroethane, the yield of **2a** decreased to 76% (Table 1, entry 8). In nonpolar solvents such as hexane and toluene the yields obtained were 34% and 65% respectively (Table 1, entries 9 and 10). When the reaction was performed in dioxane the yield of **2a** obtained was 52% (Table 1, entry 11). There were no reactions in acetonitrile and methanol even after 24 h (Table 1, entries 12 and 13). To our delight, nitromethane was found to be the best solvent, as the yield of **2a** was 89% when the reaction was carried out in it (Table 1, entry 14). When the amount of catalyst was reduced to 5 and 10 mol %, the yield of **2a** dropped to 25% and 80% respectively (Table 1, entries 15 and 16). Gratifyingly, the yield of **2a** improved to 90% when the loading of TfOH was increased to 20 mol % (Table 1, entry 17). Reduction in the amount of trimethyl orthoformate to 1.0 equiv was found to decrease the yield of **2a** to 40% (Table 1, entry 18). Subsequently, the scope of the transformation was examined with substrates having a different substitution pattern. The reaction conditions given in Table 1, entry 17, i.e., 20 mol % of TfOH and 2.0 equiv of trimethyl orthoformate in nitromethane solvent at room temperature, were used in these reactions. The results are shown in Figure 1. It is important to mention that there is no significant influence of electronic

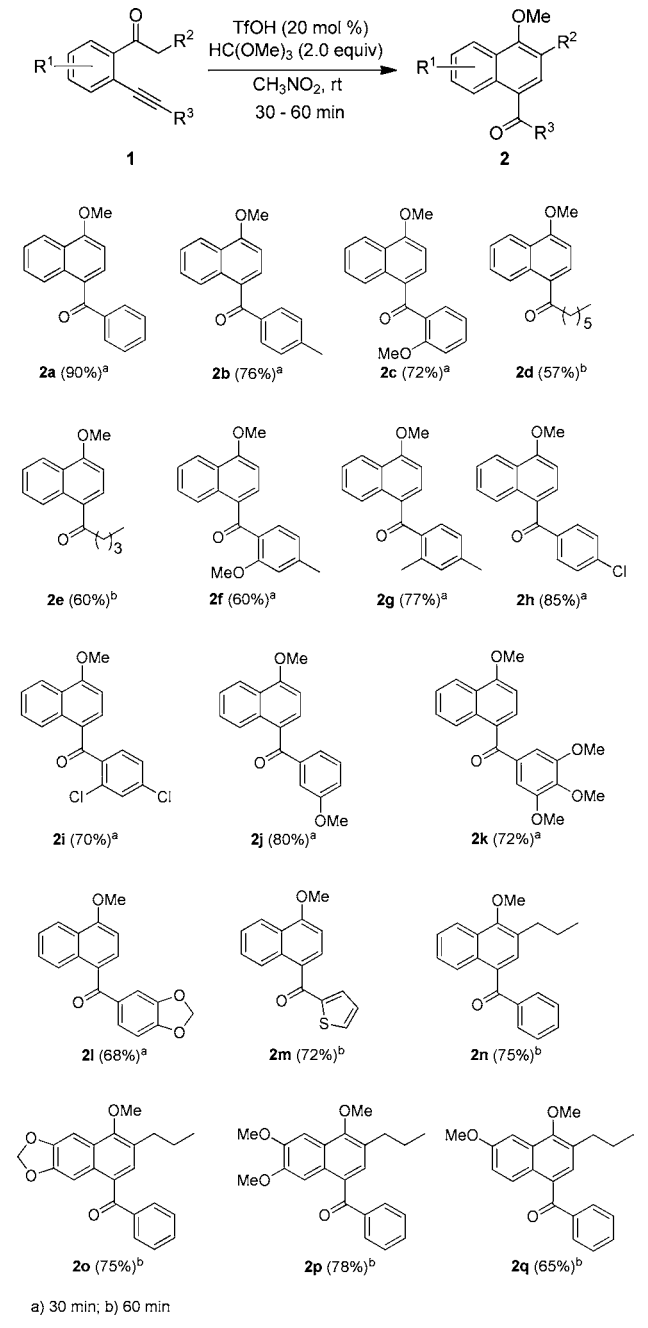


Figure 1. Scope of naphthyl ketone derivatives synthesis.

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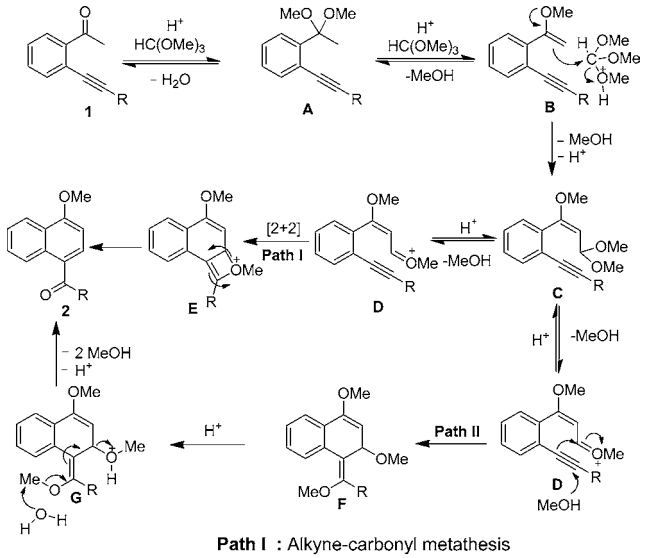
effects on the outcome of this transformation. Good yields of 1-methoxy-4-naphthyl ketone derivatives **2** were obtained with both electron-releasing groups (such as −OMe and Me) and -accepting group (such as −Cl). The reaction required 60 min for completion when either R^2 or R^3 is an alkyl group. Otherwise the reactions are fast and completed within 30 min. Moderate yields of **2d** and **2e** were obtained when R^3 is an alkyl group such as *n*-hexyl and *n*-butyl. Interestingly, heterocyclic thiophene tolerated the reaction conditions and the corresponding naphthyl ketone derivative **2m** was obtained in 72% yield. The structure of compound **2c** was further confirmed by single crystal X-ray analysis.[16] Unfortunately the reaction was not clean with a terminal alkyne (R^3 = H). This may be due to the absence of groups to stabilize the vinyl carbocation intermediate which will form during the reaction. When R^2 is a phenyl group the reaction was not clean as it resulted in a complex mixture. A similar reaction with trimethyl orthoacetate gave a complex mixture of products. Since the starting *ortho*-alkynylacetophenones **1** were prepared by a Sonogashira coupling reaction, the possible role of trace metal compound impurities (Pd and Cu compounds) as cocatalysts in the present transformation was evaluated by carrying out two control experiments. In the first experiment, the reaction of **1a** was carried out in the presence of 2 mol % each of $Pd(PPh_3)_4$ and CuI along with 20 mol % of TfOH and 2 equiv of trimethyl orthoformate. There was no appreciable acceleration in the reaction rate, as 30 min were required for completion to result in **2a** in 88% yield. The above reaction without TfOH did not result in any product even after 24 h. With these experiments, the possibility of the transition metal impurities cocatalyzing the present reaction of **1** could be ruled out.

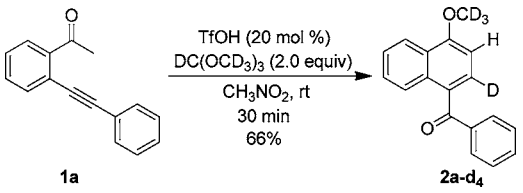
A schematic representation of plausible mechanistic pathways is shown in Scheme 2. In the presence of TfOH and trimethyl orthoformate, ketal **A** is formed from **1** which will be in equilibrium with *α*-methoxy styrene derivative **B**. The intermediate **B** attacks trimethyl orthoformate to give intermediate **C** which will be in equilibrium with the oxonium ion **D**. There are two possible pathways (Paths **I** and **II**) to construct the naphthalene skeleton **2** from **D**. As shown in path **I**, naphthalene derivative **2** will be formed *via* intramolecular [2 + 2] cycloaddition and cylcoreversion between an alkyne and oxonium ion through oxetene intermediate **E** in the presence TfOH. The pathway involving annulation could not be excluded (Path **II**). This is initiated by the electrophilic attack of an oxocarbenium ion on the alkyne. The formed vinylic carbocation is trapped by methanol formed during the reaction to give intermediate **F**. Subsequent elimination of methanol from **F** assisted by an acid would afford naphthalene derivative **2**.

Scheme 2. Plausible Reaction Mechanism



In order to confirm the proposed mechanism, fully deuterated trimethyl orthoformate ($DC(OCD_3)_3$) was prepared as per reported procedure.[17] The reaction of **1a** was carried out with $DC(OCD_3)_3$ under standard conditions (Scheme 3). Incorporation of $-OCD_3$ and D in the naphthalene **2a-d$_4$** was inferred from the ^{1}H NMR spectra. The disappearances of a singlet at 4.07 ppm corresponding to OCH_3 protons and doublet at 7.60 ppm and appearance of a singlet at 6.80 ppm corresponding to aromatic protons were observed in the ^{1}H NMR. Further, the reaction of **1b** was monitored by ^{1}H NMR to check whether the proposed intermediates are formed in the reaction. Among the proposed intermediates, the formation of ketal **A** from **1** could only be seen while recording ^{1}H NMR. This might be due to a fast domino reaction.

Scheme 3. Deuterium Incorporation Study



In summary, we have developed a new method to construct a naphthalene core through incorporation of an acetal followed by intramolecular heteroalkyne metathesis/annulation involving orthoformate and triflic acid. This is a simple and an efficient approach for the synthesis of naphthalene derivatives from readily available starting materials and reagents.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^{1}H/^{13}C spectroscopic data of all new compounds, and ORTEP of compound **2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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