Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis of Acyl Terphenyls and Higher Polyaromatics via Base-Promoted C−H Functionalization of Acetylarenes with Arylacetylenes

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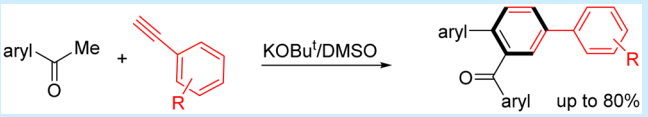
Supporting Information

ABSTRACT: KO^{t}Bu/DMSO-promoted C−H functionalization of acetylarenes with arylacetylenes (100 °C, 30 min), generating β,γ-ethylenic ketones, triggers upon further heating (100 °C, 4 h, with or without acidifying additive) the cascade assembly of acyl terphenyls and higher polyaromatics in good yields.

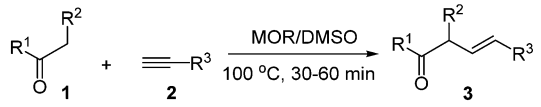


The search for straightforward and efficient methods to assemble complex molecular scaffolds, especially carbo- and heterocycles, from readily accessible precursors is one of the major and most enduring challenges in synthetic organic chemistry. In pursuit of this objective, cascade reaction processes comprising multiple structural transformations in a single synthetic step are highly attractive, especially those which proceed with good regio- and stereoselectivity.[1] Acetylenes have become increasingly attractive starting materials for such processes, due to their ability to simultaneously function as electrophilic and nucleophilic reagents. In the presence of superbases (such as alkali metal hydroxide or alkoxide/DMSO), this dual reactivity of acetylenes is most pronounced. Combination of these competing processes (acetylene deprotonation and nucleophilic addition to the triple bond) provides the possibility of new reactions, which often represent one-pot multistep assemblies of intricate structures with involvement of several molecules in the process.[1c]

It is the KOH/DMSO and KO^{t}Bu/DMSO systems that have allowed the stereoselective C−H functionalization of ketones with acetylenes to be discovered (Scheme 1).[2]

The reaction provides a straightforward entry to the chemistry of hitherto hardly accessible β,γ-ethylenic ketones **3**, which are promising building blocks for fine organic synthesis,[3] and can also be used in one-pot assemblies (without isolation of β,γ-ethylenic ketones **3**) of pharmaceutically and synthetically important functionalized carbo-[4] and heterocyclic[5] compounds.

Scheme 1. Base-Promoted Addition of Ketones to Acetylenes



R^1, R^2 = H, Alk, *cyclo*-Alk, Ar, HetAr; R^3 = Ar, HetAr
M = Na, K, Cs; R = H, Bu^t

Table 1. Optimization of the Reaction Conditions for the Synthesis of Terphenyl 4a[a]

entry	additive, equiv[b]	temp (°C)[c]	time (h)[c]	content of **3a** (%)[d]	yield of **4a** (%)[e]
1	none	100	4	15	61
2	H_2O, 1.00	120	4	50	32
3	$NaHCO_3$, 0.66	120	2	65	11
4	$NaHCO_3$, 0.66	120	3	46	32
5	$NaHCO_3$, 0.66	120	4	22	49
6	$NaHCO_3$, 0.66	120	5	none	53
7	$MeCO_2H$, 0.66	100	2	13	51
8	$MeCO_2H$, 0.66	100	4	none	72
9	$MeCO_2H$, 0.66	120	2	15	67
10	$MeCO_2H$, 0.66	120	4	none	63
11	$MeCO_2H$, 1.00	120	2	14	65
12	$MeCO_2H$, 1.00	120	4	none	66

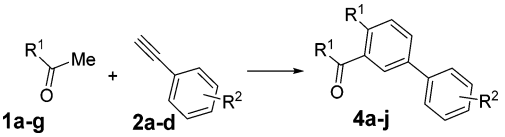
[a]Reagents and conditions: **1a** (0.605 g, 5.0 mmol), **2a** (0.510 g, 5.0 mmol), KO^{t}Bu (0.561 g, 5.0 mmol), and DMSO (15 mL), 100 °C, 30 min; additive was introduced. [b]Relative to acetophenone **1a**. [c]After heating at 100 °C for 30 min. [d]In the crude product (^{1}H NMR). [e]Isolated yield after column chromatography (Al_2O_3, eluent hexane/ethyl ether with gradient from 1:0 to 10:1).

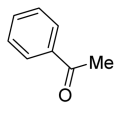
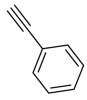
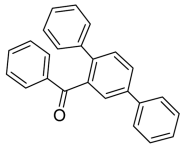
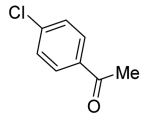
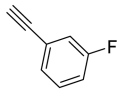
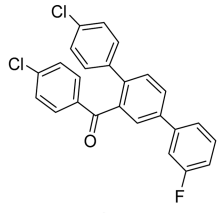
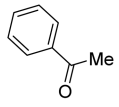
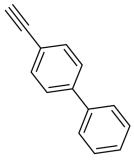
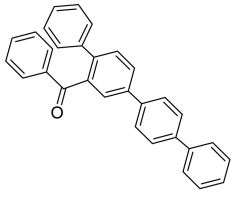
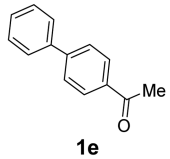
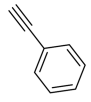
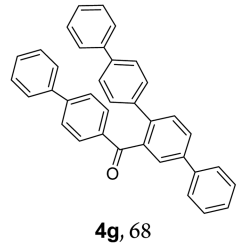
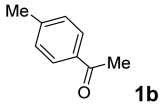
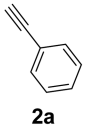
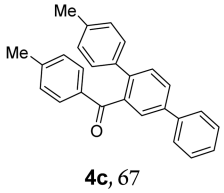
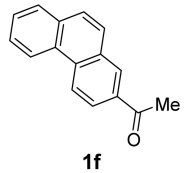
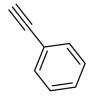
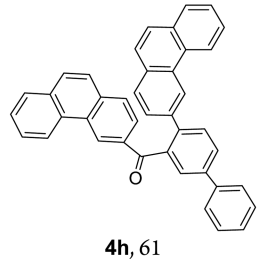
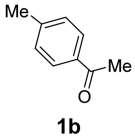
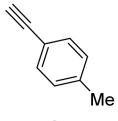
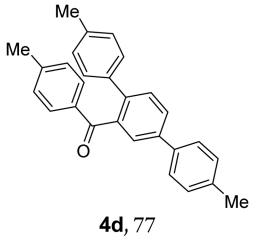
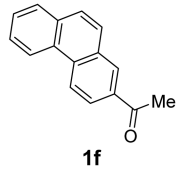
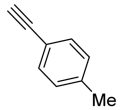
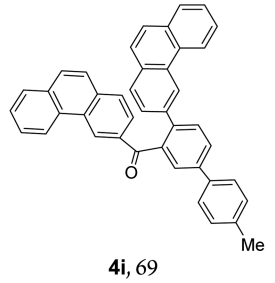
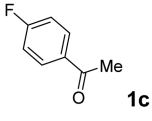
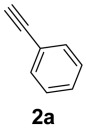
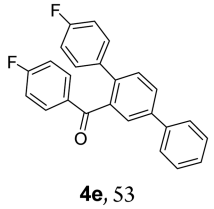
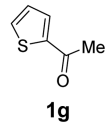
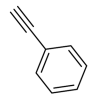
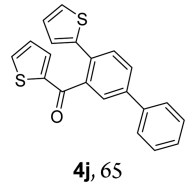
As a further development of this inspiring approach to the synthesis of valuable cyclic compounds, here, we disclose another serendipitous finding of the one-pot assembly of acylated terphenyls and related polyaromatics via the cascade reactions between readily available acetylarenes **1** and arylacetylenes **2**.

Received: March 17, 2016

DOI: 10.1021/acs.orglett.6b00782
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Substrate Scope and Product Yields for the Reaction of Acetylarenes 1a−g with Arylacetylenes 2a−d[a]



acetylarene	arylacetylene	product, yield (%)[b]	acetylarene	arylacetylene	product, yield (%)[b]
 1a	 2a	 **4a**, 72	 1d	 2d	 **4f**, 55
 1a	 2b	 **4b**, 80	 1e	 2a	 **4g**, 68
 1b	 2a	 **4c**, 67	 1f	 2a	 **4h**, 61
 1b	 2c	 **4d**, 77	 1f	 2c	 **4i**, 69
 1c	 2a	 **4e**, 53	 1g	 2a	 **4j**, 65

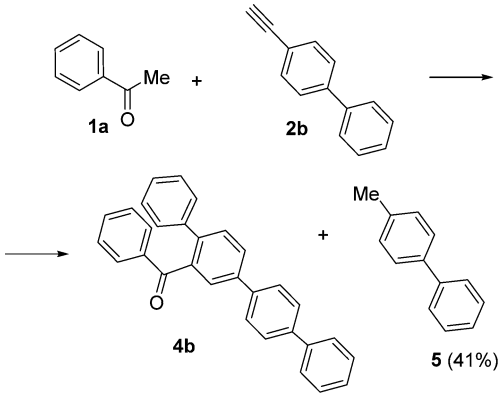
[a]Reagents and conditions: acetylarene **1** (5.0 mmol), arylacetylene **2** (5.0 mmol), KO^{t}Bu (0.561 g, 5.0 mmol), DMSO (15 mL), 100 °C, 30 min; $MeCO_2H$ (3.3 mmol), 100 °C, 4 h. [b]Isolated yield after column chromatography.

We have revealed that acetophenone **1a**, when heated with phenylacetylene **2a** in the KO^{t}Bu/DMSO system longer (4 h instead of 0.5 h) than is required for synthesis of the corresponding β,γ-unsaturated ketone **3a**,[2] gave 2-benzoylterphenyl **4a** as the major reaction product (Table 1). Afterward, we focused our efforts on optimization of this process, first on the example of this very reaction. Selected results are presented in Table 1.

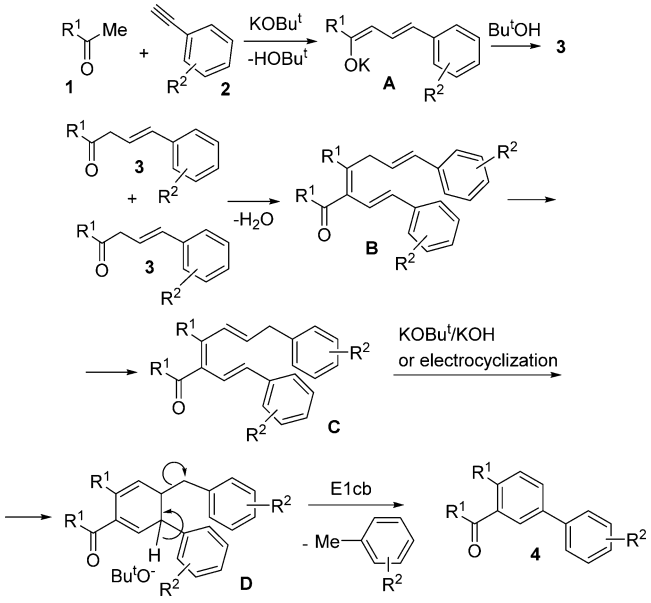
The reaction was implemented as follows: a mixture of acetophenone **1a** and phenylacetylene **2a**, in the presence of 1 equiv of KO^{t}Bu in DMSO, was heated at 100 °C for 4.5 h (entry 1). When acetic acid was added, after the above reaction mixture was kept at 100 °C for 30 min, and the heating was continued additionally for 2−5 h, terphenyl **4a** was formed in improved yield along with toluene (as detected by GLC). However, when 1 equiv (relative to **1a**) of water was added to the reaction mixture (entry 2), the yield of **4a** was reduced to 32%, even at a higher temperature (120 °C instead of 100 °C). When $NaHCO_3$ was incorporated, the yield of **4a** was also poor (entries 3−5). The best yield (72%) was attained using acetic acid as an additive at

DOI: 10.1021/acs.orglett.6b00782
Org. Lett. XXXX, XXX, XXX−XXX

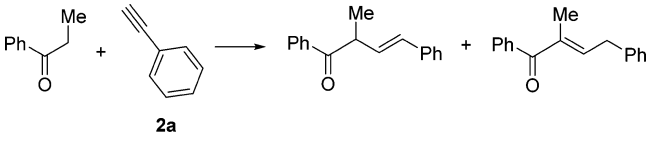
Scheme 2. Reaction of Acetophenone 2a with Acetylene 2b



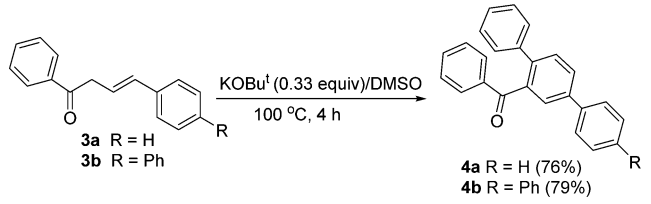
Scheme 3. Plausible Pathway for the Cascade Formation of Terphenyls 4



Scheme 4. Reaction of Propiophenone with Phenylacetylene 2a



Scheme 5. Transformation of Intermediate β,γ-Unsaturated Ketones 3 into Terphenyls 4



100 °C (entry 8), whereas at 120 °C, the yield of the target product decreased by 9% (entry 10).

Thus, based on the data of Table 1, the most suitable conditions for the synthesis of terphenyl **4a** were as follows: acetophenone **1a**, phenylacetylene **2a**, and KO^{t}Bu (molar ratio of **1a**/**2a**/KO^{t}Bu = 1:1:1) were heated for 30 min at 100 °C in DMSO, and the heating was continued with $MeCO_2H$ (0.66 equiv) for 4 h at 100 °C.

These optimized conditions were applied for the reactions of a variety of acetylarenes **1** with diverse arylacetylenes **2** (Table 2).

As can be seen from Table 2, the synthesis of acylated terphenyls and related polyaromatics was efficient for a wide range of acetylaromatics and also valid for acetyl-condensed aromatics and heteroaromatics. Various arylacetylenes worked well in this reaction to give the hitherto inaccessible substituted polyaromatic ketones in good yields. Both electron-donating and electron-withdrawing substituents (methyl, phenyl, fluoro, and chloro) in the acetylarene and arylacetylene partner were well-tolerated. Note that acetyl thiophene was also a suitable substrate for this process to provide a product with the combination of two thiophenes with two benzene rings and a carbonyl moiety all in one molecule.

In accordance with the above observation, in the crude products, there were always some amounts of β,γ-unsaturated ketones **3** (Scheme 1), which were easily separated from the major products by SiO_2 column chromatography. Also, like the formation of toluene during the synthesis of terphenyl **4a**, the analogous methyl aromatics, such as 4-methyl-1,1′-biphenyl **5** (when 4-ethynyl-1,1′-biphenyl **2b** was used), were present in the reaction mixtures, thus indicating this elimination process was a general one (Scheme 2).

The structure of products **4** was confirmed unambiguously by X-ray crystallography of one of their representatives, **4b** (CCDC 1453334; see Supporting Information).

Possibly, this assembly of the acylated terphenyls **4** involves the following cascade sequence (Scheme 3). Initially, the enolate derived from **1** adds onto the aryl(heteroaryl) acetylene to generate a stabilized vinyl anion that protonates to afford **3**[2] and re-enolizes to give **A**. The latter then does an aldol addition to deliver **B**. Next, triene **B** is isomerized into the conjugated triene **C**, which undergoes electro- or base-catalyzed cyclization to dihydrobenzene **D**. Elimination of methyl aromatics from the dihydrobenzene moiety leads to its aromatization, with the latter being the driving force of this elimination.

As stated above, this elimination of the methyl aromatics at the final stage of this cascade sequence was confirmed experimentally.

Notably, when propiophenone reacted with phenylacetylene **2a** under the above conditions, only an equilibrium mixture of the isomeric β,γ- and α,β-ethylenic ketones in a 2:1 ratio was formed (Scheme 4). Evidently, this cascade sequence was impossible.

To obtain additional robust support for the mechanism of this transformation, we have implemented the self-condensation of the preliminarily isolated β,γ-unsaturated ketone intermediates **3a**,**b**, and these afforded the expected terphenyls **4a**,**b** in good yields (Scheme 5). Thus, unambiguous evidence for the suggested mechanism was provided.

To assess the practical value and feasibility of the developed methodology, we performed the reaction of acetophenone **1a** with phenylacetylene **2a** on a larger scale (25 mmol each, 5.575 g all together). The expected terphenyl **4a** was obtained in 77% yield. This proves the scalability of the process.

It is relevant to note here that functionalized terphenyls are widely used in materials science as important building blocks for the preparation of laser dyes, scintillators, heat-resistant polymeric materials, heat storage, and transfer agents.[6] Some

DOI: 10.1021/acs.orglett.6b00782
Org. Lett. XXXX, XXX, XXX−XXX

terphenyls exhibit significant biological activities, such as cytotoxic, immunosuppressant, neuroprotective, anti-thrombotic, and anticoagulant agents.[7] This is why terphenyls generate an ever-increasing research interest.

The classic methods for the synthesis of substituted terphenyls involve free-radical substitution of an aromatic ring as well as Ullmann and related reactions and condensations of quinones.[7b] Separate substituted terphenyl compounds are prepared by methods with more limited scope.[7b] Recently, syntheses of terphenyls using Pd-catalyzed cross-coupling of bis(triflates) of dihydrobenzophenones,[8] Mn-catalyzed dehydrative [2 + 2 + 2] coupling of 1,3-dicarbonyl compounds and terminal acetylenes,[9] and Au-catalyzed [4 + 2] benzannulation between enynals and enols[10] were published. Therefore, this conceptually new methodology reported here, which is based on inexpensive readily available starting materials (acetylarenes and arylacetylenes) and a common superbase catalytic system (KO^{t}Bu/DMSO), increases the accessibility and structural variety of terphenyls and related polyaromatics.

In summary, a new facile and efficient methodology for construction of acyl terphenyls and higher polyaromatics via a base-promoted C−H functionalization of acetylarenes with arylacetylenes was developed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00782.

Experimental procedure, compound characterization, ^{1}H and ^{13}C NMR spectra of all compounds, and crystallographic data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a grant from the Russian Scientific Foundation (Project No. 14-13-00588).

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DOI: 10.1021/acs.orglett.6b00782
Org. Lett. XXXX, XXX, XXX−XXX