Low-valent Nb(III)-mediated synthesis of 1,1,2-trisubstituted-1H-indenes from aliphatic ketones and aryl-substituted alkynes†

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A variety of 1,1,2-trisubstituted-1H-indenes are synthesized by the reaction of aliphatic ketones, aryl-substituted alkynes and NbCl₃(DME) in 1,2-dichloroethane under reflux conditions.

The study of low-valent transition-metal mediated carbon–carbon bond formation reactions is intriguing. In particular, reactions with Ti(II)[1] and Zr(II)[2] are intensively explored. We have recently reported the novel cross-coupling reaction of Ti(II)–alkynes with aryl iodides in the presence of a Ni catalyst.[3] In contrast, less attention has been paid to low-valent Nb(III)-mediated reactions.[4,5] In this communication, we wish to report a novel synthetic method for the preparation of 1,1,2-trisubstituted-1H-indenes (**3**) by the reaction of *aliphatic* ketones (**1**) with aryl-substituted alkynes (**2**) in the presence of NbCl₃(DME) (eqn. (1)). NbCl₃(DME) is a commercially available and thermally stable low-valent Nb(III) reagent, and utilized in several organic syntheses.[5]

As for metal-mediated syntheses of indene and its derivatives, reactions of *ortho*-manganated acetophenones with alkynes to afford 1,2,3-substituted *indenols* have been reported.[6] Recently, Takahashi and co-workers reported that Zr(II)-induced reaction of aromatic ketones with alkynes gave oxazircononacyclopentanes, which upon hydrolysis with HCl(aq) afforded 1,2,3-trisubstituted indenes.[7] However, only aromatic ketones could be used in these methods. To the best of our knowledge, the present reaction provides the first example of a preparation route to relatively rare 1,1-disubstituted indene derivatives[8] from aliphatic ketones.


$$(1)$$
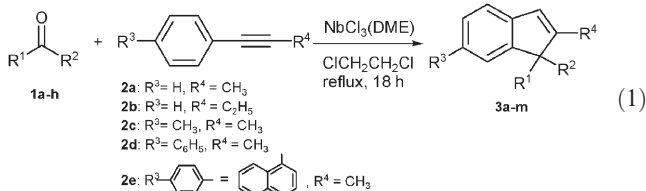
Results are listed in Table 1. Reaction of 3-hexanone (**1a**) with 1-phenyl-1-propyne (**2a**) in the presence of NbCl₃(DME) in 1,2-dichloroethane under reflux gave 1-ethyl-1-propyl-2-methyl-1H-indene (**3a**) in 78% isolated yield (84% GLC yield, entry 1).‡ As shown in entry 1, the yield of **3a** was high for the reaction of **1a** when an excess (4 equiv.) of **2a** and NbCl₃(DME) were employed. However, even if **1a**, **2a** and NbCl₃(DME) were allowed to react in a 1:2:2 or even 1:1:1 molar ratio, yields of **3a** were still high to moderate (72 and 59% yields respectively, entries 2 and 3). In the present reaction, yields of the indene were high in dichloroethane (entry 1), chlorobenzene (entry 4) and 1,4-dichlorobutane (entry 5).

On the other hand, when THF was employed as solvent, no trace of indene was detected, but the 1,3-diene (**5b** in Scheme 1) was afforded in low yield (33%, entry 6). Various aliphatic ketones gave the corresponding indenes (**3b–f**) in high to moderate yields under the same reaction conditions as entry 1 (entries 7–11). Aliphatic ketones with certain functionalities, such as chloro and ester groups (**1g** and **1h**), were tolerated in the present reaction with **2a** to afford **3g** and **3h**, respectively (entries 13–14). As for alkynes, several 1-aryl-1-propynes as well as 1-phenyl-1-butyne (**2a–e**) were employed and the corresponding 1,1,2-trisubstituted indenes were obtained (entries 15–19).

Table 1 Nb(III)-mediated reaction of alkynes with ketones[a]

Entry	Ketone (1) R¹	R²	Alkyne (2)	Indene (3)	Yield of 3/%[b]
1	C₂H₅	n-C₃H₇	1a	2a	3a	78 (84)
2[c]	C₂H₅	n-C₃H₇	1a	2a	3a	(72)
3[d]	C₂H₅	n-C₃H₇	1a	2a	3a	(59)
4[e]	C₂H₅	n-C₃H₇	1a	2a	3a	(72)
5[f]	C₂H₅	n-C₃H₇	1a	2a	3a	(71)
6[g]	C₂H₅	n-C₃H₇	1a	2a	3a	0[h]
7	n-C₃H₇	n-C₃H₇	1b	2a	3b	76 (81)
8	n-C₄H₉	n-C₃H₇	1c	2a	3c	76
9	n-C₄H₉	n-C₄H₉	1d	2a	3d	74
10	C₂H₅	C₂H₅	1e	2a	3e	64
11[i]	C₂H₅	C₂H₅	1e	2a	3e	34
12	C₆H₅(CH₂)₂	CH₃	1f	2a	3f	45
13	Cl(CH₂)₃	CH₃	1g	2a	3g	59
14	C₂H₅OCO(CH₂)₂	CH₃	1h	2a	3h	53
15	n-C₃H₇	n-C₃H₇	1b	2b	3i	65
16	n-C₃H₇	n-C₃H₇	1b	2c	3j	65
17	n-C₃H₇	n-C₃H₇	1b	2d	3k	71
18	C₂H₅	C₂H₅	1e	2d	3l	68
19	n-C₃H₇	n-C₃H₇	1b	2e	3m	70

[a] Conditions **1** (0.3 mmol), **2** (1.2 mmol), NbCl₃(DME) (1.2 mmol) in 1,2-dichloroethane under reflux unless otherwise noted. [b] Isolated yields. The numbers in the parentheses show GLC yields determined by the internal standard method. [c] Ratio of **1a**:**2a**:[Nb] = 1:2:2. [d] Ratio of **1a**:**2a**:[Nb] = 1:1:1. [e] Chlorobenzene was used as solvent at 90 °C. [f] 1,4-Dichlorobutane was used as solvent at 90 °C. [g] THF was used as solvent. [h] **5b** in 33% yield. [i] Ratio of **1e**:**2a**:[Nb] = 1:4:2 at 70 °C.
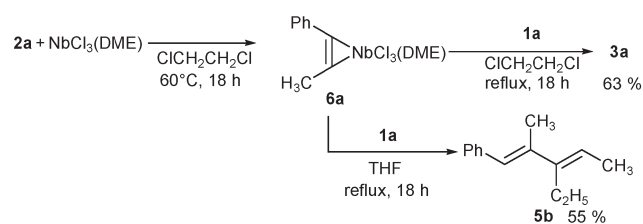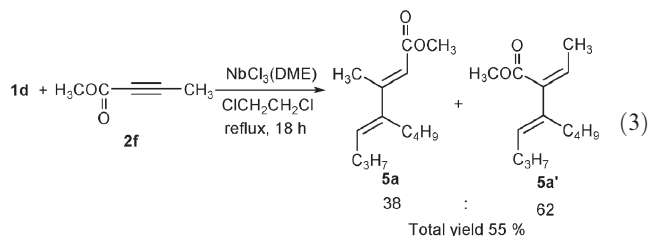

Scheme 1

The present reaction successfully provides indenes from aliphatic ketones. However, no trace of indene was obtained from aromatic ketones such as benzophenone or acetophenone with **2a** under the same reaction conditions as entry 1. In these cases, the reactions were not so clean and the McMurry type reductive coupling[9,10] of ketones took place to afford 1,1,2,2-tetraphenylethene (20% yield) and 1,2-dimethyl-1,2-diphenylethene (35% yield) respectively.

In the reaction, a low-valent Nb(III) reagent efficiently mediated indene formation. Under the same reaction conditions, the use of Nb(v) reagents (NbCl$_5$ and Nb(OEt)$_5$) or some Lewis acids (TiCl$_3$, TiCl$_4$, AlCl$_3$ and BF$_3$·OEt$_2$) *in lieu* of NbCl$_3$(DME) did not afford any indene products. To compare the reactivity of the Nb(III) reagent with that of Ti(II),[1] we conducted the reaction of **1b** with **2a** in the presence of (η^2-propene)Ti(O-*i*-Pr)$_2$[11] under the same reaction conditions as reported by Sato and co-workers.[11] As a result, no indene was detected in the reaction mixture, but two allylic alcohols (**4a** and **4a′**) were obtained as a mixture of regioisomers (28:72) in 61% total yield after aqueous work-up of the reaction mixture (eqn. (2)). In contrast, no allylic alcohols (such as **4a** and **4a′**) formed in the Nb(III)-mediated reactions (Table 1).

$$\textbf{1b} + \textbf{2a} \xrightarrow[\text{H}^+]{\text{Ti(II)}} \quad \textbf{4a} \quad + \quad \textbf{4a'} \qquad (2)$$

28 : 72

Total yield 61 %
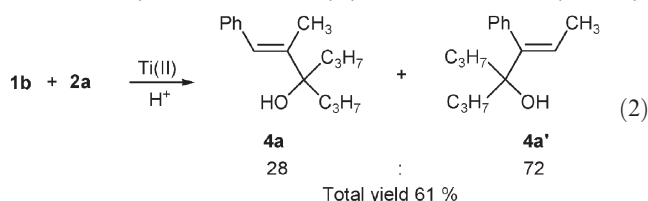
When the NbCl$_3$(DME)-mediated reaction of **1d** was carried out with tetrolic acid methyl ester (**2f**), an internal acetylene without aromatic functionality, under the same reaction conditions as entry 1 (Table 1), the 1,3-dienes (**5a** and **5a′**) were obtained in 55% total yield in a 38:62 regioisomer ratio (eqn. (3)).

$$\textbf{1d} + \text{H}_3\text{COC} \equiv \text{CH}_3 \xrightarrow[\substack{\text{ClCH}_2\text{CH}_2\text{Cl} \\ \text{reflux, 18 h}}]{\text{NbCl}_3\text{(DME)}} \quad \textbf{5a} \quad + \quad \textbf{5a'} \qquad (3)$$

2f

38 : 62

Total yield 55 %

In the present reaction, *in situ* formation of an Nb(III)–alkyne complex (**6**) will be crucial. Indeed, Nb(III)–alkyne complex (**6a**) prepared from NbCl$_3$(DME) and **2a** by the reported method[5] reacted with **1a** (**1a**:**2a**:[Nb] = 1:1:1.2) in 1,2-dichloroethane and afforded **3a** exclusively in 63% yield (Scheme 1). The nature of the solvent affected the reaction route drastically: use of THF as the
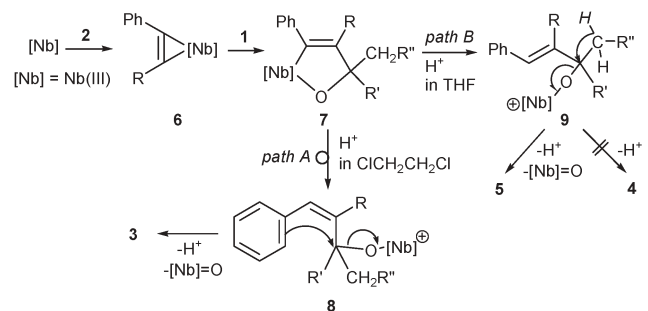
solvent gave the 1,3-diene (**5b**) without the formation of **3a** as observed in entry 6, Table 1.

A possible reaction route is shown in Scheme 2. Alkyne (**2**) and the low-valent Nb(III) yield the Nb(III)–alkyne complex (**6**).[5] Ketones (**1**) react with **6** to afford the 4-oxa-3-nioba-1-cyclopentene intermediate (**7**).[5,12] In 1,2-dichloroethane, **7** is isomerised to **8**, which affords indene (**3**) with liberation of Nb(v)=O (*path A*). In THF, **5** is obtained from **7** *via* **9** (*path B*).

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Notes and references

‡ Typical experimental procedure: a mixture of 3-hexanone (30 mg, 0.3 mmol), 3-phenyl-1-propyne (139 mg, 1.2 mmol), NbCl$_3$(DME) (347 mg, 1.2 mmol) and dichloroethane (6.0 ml) was placed, with a magnetic stirring bar, in a 20 ml round-bottomed flask under an argon flow. The reaction was carried out under reflux for 16 h. After the reaction, silica gel column chromatography with hexane as eluent afforded **3a** (47 mg, 78% isolated yield): ^{1}H NMR (CDCl$_3$) δ 0.32.(t, *J* = 7 Hz, 3H), 0.54–0.58.(m, 1H), 0.73.(t, *J* = 7 Hz, 3H), 0.75–0.83.(m, 1H), 1.60–1.87.(m, 4H), 1.88.(d, *J* = 1 Hz, 3H), 6.45.(d, *J* = 1 Hz, 1H), 7.09–7.20.(m, 4H). ^{13}C NMR (CDCl$_3$) δ 8.1.(CH$_3$), 13.2.(CH$_3$), 14.9.(CH$_3$), 17.1.(CH$_2$), 30.3.(CH$_2$), 40.1.(CH$_2$), 59.0.(C), 119.9.(CH), 121.7.(CH), 123.9.(CH), 126.5.(CH), 127.2.(CH), 145.5.(C), 150.3.(C), 151.6.(C). MS (EI, relative intensity) *m/z* 115(48), 127(16), 128(56), 129(76), 141(60), 142(69), 143(100), 144(12), 157(56), 158(27), 171(66), 172(12), 200(M$^+$, 63) HRMS calc. for C$_{15}$H$_{20}$: *m/z* 200.1565. Found *m/z* 200.1571. Anal. Calc. for C$_{15}$H$_{20}$: C, 89.94; H, 10.06. Found: C, 89.68; H, 10.36%.

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Scheme 2