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# Fischer Carbene Pentannulation with Alkynes Having Adjacent Carbonate or Acyloxy Groups: Synthesis of 3-Substituted 1-Indanones

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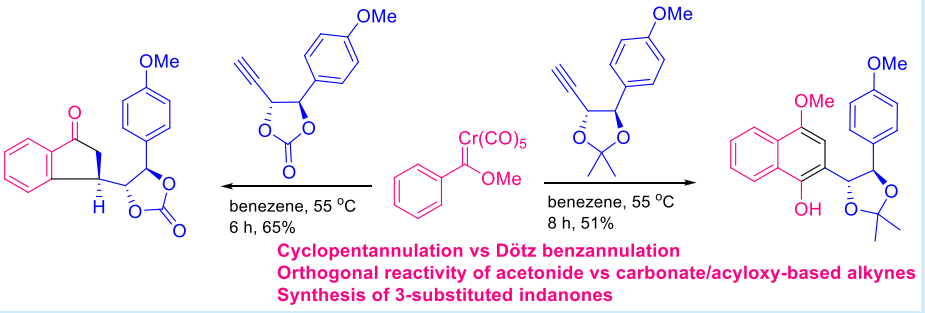


**ABSTRACT:** Various aryl Fischer carbenes reacted with alkynes having adjacent acyloxy or carbonate groups to regioselectively deliver 3-substituted 1-indanones. The acyloxy or carbonate group probably coordinates with the Cr metal to give a tetracoordinated chromium complex forming a six-membered ring that retards CO insertion for ketene formation, which is required for benzannulation. Alternatively, the ortho position aryl ring attack results in pentannulation, providing regioselectively 3-substituted 1-indanones. The method is extended to the synthesis of the core structure of 3-*epi*-mutisianthol.



Fischer carbenes are extensively used to synthesize various aromatic, aliphatic, and heterocyclic synthetic building blocks and biologically active molecules.[1,2] Dötz benzannulation is a well-established reaction involving the thermal [3 + 2 + 1] benzannulation of $\alpha,\beta$-unsaturated Fischer carbenes with alkynes to provide the naphthalene moiety.[2,3] Apart from the normally explored Fischer carbene benzannulation by the Dötz pathway,[2b] the competing pentannulation is less explored. Initially, Dötz and coworkers reported the pentannulation reaction of nucleophilic aminated alkynes with Fischer carbenes to produce diaminated indanes and indanones in moderate yields.[4] Similarly, pentannulation was observed in the reaction of pentacarbonyl chromium carbene with diphenylacetylene in poorly coordinating solvent.[5] The use of aminocarbene complexes for the cyclopentannulation reaction was later separately explored by Dötz and Yamashita.[6] de Meijere disclosed the [3 + 2] cycloadditions of $\beta$-amino-$\alpha,\beta$-unsaturated pentacarbonylcarbenechromium complexes with alkynes to give substituted cyclopentadienes.[7a] Later, Wulff et al. reported the interesting reaction of methoxy pentacarbonyl chromium carbenes with alkynones to give the pentannulated lactone products.[7b] The stereoelectronic effects were found to determine the geometry of intermediate E or Z isomers of the $\eta^1,\eta^3$-vinyl carbene complex, which further influences the benzannulation or pentannulation outcome of the reaction.[7b] Barluenga's work on controlling the reaction results by the transmetalation of Fischer carbenes to Ni or Rh to obtain cyclopentenones is also noteworthy.[7c,d]

We have been actively involved for over a decade in the application of the Dötz benzannulation reaction in the total synthesis of various biologically active napthoquinone natural products.[3c,8] In our recent synthesis of (+)-kalafungin, (+)-frenolicin B, and related molecules, the Dötz benzannulation of Fischer carbene **1a** with alkyne **2** provided the naphthalene compound **3** in 51% yield (Scheme 1).[8f] This was elaborated to **4** and then to the previously mentioned natural products. We visualized that the use of alkyne **5a** would directly give product **4** (after phenolic OH methylation), thereby reducing the functionalization steps post Dötz benzannulation. This also appeared promising when using the dimeric Fischer carbenes toward the synthesis of actinorhodins.[8h] Alkyne **5a** was prepared from D-glucono-$\delta$-

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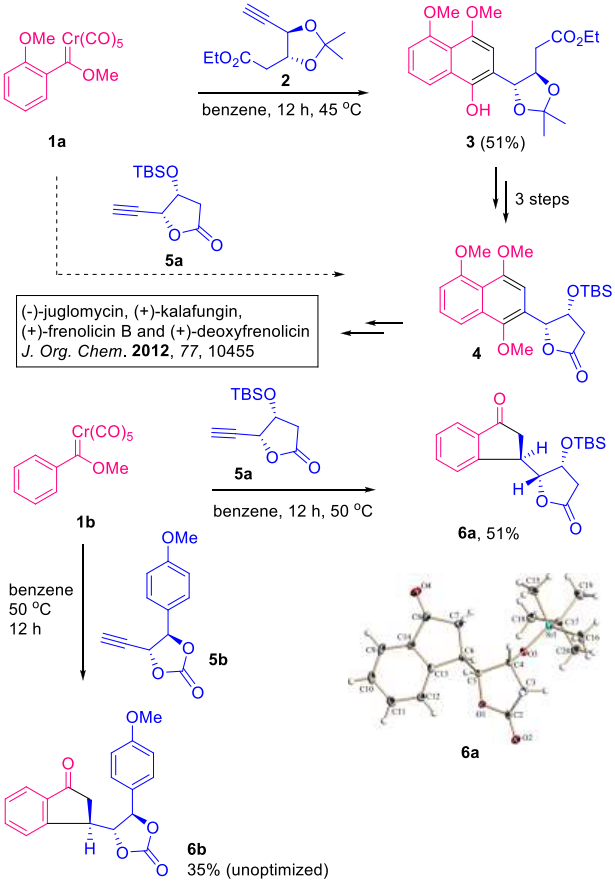
**Scheme 1. Product Variation in Dötz Reaction**




lactone in six steps.[9] The former on reaction with Fischer carbene **1b** surprisingly furnished the cyclopentannulation product **6a** in 51% yield as a single diastereomer. The structure was fully characterized by using spectroscopic methods and unambiguously confirmed by single-crystal X-ray data. We could not isolate any other product from the reaction mixture because it showed a trail of spots on TLC, probably of the competing inseparable minor benzannulated or furan compounds for the remaining mass balance. Considering the alkyne **5a** to have a acyloxy group adjacent to the alkyne, we considered that a carbonate group would also give a similar reaction. Thus the reaction of Fischer carbene **1b** with alkyne **5b** also provided the indanone product **6b** in 35% yield.

The indanone moiety has immense significance. First, it is present in many natural products, for example, taiwaniaquinol B (**7a**),[10a−d] dichroanal A (**7b**),[10e] jungianol (**7c**),[10f] mutisianthol (**7d**),[10g] kinamycins A−J (**7e**),[10h−j] nakiterpiosin (**7f**),[10k,l] veratramine (**7g**),[10m] and so on (Figure 1). Second, the indanone derivatives are used in medicine and show various bioactivities.[11,12] Considering a few reports on the Fischer carbene pentannulation reaction and the significance of the indanone moiety in many natural products and bioactive molecules, we considered exploring the scope and limitation of this reaction.

The reaction of Fisher carbene **1b** with alkyne **5b** as model substrates was considered for optimization. (See Table S1 for details.) The reaction of **1b** with **5b** (1.5 equiv) in benzene at 50 °C gave indanone **6b** in 35% yield. An inseparable trail of spots was observed on TLC for the reaction mixture. We could isolate compound **6b** as the major product, whereas others

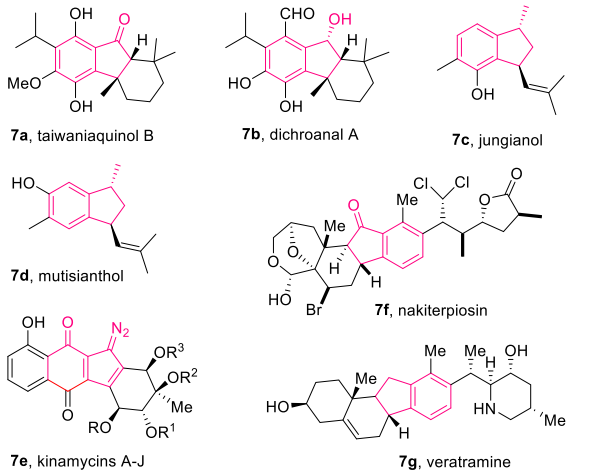



**Figure 1.** Indanone and indane core natural products.

were an inseparable mixture, indicating possible benzannulated and furan products. After systematically varying the solvents, alkyne concentration, and temperature, the optimum conditions were found to be performing the reaction of **1b** with alkyne **5b** (0.95 equiv) in benzene (calcd 0.032 M) at 55 °C. With the optimized conditions in hand, the scope of this Fischer carbene pentannulation reaction to 3-substituted 1-indanones was next examined. As shown in Scheme 2, the reaction of Fischer carbene **1b** with carbonate-based alkynes delivered the indanone products **6b−d** as single diastereomers in moderate to good yields (42−65%). Alkynes with acyloxy group gave the indanones **6e−h** in 22−61% yields. A dimer alkyne (prepared from propargyl alcohol and 1,8-octanedicarboxylic acid) furnished the dimer indanone **6i** in 36% yield. The butyrolactone-based alkynes reacted with **1b** to provide the indanones **6j** and **6a** in 45 and 51% yields, respectively. Similarly, the Fischer carbene **1a** with an *ortho*-methoxy group reacted with different alkynes to deliver the indanones **6k−p** in 21−52% yields. The 4-methoxy-, 2,3-dimethoxy-, 2-methoxy-3-benzyloxy-, 2-methoxy-4-TBSO-, and 2-benzyloxy-4-TBSO-based Fischer carbenes reacted with different alkynes and gave the indanones **6q−u**, respectively, in 41−52% yields. Interestingly, the dimeric biphenyl Fischer carbene[8b] reacted with propargyl benzoate to give dimeric indanone **6v** in 25% yield. A reaction of Fischer carbene **1b** on a 1.1 mmol scale with alkyne **5h** (1.046 mmol) resulted in indanone **6e** in 46% yield (Scheme 2). With alkynes having a stereocenter (and being enantiopure), the indanones **6b−d**, **6a**, **6k**, **6l**, and **6p−u** were obtained as single enantiopure diastereomers, as inferred by NMR data and the relative stereochemistry corroborated from the X-ray structure of **6a**. For racemic alkynes with a stereocenter, the racemic indanones **6g**, **6h**, **6j**, **6n**, and **6o** were also obtained as single diastereomers, as analyzed from the NMR data.

We next examined the alkyne selectivity toward pentannulation versus the benzannulation of Fischer carbene, as shown in Scheme 3. Ethyl propiolate (**8**) reacted with Fischer carbene **1b** to deliver the known naphthol **9** in 46% yield.[13] No pentannulation product could be isolated in this reaction from the trail of other minor reaction products. Similarly, the acyloxy alkyne **10** from homopropargyl alcohol reacted with **1b** to provide naphthol **11** in 55% yield. The acetonide-based alkyne **5b′** reacted with **1b** to give naphthol **12** in 51% yield. As previously discussed, acetonide alkyne **2** reacted with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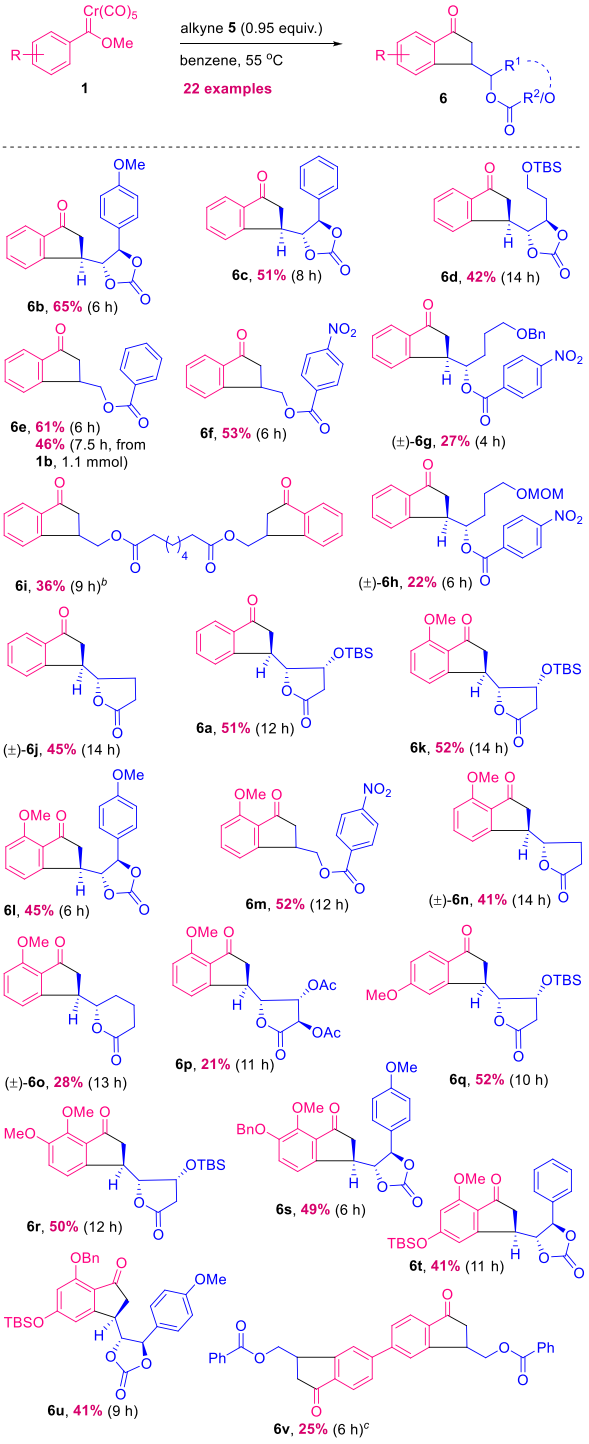
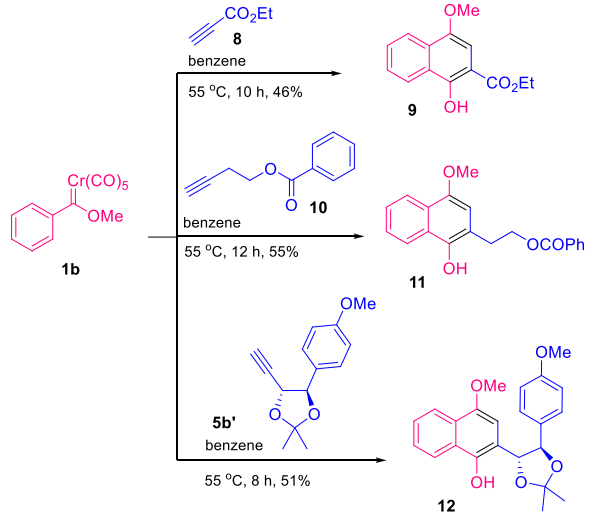
**Scheme 2. Substrate Scope for Indanone Synthesis**[a]

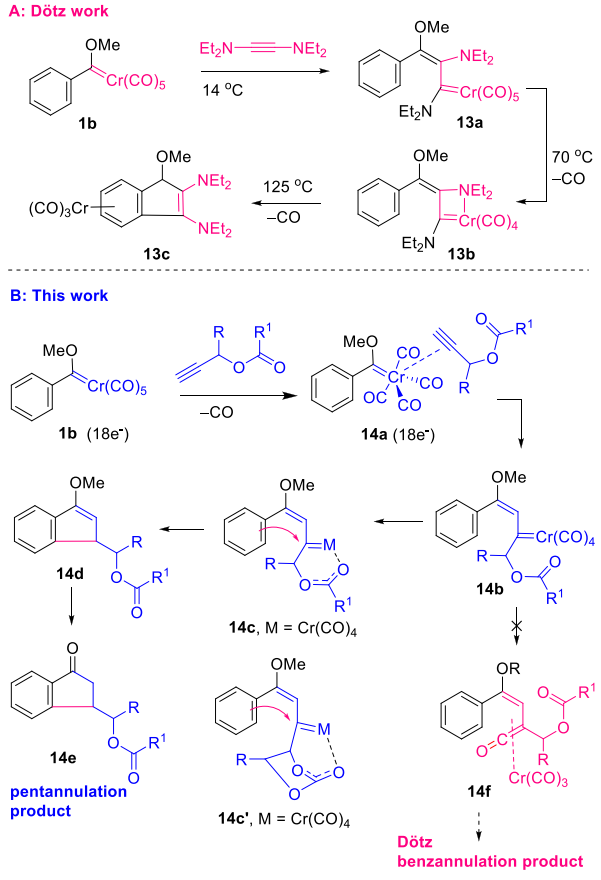



[a]Optimum conditions: Fischer carbene **1** (0.32 mmol), alkyne **5** (0.304 mmol, 0.95 equiv), benzene (10 mL), 55 °C. [b]Fischer carbene (0.64 mmol) used. [c]Alkyne (0.608 mmol) used.

**Scheme 3. Alkyne Selectivity for Benzannulation**




**Scheme 4. Plausible Mechanism**




Fischer carbene **1a** and gave naphthol product **3** (Scheme 1). From these experiments, we concluded that the acyloxy or carbonate group adjacent to the alkyne has a role to play in deciding the pentannulation reaction. It is also inferred from the previous Dötz work[4] (Scheme 4A) using diaminoalkyne that the amine group on the styryl bond of **13a** intramolecularly displaces the CO ligand, giving the tetracarbonyl chromium complex **13b** having the four-membered ring. This probably prevents the CO insertion required for benzannulation. On the contrary, the direct loss of the CO group from this complex results in aryl ring attack at the ortho position, leading to pentannulation product **13c**. Similarly, in our work, the reaction of Fischer carbene **1b** with the alkyne having the acyloxy or carbonate group gives the 18-electron chromium complex **14a** (Scheme 4B). Furthermore, the insertion of alkyne to carbene furnishes the metallotriene **14b**. If the CO insertion occurs, then this would give the ketene **14f** required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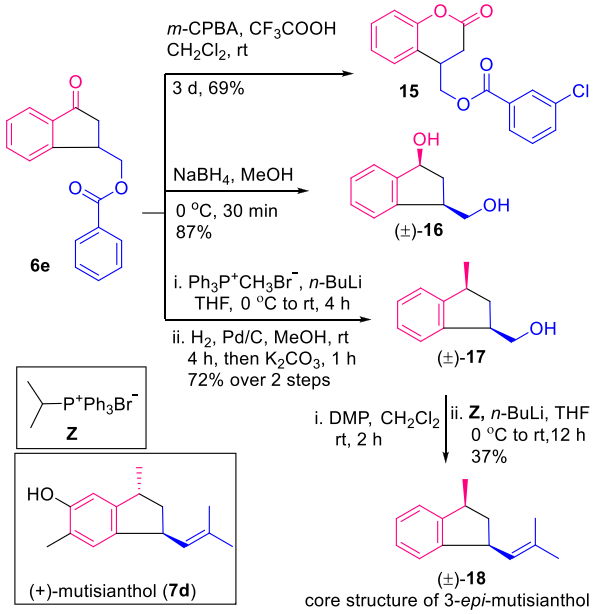
for the Dötz benzannulation. However, in this work, the acyloxy or carbonate carbonyl group adjacent to the alkyne probably coordinates with the Cr metal, giving the tetracarbonyl chromium complex **14c** or **14c′** involving a six-membered ring. This possibly prevents the CO insertion, and hence the intramolecular ortho attack of the aryl ring results in the indanone enol-ether **14d**, which hydrolyzes to the indanone **14e**.

We further considered synthetic modifications of indanone compound **6e** and also elaborated it to the core structure of mutisianthol **7d** (Scheme 5). The latter is an indane natural

**Scheme 5. Synthetic Transformations of Indanone 6e and Synthesis of the Core Structure of Mutisianthol**




product isolated from the roots of *Mutisia homoeantha*.[10g] The indanone **6e** on Baeyer–Villiger oxidation furnished dihydrocoumarin **15** in 69% yield. Here transesterification occurred with the generated *m*-chlorobenzoic acid. The $NaBH_4$ reduction of **6e** gave the known cis isomer of diol **16** (87%).[14] One-carbon Wittig olefination on **6e** provided the exomethylene compound, which on subsequent hydrogenation, furnished the single cis diastereomer that on in situ benzoate ester hydrolysis gave alcohol **17** in 72% yield (from **6e**). Further oxidation of alcohol **17** with Dess–Martin periodinane (DMP) to the aldehyde and Wittig olefination with the ylide from **Z** furnished core structure **18**[15] of 3-*epi*-mutisianthol.

In summary, in this Letter, we have developed Fischer carbene pentannulation with alkynes having the adjacent acyloxy or carbonate groups. Various 3-substituted 1-indanones (22 examples) have been prepared by this method. In the case of chiral enantiopure alkynes, the reaction afforded single enantiopure diastereomers. The acyloxy or carbonate carbonyl group probably coordinates with the Cr metal, retarding the CO insertion to give the ketene intermediate required for benzannulation. The diverted reaction results in an aryl ring giving an ortho attack, resulting in pentannulation leading to indanone compounds. The method has been elaborated to complete the synthesis of the core structure of 3-*epi*-mutisianthol.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00901.

Experimental procedures, characterization data, and NMR spectra of all compounds and X-ray data for **6a** (PDF)

### Accession Codes

CCDC 1945347 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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(9) The synthesis of alkyne **5a** required six steps from D-glucono-$\delta$-lactone. The preparation of precursor **2** for **5a** is reported by us. (See ref 8f.) The last steps of lactonization and TBS protection are given in the Supporting Information.

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