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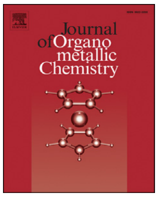

# Synthesis of α-pyrones by catalytic oxidative coupling of terminal alkynes and carbon dioxide

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ABSTRACT

The use of the complex [(dippe)Ni(μ-H)]$_2$ (**1**) as a catalyst precursor (10 mol%) in the presence of a variety of terminal alkynes and $CO_2$ allowed the production of substituted α−pyrones. This reaction occurs using relatively mild conditions (50 °C, 150 psi of $CO_2$) with good to modest yields, depending on the nature of the substituents in the corresponding alkyne. The produced α−pyrones were characterized by different analytical methods and spectroscopic techniques.

## 1. Introduction

The increasing amount of atmospheric $CO_2$ from anthropogenic sources is a concerning issue of global proportions [1]; therefore, transforming this pollutant gas into useful products, such as fuels [2] and co-polymers [3], among many others, is still a pending task. There are several chemical strategies to use $CO_2$ as a building block toward more complex materials, e.g., the partial hydrogenation to yield formates [4], the reduction to CO for further use in a variety of processes [5], and the incorporation of $CO_2$ into alkenes, dienes, allenes, and alkynes [6].

The insertion reaction of $CO_2$ into M-C bonds has been reported, and Allen and co-workers have documented some relevant examples for Ru [7] and Fe [8]; in these cases, the single or double insertion of $CO_2$ gives acetates, depending on the pressure of $CO_2$ used.

The oxidative coupling of alkenes with $CO_2$ mediated by nickel to yield carboxylic acids, via the formation of nickela-lactone intermediates followed by hydrolysis, was reported by Hoberg and co-workers [9]. A closely related process is the sodium acrylate synthesis, reported by Limbach and co-workers, using ethylene and $CO_2$ catalyzed by Ni(0) [10], later improved on by other groups [11]. Similarly, dienes have also been used to produce corresponding α-pyrones with $CO_2$ catalyzed by palladium [12].

Regarding the coupling of alkynes and $CO_2$ catalyzed by nickel, reports from 1977 by Inoue et al. indicate the use of [Ni(COD)$_2$] and bidentate aromatic phosphines to produce corresponding 2-pyrone or alkyne cyclotrimerization products [13]. Tsuda and co-workers reported on the co-polymerization of diynes with $CO_2$ catalyzed by [Ni(COD)$_2$] using monodentate alkyl phosphines to produce poly-(2-pyrones) [14] and, with a closely related method, bicyclic α-pyrones [15]. Also worthy to mention are the contributions from Walther [16] and Saegusa [17] using low-valent nickel complexes and alkyl-substituted alkynes to yield pyrones with low to moderate yields. Other relevant reports on that field include the use of nickel (0) catalysts and $CO_2$ along with organo-zinc compounds to produce acrylic acid derivatives [18], recently expanded to the hydrocarboxylation of alkynes using alcohols as proton sources [19] and the production of maleic acid by the double insertion of $CO_2$ using Zn powder and $MgBr_2$ [20].

In recent years, our group has been interested in a variety of methods for $CO_2$ activation and transformations catalyzed by nickel, including the characterization of intermediates in the reduction of $CO_2$ [21]; these methods includes catalytic

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applications in the hydroesterification of styrenes [22], hydrosililation to yield formic acid and formates [23], and the production of aliphatic N-methylamines [24].

Here, we want to disclose our findings in the study of the oxidative coupling of a variety of substituted terminal alkynes with $CO_2$ (99.998%) to produce α−pyrones catalyzed by nickel with good to low yields, depending on the electronic donor/withdrawing characteristic of the substituents at the alkyne moiety.

## 2. Results and discussion

The optimized reaction conditions were established using phenylacetylene as a model substrate and $[(\text{dippe})\text{Ni}(\mu\text{-H})]_2$ (**1**) as a catalyst precursor with variations of reaction time, solvent, catalyst load, temperature, and $CO_2$ pressure; thus, we found that the use of 69 h, toluene, 10 mol% of **1**, 50 °C, and 150 psi of $CO_2$ were the best reaction conditions to achieve a 100% conversion of the substrate, with the best selectivity towards the production of the corresponding α−pyrone (4,6-diphenyl-2-pyrone), as represented in Scheme 1.

The produced 4,6-diphenyl-2-pyrone was isolated from the reaction mixture by column chromatography and then fully characterized by a variety of analytical techniques, including $^1H$, $^{13}C\{^1H\}$, COSY, and HETCOR; see SI section.

Considering that a 100% transformation of phenylacetylene was achieved under the reaction conditions (*vide supra*), the scope of the reaction was extended to closely related alkynes, some of which had electron donor or electron withdrawing substituents or small structural variations; the corresponding results are summarized in Table 1.

As seen in Table 1, the use of terminal phenyl-acetylenes with electron donor substituents in the *para* position (entry 2) of the benzenic ring produce a high conversion and selectivity (91%) towards the production of the corresponding 2-pyrone, compared to the unsubstituted phenyl alkyne (entry 1). A sharp contrast can be seen in entry 3 for the *p*-methoxyphenylalkyne, but this result was due to the low solubility of this alkyne in toluene; efforts to overcome that by using solvent mixtures of toluene/THF did not increase the conversion rate. The use of another electron donor substituent, such as an amino group in the *ortho* position, mostly favored the homocoupling products (96%) and the production of small amounts (2%) of indole as a product of internal cyclization.

Closely related structural variations, like adding a methylene between the triple bond and the phenyl ring, decreased the yield, probably due to increased system flexibility and a lack of conjugation. The use of an internal alkyne yielded a dramatic drop in reactivity (entry 6) to barely produce only 5% hydrogenation; thus, the use of internal akynes was not further assessed.

The use of mono-fluorinated phenyl alkynes gave a complete conversion (entries 7–9), but with a low selectivity to the corresponding pyrone and an increasing preference for the cyclotrimerization and homo-coupling products; this was probably due to the high electronegativity of the fluorine atom and the decreasing electronic density in the aromatic ring, compared to simple phenyl acetylene.

To further explore this behavior, we decided to assess the reactivity of trifluoromethyl-substituted phenylacetylenes (entries 10–12); similarly, we observed high conversion of the starting material but with a poor selectivity to the corresponding pyrones, along with an increased preference towards the production of homocoupling and cyclotrimerization products, i.e., products where $CO_2$ was not incorporated.

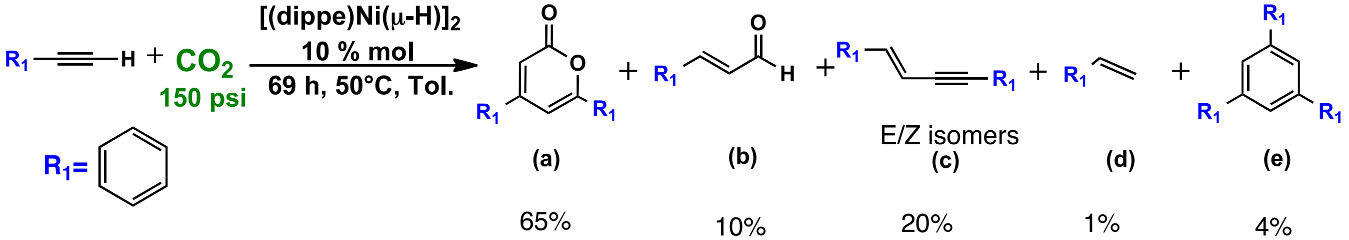
Inspired in the mechanistic reports in the literature [13] [25], and the current observations, a mechanistic proposal for the formation of α−pyrones is depicted in Scheme 2.

As represented in Scheme 2, we envisage the formation of the five-membered nickelacycle **(A)** where the incoming $CO_2$ can be inserted to yield the corresponding seven-membered metallalactone **(B)**, and ultimately giving the corresponding pyrone by having electron-donating substituents at the aromatic ring in the alkyne; this favors a nucleophilic attack at the electrophilic carbon of the incoming $CO_2$. On the other hand, the cyclo trimerization pathway, which yields the seven-membered metallacycle **(C)** leading to the production of benzenic products, would be favored, with electron-withdrawing substituents at the aromatic ring in the alkyne by insertion of a third alkyne instead of $CO_2$. A similar scenario might be expected in the case of homocoupling products; however, this would occur by a different mechanistic proposal, see SI section. Thus, the proposal for the formation of **(A)** as a key intermediate instead of a nickelalactone proposed by Hoberg [26] is consistent with the electronic properties of the substituents in the aromatic ring, to produce **(B)** or **(C)** having **(A)** as a common intermediate. However, we do not discard at all the formation of the above-mentioned metalla-lactone.

The use of 1 mol% of additives, such as $BEt_3$ and $NaBPh_4$, did not increased the observed yields; only in the case of $NaBPh_4$ could the nickel catalyst load be reduced from 10 to 5 mol%, with a very similar product distribution. Last but not least, the cinnamaldehyde formation may be due to a competing reaction of reduction of $CO_2$ to yield CO, as previously reported by our group [21], along with the hemi-reduction of the corresponding alkyne, followed by CO insertion and reductive elimination.

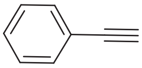
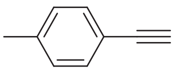
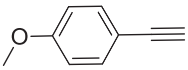
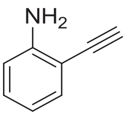
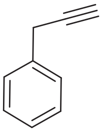
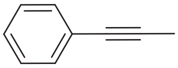
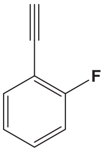
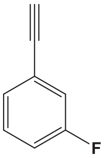
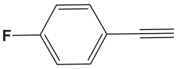
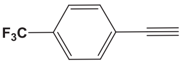
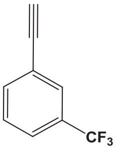
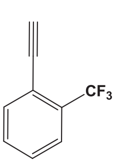
## 3. Conclusions

The oxidative coupling of terminal aromatic alkynes with $CO_2$ catalyzed with nickel to yield α−pyrones (lactones) was achieved in good yields on electron-donating substituents in the aromatic ring. However, the substitution with electron-withdrawing substituents favors the production of cyclotrimerization and homocoupling products instead.



**Scheme 1.** Optimized reaction conditions with phenylacetylene.

**Table 1**
$CO_2$ oxidative coupling with aromatic alkynes[a].

| Entry | Alkyne | Conversion (%) | Yield (%) | | | | |
|---|---|---|---|---|---|---|---|
| | | | a | b | c | d | e |
| 1 |  | 100 | 65 | 10 | 20 | 1 | 4 |
| 2 |  | 100 | 91 | 6 | 3 | 0 | 0 |
| 3 |  | 5 | 3 | 0 | 2 | 0 | 0 |
| 4[b] |  | 100 | 0 | 0 | 96 | 2 | 0 |
| 5 |  | 45 | 14 | 17 | 10 | 4 | 0 |
| 6 |  | 5 | 0 | 0 | 0 | 5 | 0 |
| 7 |  | 100 | 50 | 4 | 17 | 0 | 29 |
| 8 |  | 100 | 25 | 8 | 49 | 0 | 18 |
| 9 |  | 100 | 47 | 9 | 15 | 0 | 29 |
| 10 |  | 100 | 14 | 3 | 32 | 7 | 44 |
| 11 |  | 100 | 11 | 3 | 23 | 7 | 56 |
| 12 |  | 100 | 10 | 0 | 65 | 5 | 20 |

[a] Reaction conditions according to Scheme 1.
[b] Additional 2% of indole was observed.

## 4. Experimental section

### 4.1. General considerations

Unless otherwise noted, all manipulations were performed using standard Schlenk techniques in an inert-gas/vacuum double manifold or under an argon atmosphere (Praxair 99.998) in an MBraun UniLab glovebox (<1 ppm $H_2O$ and $O_2$). All liquid reagents were purchased as reagent grade and degassed before use. All alkynes and $NiCl_2$ were purchased from Aldrich and stored in a glovebox for their use. The complex $[(\text{dippe})Ni(\mu\text{-}H)]_2$ (**1**) was prepared from a *n*-hexane slurry of $[(\text{dippe})NiCl_2]$ using Super-Hydride ($LiHBEt_3$), according to the reported procedure [27]. The solvents were dried using standard techniques and stored in the glove box before use. Deuterated solvents were purchased from Cambridge Isotope Laboratories and stored under 4 Å molecular sieves for 24 h before use. NMR spectra were recorded at room temperature on a 300 MHz Varian Unity spectrometer unless otherwise noted. $^1H$ NMR spectra ($\delta$ parts per million) are reported relative to the residual protio-solvent. $^{13}C\{^1H\}$ spectra give the characteristic carbon signal of each solvent. $^{31}P\{^1H\}$ NMR chemical shifts ($\delta$ parts per million) are reported relative to external 85% $H_3PO_4$. Coupling constants ($J$ values) are given in Hz. The following abbreviations are used for the NMR data: s = singlet; d = doublet; t = triplet, m = multiplet; and br = broad. GC-MS determinations were performed using an Agilent Technologies G3171A equipped with the following column: 5% phenylmethylsilicone, 30 m * .25 mm * .25 µm $^1H$ and $^{13}C\{^1H\}$ NMR spectra of the reduction products were obtained in $CDCl_3$. Catalytic experiments were carried out in a 100-mL stainless steel Parr T315SS reactor. Elemental analyses (EAs) were performed by USAII-FQ-UNAM or USAI-UNAM using a PerkinElmer microanalizer 2400.

### 4.2. Catalytic experiments

#### 4.2.1. General procedure for the catalytic production of α−pyrones

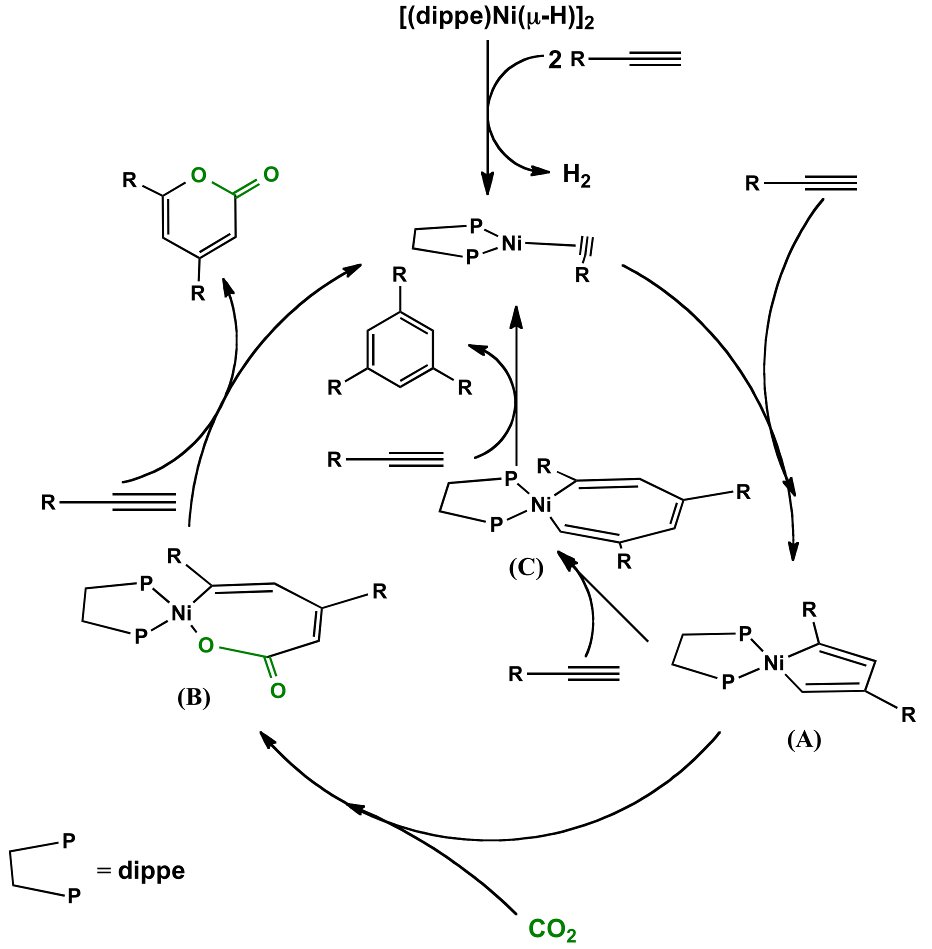
$[(\text{dippe})Ni(\mu\text{-}H)]_2$ (**1**) (0.031 mmol) and the corresponding alkyne (0.311 mmol) and toluene (10 mL) were charged in a 100-mL Parr reactor. On reacting **1** with all acetylenes, a color change from wine red to brown was observed with a light bubbling; the reactor was immediately closed and then pressurized out of the dry box with $CO_2$ (150 psi). Afterward, the reaction vessel was heated up to 50 °C for 69 h. After this time, the reactor was cooled down to room temperature and vented into a hood; the reaction mixture was directly analyzed by GC-MS.

#### 4.2.2. General procedure for the catalytic production of α−pyrones with additives

For these reactions, a similar experimental procedure as above was followed but included adding $BEt_3$ or $NaBPh_4$ (0.0031 mmol) before closing the reactor. $NaBPh_4$ was handled by protecting this reagent from light using aluminum foil.

#### 4.2.3. Isolation and purification of 4,6-diphenyl-2-pyrone

The reaction mixture obtained was evaporated to dryness with silica gel and then eluted in a silica-gel column (0.2–0.5 mm, Merck), using a mixture of 80% hexane and 20% ethyl acetate (V/V) as the eluting agent; the desired fraction was concentrated in the rotary evaporator and further dried in high vacuum for 2 h. Elemental Analysis: calc. for $C_{17}H_{12}O2$, %C 82.24, %H 4.87; exp. %C 82.31, %H 4.83, $m/z = 248.1$. Relevant NMR spectra are included in the SI section.



**Scheme 2.** Mechanistic proposal for the α–pyrone production vs. cyclotrimerization.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2016.12.033.

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