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Efficient preparation of carboxylic acids from alkynes

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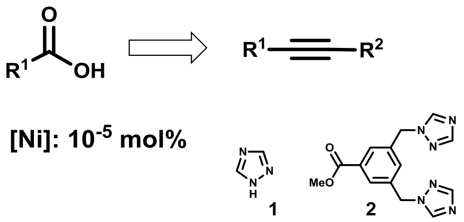
Graphical Abstract



Abstract.

The preparation of carboxylic acids from arylacetylenes has traditionally been carried out by ozonolysis or other harmful oxidants, alone or in presence of some metal catalysts. In spite of the safety, availability and environmental benignity of molecular oxygen, the selective cleavage of unsaturated hydrocarbons mediated by the latter oxidant has been rarely reported. Herein we wish to present the efficient preparation of carboxylic acid derivatives from alkynes employing molecular oxygen as the only oxidant and in the presence of a Ni(II) salt and 1,2,4-triazole ligands.

Introduction

Carboxylic acids are prepared from a variety of oxidative processes[1] including the cleavage of C-C triple bonds, traditionally performed by ozonolysis.[2] However, it requires specific equipments to avoid secondary reactions like explosions. In addition, ozone is considered to be toxic. To avoid the use of the latter oxidant and the necessity of specific equipments new alternatives have been developed. For instance, oxidants as oxone, H_2O_2, tert-butyl hydroperoxide or I(III) reagents[3] have been reported to provide carboxylic acids from alkynes, in most of the cases in stoichiometric amounts. The afore mentioned oxidants could work alone or in presence of a metal catalyst as W, Ru, Os, Fe and In among others.[4] Therefore, the use of molecular oxygen in these context or in any oxidative process avoid the use of harmful chemicals as there could be the mentioned oxidants.

Molecular oxygen is has been considerate as the most sustainable oxidant for many oxidative processes due to it safety, easy availability and low cost. However, to the best of knowledge there is an only example about the utility of dioxygen as oxidant in these kind of transformations. Itoh reported the photooxidative aerobic cleavage of alkynes employing carbon tetrabromide as catalyst under photoirradiation from a 400 W mercury lamp.[5] Following with the experience of the group in the aerobic oxidative processes[6] we envisioned to perform the preparation of carboxylic acids from alkynes in presence of a nickel(II) salt and a 1,2,4-triazole derivative ligand as catalytic media under molecular oxygen atmosphere.

Materials and Methods

A round bottom flask equipped with a magnetic stirrer bar was charged with the alkyne (1 mmol), NaOAc (8.0 mg, 0.1 mmol), NiBr2 (20 µL of a 5 x 10-6M solution in PEG-400, 10-7 mmol), **1** or **2** (20 µL of a 5 x 10-6M solution in PEG-400, 10-7 mmol) and PEG 400 (1 mL) at room temperature. The system was purged with molecular oxygen, an oxygen-filled balloon (1-1.2 atm) was connected. The mixture was heated at 120 ºC under stirring for 48 h. The reaction outcome was monitored by ^{1}H-NMR. Upon completion, the mixture was cooled to room temperature and water was added (50 mL aprox.). The resulting solution was acidified with HCl 1M (pH≈1-2), extracted with Et2O (4 x 6 mL) and the combined organic layers were washed with brine, dried over anhydrous Na2SO4 and evaporated in vacuo to give a residue which was purified by flash column chromatography using hexane:ethyl acetate as eluent.

Results and Discussion

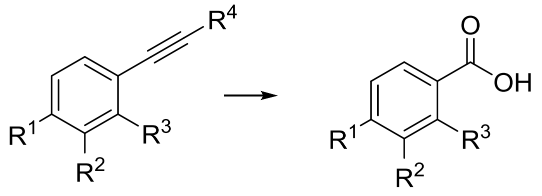
With the only intention of expanding our experience on the aerobic oxidative process, and following with the unexpected results obtained in the oxidation of 3-phenyl-2-propyn-1-ol and 1-phenyl-2-propyn-1-ol[6b] in presence of nickel(II) bromide and 1,2,4-triazole derivative ligand, in which instead of obtaining the corresponding oxidation product, 3-phenyl-2-propynoic acid and 1-phenyl-2-propyn-1-one respectively benzoic acid was observed, we decided to continue with the aerobic cleavage of alkynes. According with the initial assays carried out on the aerobic cleavage of phenylacetylene we decide to use $NiBr_2$, **1** or **2** and NaOAc in an envaironmentally friendly solvent as it is PEG 400 for a heating (120 ºC) during 48 hours under atmospheric pressure of O_2. After a decrease of the catalytic amount we decided to continue with an amount of 10^{-5} mol% of Ni and **1**/**2**. Blank experiments showed not only that the metal was essential to cleavage selectively phenylacetylene but also that 1,2,4-triazole derivative ligands **1** or **2** were necessary.

To test if other alkynes could also selectively cleavage to the corresponding carboxylic acid a variety of commercially available arylacetylenes were submitted under the optimized conditions as summaries in Table 1. As it can be appreciate many arylacetylenes were successfully cleavage to the corresponding benzoic acid with excellent results in most of the cases regardless the electronic and steric nature of the arylacetylene, with the only exception of the 1,4-diethynylbenzene.

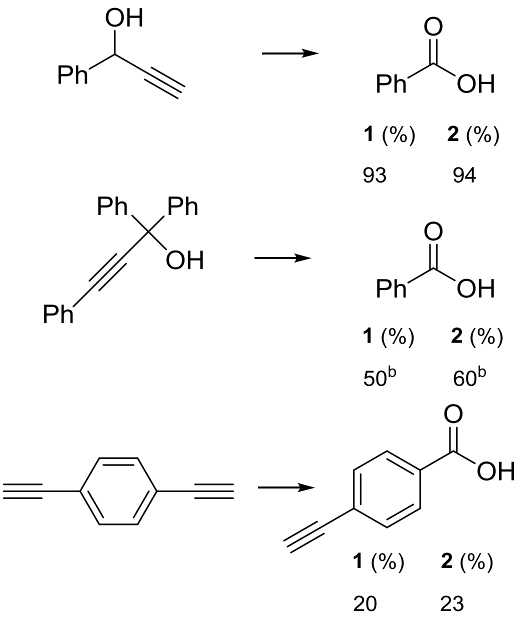
In respect to the catalytic system Ni/**1** or Ni/**2** differences between both could be appreciated, being the catalytic system formed by $NiBr_2$ and tricoordinated ligand **2** the most efficient one. In some cases when the other catalytic system, Ni/**1**, was employed the oxidative cleavage failed to provide the corresponding oxidized products, a result that was not altered by lengthening reaction times or increasing catalytic loadings.

Even more, the novel protocol has not only been successfully applied to substrates bearing halogen (F, Br, Cl), alkyl, carboxy, keto and ester moieties, but also it was useful to carried out the aerobic cleavage of phenylacetylene in gram scale. In addition to the fact that oxygen mediates this transformation at atmospheric pressure, it should be also pointed that the reaction is conducted in an environmentally friendly solvent, PEG-400, widely used as a very convenient media for chemical and medicinal purposes. The role of this solvent in the reported oxidative process might be related to its unusual coordinating properties, similar to those of crown ethers.[7]

Table 1. Oxidative cleavage of alkynes.[a]



	1 (%)	**2** (%)
$R^1 = R^2 = R^3 = R^4 = H$	90	92
$R^1 = Bu$; $R^2 = R^3 = R^4 = H$	89	91
$R^1 = Br$; $R^2 = R^3 = R^4 = H$	-	79
$R^1 = R^3 = F$; $R^2 = R^4 = H$	68	71
$R^1 = OMe$; $R^2 = R^4 = H$; $R^3 = Me$	88	97
$R^1 = R^2 = Cl$; $R^3 = R^4 = H$	85	90
$R^1 = R^2 = R^3 = H$; $R^4 = Ph$	-	96
$R^1 = R^2 = R^3 = H$; $R^4 = CH_2OH$	80	94
$R^1 = R^2 = R^3 = H$; $R^4 = Me$	-	88
$R^1 = R^2 = R^3 = H$; $R^4 = COOH$	72	75
$R^1 = R^2 = R^3 = H$; $R^4 = COOEt$	60	90
$R^1 = R^2 = R^3 = H$; $R^4 = Bz$	82	86
$R^1 = COMe$; $R^2 = R^3 = H$; $R^4 = Ph$	34[c]	46[c]



[a] Reaction conditions: O_2 (1 atm), $NiBr_2$ (10^{-5} mol%), **1** or **2** (10^{-5} mol%), NaOAc, PEG-400, 120ºC, 48h; [b] Benzoic acid was also obtained (35% from **1** and 47% from **2**). [c] Benzophenone was also isolated (30% from **1** and 20% from **2**).

Conclusions

To sum up, the presented protocol not only showed to be suitable to carried out the selective aerobic oxidation of arylacetylenes to corresponding benzoic acids, but also to be respective with the environment, associated to the use of molecular oxygen as only oxidant and in an ecofriendly solvent as it is PEG 400. Even more, the use of infinitesimal amounts of metal/ligand system allow isolation of "*metal-free*" compounds for pharmaceutical uses. These features is close to those exhibited by oxidase enzymes.

Acknowledgments

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