

[A004]



Sonogashira *versus* Stephens-Castro Mediated Synthesis of *o*-Phenylethynylbenzoic Acids, Convenient Precursors of 3-Phenylisocoumarins.

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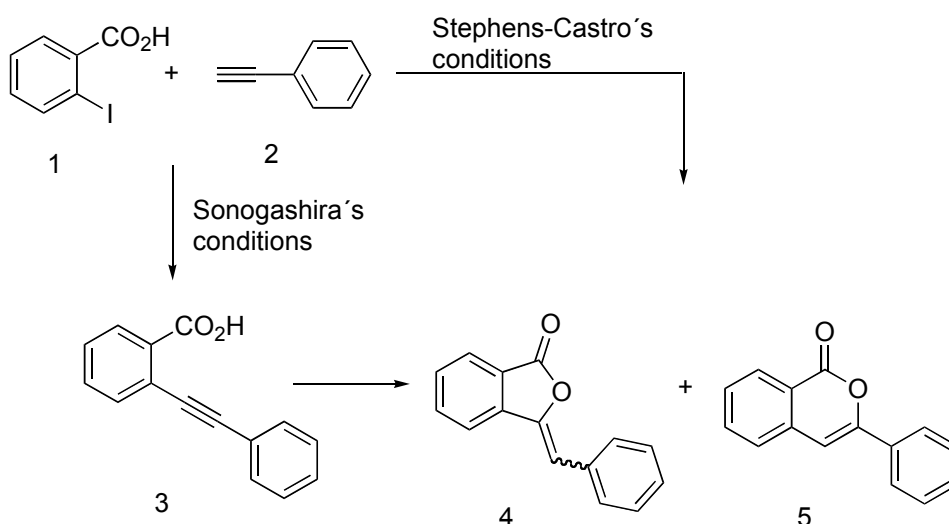
ABSTRACT.

We describe herein two synthetic approaches to 3-phenyl-5-nitro-isocoumarines, both based on a nitro-facilitated cyclization of *o*-phenylethynylbenzoic acids obtained by Sonogashira or Stephens-Castro mediated coupling of *o*-iodobenzoic acids and phenylacetylenes.

INTRODUCTION.

O-diphenylacetylenes **3** have recently become powerful synthetic tools on account of their easy preparation and their usefulness for the synthesis of heterocycles by heteroannulation reactions involving the *o*-substituent and the carbon-carbon triple bond. Thus, diphenylacetylenes **3** were first obtained in the sixties by Castro and co-workers¹ by coupling processes that involved a nucleophilic attack of a phenyl-ethynyl cuprate on aryl halides, being applied to the synthesis of indoles (from *o*-aminodiphenylacetylenes), benzofurans (from *o*-hidroxydiphenylacetylenes), phthalides **4** and isocoumarines **5** (from *o*-phenylethynylbenzoic acids), etc. But the drastic reaction conditions required limited the scope of this novel chemistry until seventies, when Songashira and co-workers² developed a variant of the Castro's reaction which allowed the preparation of arylacetylenes **2** under milder conditions.

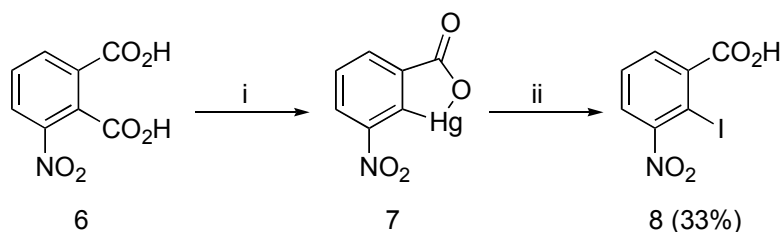




RESULTS AND DISCUSSION.

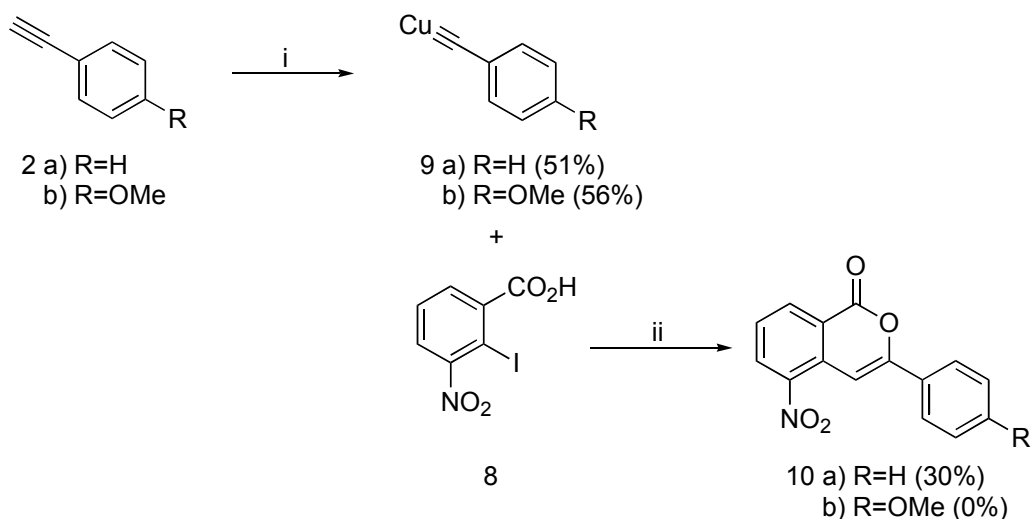
In connection with our previous work in this field, we present here our recent results concerning to the syntheses of the novel *o*-nitrophenylacetylenes **13** as synthetical precursors of the 3-phenylisocoumarins **10**.

The synthesis of this key phenylacetylenes **13** was first approached by the Stephens-Castro methodology, starting from 2-phenylacetylenes **2** and 2-iodo-3-nitrobenzoic acid (**8**) prepared in a two steps sequence from 3-nitrophthalic acid **6**.³



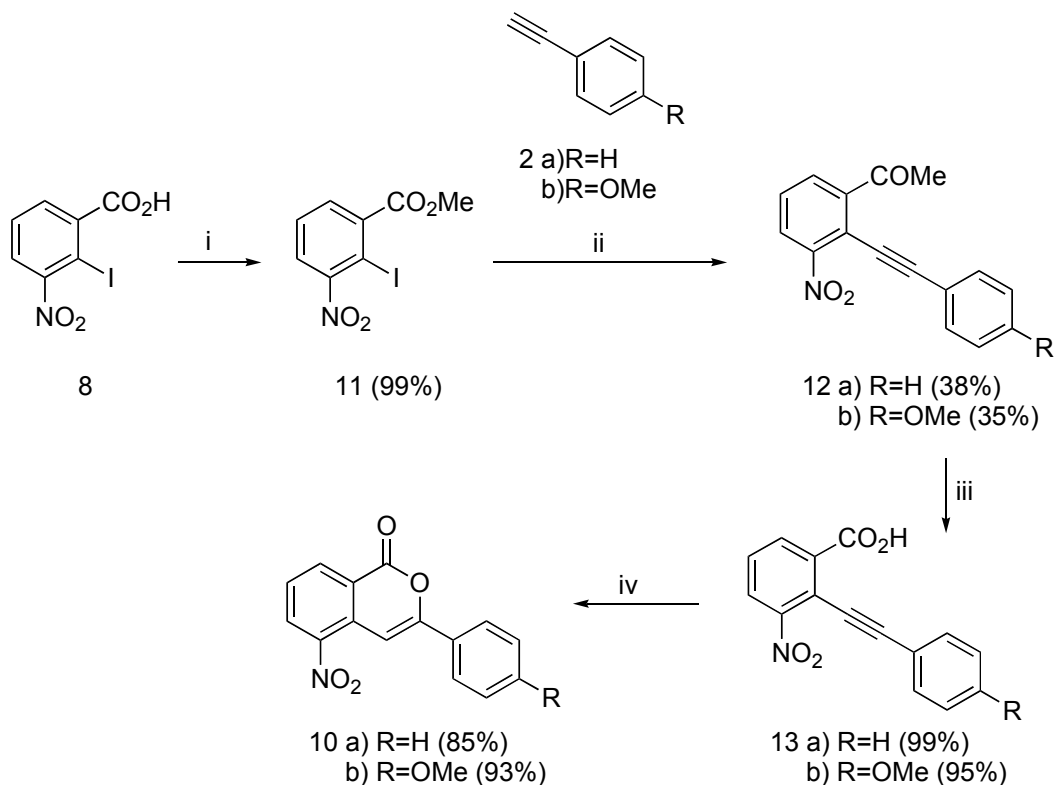
Scheme 2: i) Hg(OAc)₂, NaOH (10%), AcOH, H₂O, ref., 72 h.
ii) I₂, KI, NaOH (1M), HCl, AcOH, H₂O, ref., 12 h

The phenylethynylcuprate (**9a**) was prepared treating the phenylacetylene (**2a**) with CuI in NH₃, as described below. The coupling between 2-iodo-3-nitrobenzoic acid (**8**) and phenylethynylcuprate (**9a**) by the Stephens-Castro's conditions let us to the 5-nitro-3-phenylisocoumarin **10a**. The synthesis of the 3-(4-methoxyphenyl)-5-nitroisocoumarin (**10b**) using the same conditions was not possible, instead the high temperature condition required for this coupling.



Scheme 3: i) CuI, NH₃ (ac.), EtOH, t.a., 10 min. ii) py, ref., 30 min

We studied a new approach to the synthesis of 5-nitro-3-phenylisocoumarins **10** involving a Sonogashira coupling. The esterification of 2-iodo-3-nitrobenzoic acid (**8**) with MeOH in acidic media, and the subsequent Pd catalyzed coupling⁴ of this ester **11** with phenylacetylene (**2a**) let us to methyl 3-nitro-2-phenylethynylbenzoate (**12a**). This ester was converted to the 5-nitro-3-phenylisocoumarin (**10a**) after a basic hidrolisis and treatment of the resulting acid **13** with refluxing pyridine.



Scheme 4: i) H₂SO₄ (conc.), MeOH, ref., 5 h. ii) (PPh₃)₂PdCl₂, CuI, THF, Et₃N, t.a., 4-20 h. iii) NaOH, MeOH, t.a., 5-20 h. iv) Cu, py, 110°C, 1-2 h

The same conditions were employed to the synthesis of the 3-(4-methoxyphenyl)-5-nitro-isocumarine (**10b**).

CONCLUSION.

The Stephens-Castro's conditions employed in this work for the synthesis of phenylisocumarines allowed us to synthesized in a two step sequence the 5-nitro-3-phenylisocumarine (**10a**), but not the 3-(4-methoxyphenyl)-5-nitroisocumarine (**10b**) instead the high temperature requirements of this coupling. The modifications introduced by Sonogashira and co-workers permitted us the synthesis of both desired isocumarines **10** in a four step sequence with a moderate overall yield.

ACKNOWLEDGEMENTS.

We thank the Spanish Ministry Science and Innovation and Xunta de Galicia for financial support.

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 - 2 Sonogashira, K.; Tohda, Y.;Hagihara, N.; *Tetrahedron Lett.*, **1975**, *50*, 4467.
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