

Diethyl Acetylenedicarboxylate

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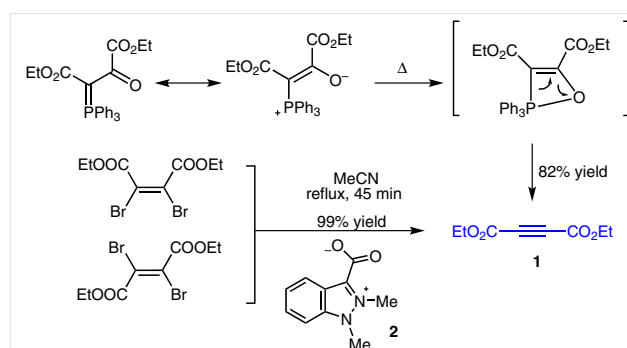
Rui-Xia Yang was born in Yunnan, China, in 1991. She received her B.Sc. in applied chemistry in 2014 from Yunnan University. Under the supervision of Prof. Jun Lin and Prof. Sheng-jiao Yan, she is currently working towards her M.Sc. at the same university. Her research interests focus on the synthesis of heterocyclic compounds and their applications.



Introduction

Diethyl acetylenedicarboxylate (**1**) is a light yellow liquid which has a disagreeable smell. It is a cheap and readily available material in industry. The triple bond is a critical and useful functional group, and it has extensive applications in organic synthesis. It can react with amines, aldehydes, ketones, etc. Therefore it can be used to form various heterocycles. This article mainly reviews the major applications of diethyl acetylenedicarboxylate in the synthesis of heterocycles, as well as some improvements in reaction conditions. Diethyl acetylenedicarboxylate (**1**) can be prepared using different methods. For example, it can be prepared using a mixture of (*Z*)-diethyl-2,3-dibromomaleate and (*E*)-diethyl-2,3-dibromofumarate in the presence of

1,2-dimethylindazolium-3-carboxylate (**2**) in acetonitrile under reflux within 45 min.¹ It can also be prepared using triphenylphosphonium ylides (Scheme 1)².

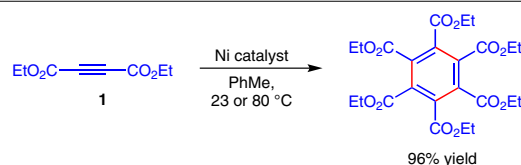


Scheme 1 Synthesis of diethyl acetylenedicarboxylate (**1**)

Table 1 Use of Diethyl Acetylenedicarboxylate

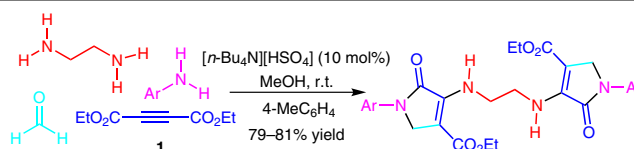
(A) Self-condensation reaction:

A one-pot reaction of aldehydes, amines and **1** can be realized in the presence of acetic acid at room temperature. Good to excellent yields are achieved within short times. These product skeletons show a wide range of biological activities, such as antimicrobial, antifungal, anti-inflammatory, anticancer, and anti-viral HIV-1.³



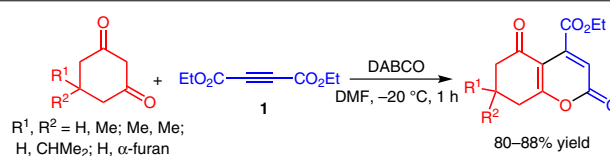
(B) Mannich reaction catalyzed by ammonium salt:

Sajadikhah and Hazeri reported that, with the help of [*n*-Bu₄N][HSO₄], the Mannich (one-pot) reaction of amines, **1** and formaldehyde can be achieved with excellent yield in methanol at ambient temperature. The isolation of the reaction product is possible without column chromatography.⁴



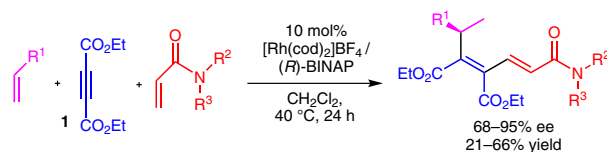
(C) Reaction with dicarbonyl compounds:

In 2012, Cao's group found that DABCO is a convenient catalyst for the reaction between 1,3-dicarbonyl compounds and **1**. DABCO showed high catalyst efficiency in the formation of C–C bond Michael addition.⁵



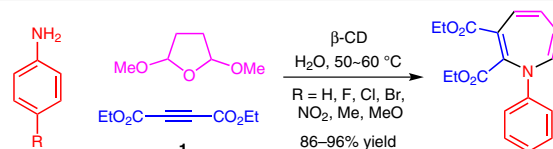
(D) Rhodium-catalyzed linear cross-trimerization:

Kobayashi and Tanaka reported the cross-trimerization of an alkene, **1** and a different alkyne which is catalyzed by cationic rhodium(I)-biaryl bisphosphine complexes. The products turned out to be linear and were formed with excellent enantioselectivity.⁶



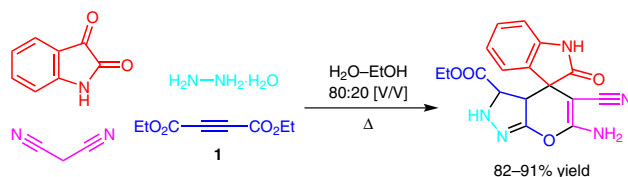
(E) Synthesis of 1-phenyl-1H-azepines:

Ramesh et al. showed a new method to synthesize N-substituted azepines. In the presence of β-cyclodextrin, aromatic amines, **1**, and 2,5-dimethoxytetrahydrofuran react well and with very good yield in water under neutral conditions. Besides, β-cyclodextrin can be recycled and reused, and shows high catalysis efficiency.⁷



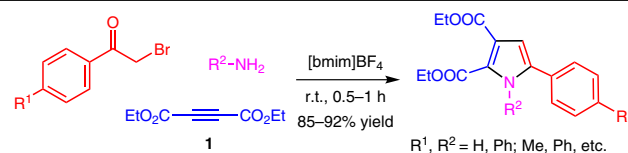
(F) Synthesis of spiro-pyranopyrazoles:

Pore et al. utilized a green path to synthesize a wide range of novel spiro-pyranopyrazole derivatives without catalyst. The one-pot reaction of **1**, hydrazine hydrate, malonitrile and istan can be conducted at room temperature in a mixed green solvent (H₂O-EtOH = 80:20) and leads to the product in very good yield.⁸



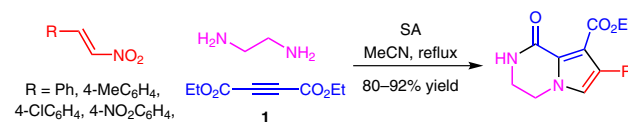
(G) Synthesis of pyrroles:

Siddiqui et al. found that ionic liquid [bmim]BF₄ is an ideal reaction medium for the synthesis of multiple pyrrole derivatives. The reaction can achieve excellent yield quickly at room temperature without any catalyst. Moreover, [bmim]BF₄ is easily available and can be recycled.⁹



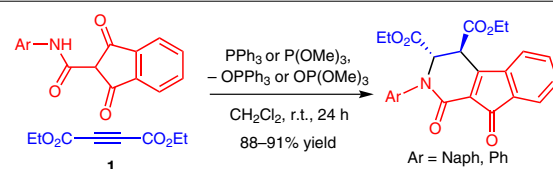
(H) Synthesis of pyrrolo[1,2-a]pyrazines:

Moradi et al. found that sulfamic acid (SA) is an effective catalyst for the one-pot reaction of ethylenediamine, **1** and β-nitro styrene derivatives. This provides a short path for the synthesis of pyrrolo[1,2-a]pyrazines in good yield.¹⁰



(I) Synthesis of tricyclic piperidin-2-ones:

Mosslemin et al. used Ph₃P or P(OMe)₃ instead of a catalyst in the synthesis of N-substituted tetrahydro-1H-indeno[2,1-c]pyridine derivatives. It is a simple and high-yielding one-pot reaction of 1,3-dioxo-N-aryl-2,3-dihydro-1H-indene-2-carboxamides **1**, and Ph₃P or P(OMe)₃.¹¹



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