SYNLETT Spotlight 246

Diketene

Compiled by Nasrin Zohreh

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Nasrin Zohreh was born in Qom, Iran in 1983. She received her B.Sc. in chemistry (2005) from Shahid Beheshti University, Tehran, Iran and her M.Sc. in organic chemistry (2007) from Tarbiat Modares University (TMU), Tehran, Iran. She is currently working towards her Ph.D. at TMU under the supervision of Dr. Abdolali Alizadeh. Their research field is multicomponent reactions and currently she is focused on the synthesis of new organic compounds, especially heterocycles, with application of diketene in multicomponent reactions.

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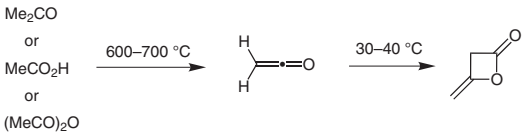
Introduction

Diketene (ketene dimer) is a reactive and versatile reagent in organic chemistry, which is used for the introduction of functionalized C_2, C_3, and C_4 units into organic compounds. Diketene is mostly used for the preparation of acetoacetate esters and acetoacetamides, which are important synthetic intermediates used in agrichemical, pharmaceutical, and dyestuffs industries.[1] Synthesis of five- and six-membered heterocycles by using diketene has been widely studied.[2] Reactions of the exocyclic olefin bond, for example photochemical [2+2] reactions, are other important reactions of diketene.[3]

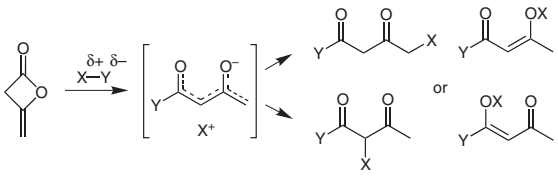
In 1908, Wilsmore prepared the first pure sample of the ketene dimer via thermolysis of acetic anhydride or acetone with a hot platinum wire.[4] Although diketene is a small molecule ($C_4H_4O_2$), in the absence of modern spectral techniques, it took 40 years to establish its structure definitely as 4-methylene-2-oxetanone.[5]

Nowadays, diketene is obtained by ketene dimerization in trickle towers, into which a liquid stream of the diketene is introduced in counter current to ketene at 35–40 °C (Scheme 1).[6]



Scheme 1

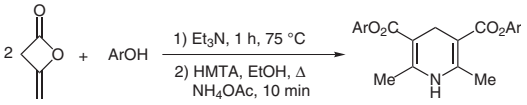
In general, depending on the applied reagents and reaction conditions, ring-opening of diketene results in formation of one of these four structures which usually undergo further reactions to reach the desired compounds. (Scheme 2).[7]



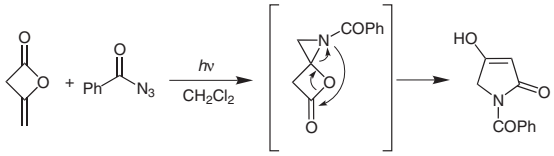
Scheme 2

Abstracts

(A) An important reaction involving diketene provides series of substituted pyridines. Symmetrical Hantzsch dihydropyridines, which are easily oxidized to pyridine, are prepared in two steps by condensation of diketene, alcohols, and aldehydes or their equivalent.[8]



(B) Almost all the reactions of the exocyclic olefin in diketene can be categorized as radical addition reactions, carbene or nitrene additions, or photochemical [2+2] reactions. For example, nitrenes generated from acyl azides add to the exocyclic double bond of diketene; the spirocyclic intermediates which are produced rapidly rearrange to afford *N*-acyltetramic acids.[9]



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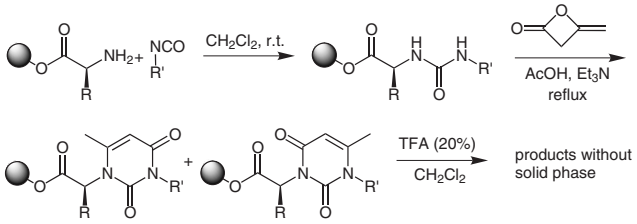
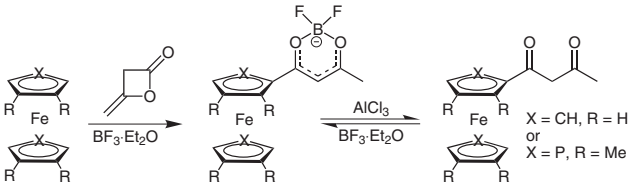
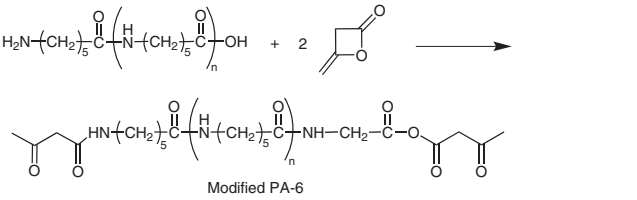
(C) One of the best methods for the synthesis of 1,3-disubstituted uracils is the solid-phase condensation of resin-bound unsymmetrically substituted ureas with diketene in acetic acid and then cleavage from the solid phase with TFA.[10]



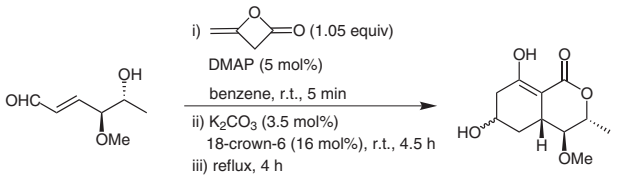
(D) Ferrocenyl ketones, which are valuable starting materials for further synthesis, are prepared in a Friedel–Crafts-type reaction of ferrocene with diketene in the presence of a Lewis acid (boron trifluoride or aluminum trichloride), which introduces directly the acetoacetyl function (or its metal chelate) into the ferrocene.[11]



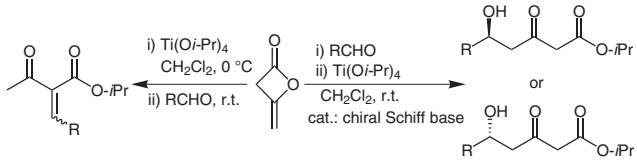
(E) Industries use diketene for the synthesis or modification of some polymers. Modification of the amine end groups of polyamide-6 (PA-6) granules with diketene in supercritical and subcritical CO_2 is reported by de Gooijer and co-workers.[12]



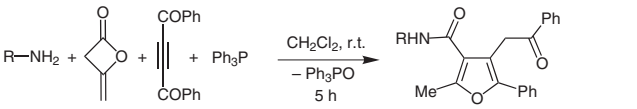
(F) One-pot esterification–Michael addition–aldol reaction of δ-hydroxy α,β-unsaturated aldehyde and diketene is used as a key step for the total synthesis of various natural products such as the insecticide tetrahydroisocoumarin.[13]



(G) Diketene is used in Knoevenagel-type reactions with aldehydes in the presence of Ti(O*i*-Pr)$_4$ for the synthesis of δ-hydroxy-β-keto esters. The chemoselectivity of the reaction depends on the addition steps and the enantioselectivity on the type of catalysis.[14]



(H) Recently Alizadeh and co-workers have applied diketene in diketene-based multicomponent reactions for the synthesis of different heterocyclic compounds. The reaction between primary amines, diketene, and DBA in the presence of triphenylphosphine produces highly functionalized furamides.[15]



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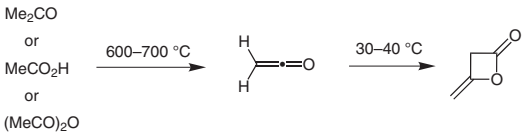

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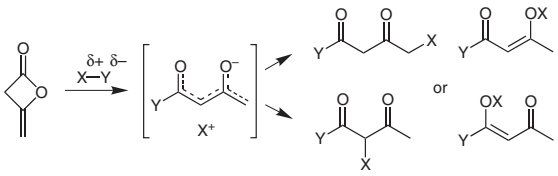

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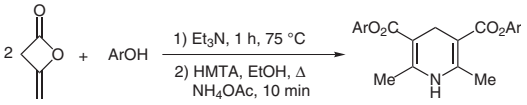

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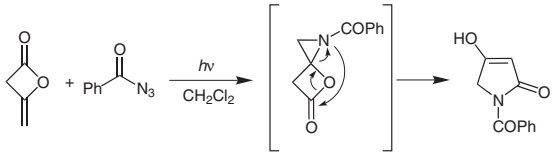

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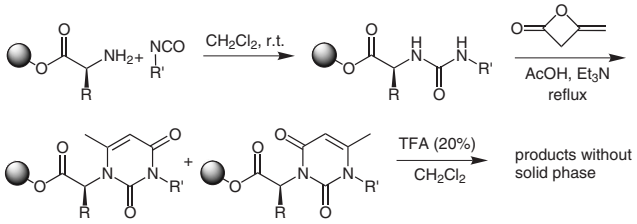

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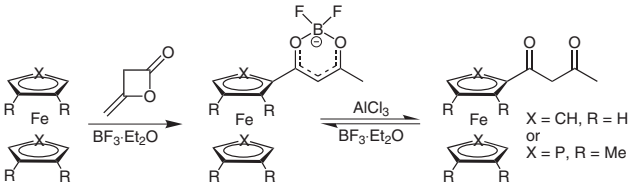

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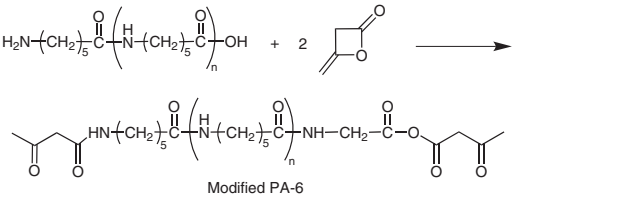

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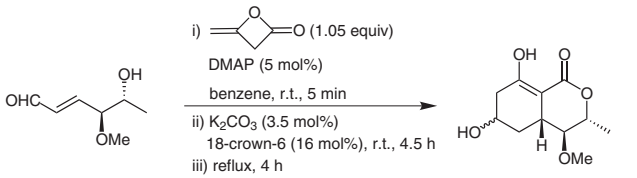

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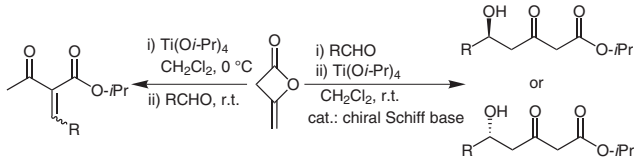

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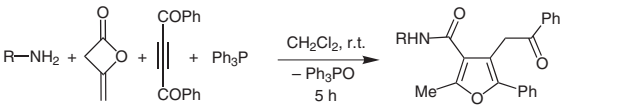

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