Ethyl Diazoacetate

Gabriel A. S. Aquino *[a]
Floriano P. Silva-Jr.[b]
Sabrina B. Ferreira[a]

[a] Laboratory of Organic Synthesis and Biological Prospecting, Chemistry Institute, Universidade Federal do Rio de Janeiro, Avenida Athos da Silveira Ramos, nº 149, Bloco A, 7º andar, Centro de Tecnologia, Cidade Universitária, Rio de Janeiro, RJ, 21941-909, Brasil
[b] Laboratory of Experimental and Computational Biochemistry of Drugs, Oswaldo Cruz Institute, Fiocruz, Avenida Brasil, nº 4365, Pavilhão Leonidas Deane, Sl. 309, Rio de Janeiro, RJ, 21040-900, Brasil
gabrielalves.aq@gmail.com

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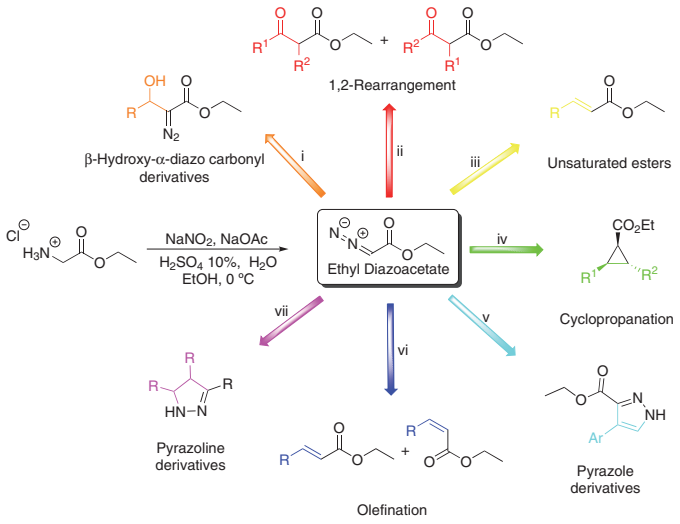
Ethyl diazoacetate (EDA; $C_4H_6N_2O_2$) is a yellow liquid with a pungent odor used mainly in organic synthesis for cyclopropanation of unsaturated compounds, but also for cyclopropanation, cycloaddition reactions, synthesis of triazoles and pyrazolines, and insertion reactions (Scheme 1).[1–3] The use of EDA is also studied in continuous-flow methods with homogeneous and heterogeneous catalysis with transition metals, for example, in selective olefination of aldehydes using copper(II) complexes.[3,4] It can be prepared through reaction between sodium nitrite and glycine ethyl ester hydrochloride in the presence of diluted sulfuric acid, ethanol, and sodium acetate. Commercially, it is available in dichloromethane or toluene solutions since it is flammable, shock sensitive, and toxic.[1,2] Nevertheless, EDA is an important synthon for organic synthesis (Table 1).

Gabriel A. S. Aquino is a pharmacist and, currently, a PhD student at the Federal University of Rio de Janeiro (UFRJ) under the supervision of Prof. Sabrina B. Ferreira and Prof. Floriano P. Silva Jr. His work involves the synthesis and evaluation of novel nitrogenated heterocycles to test against SARS-CoV-2.

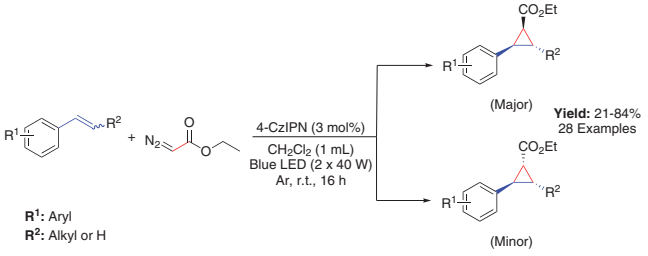
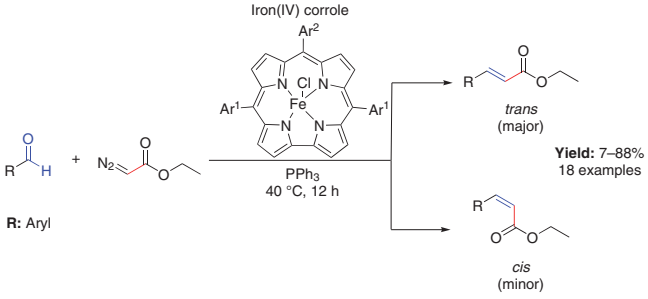
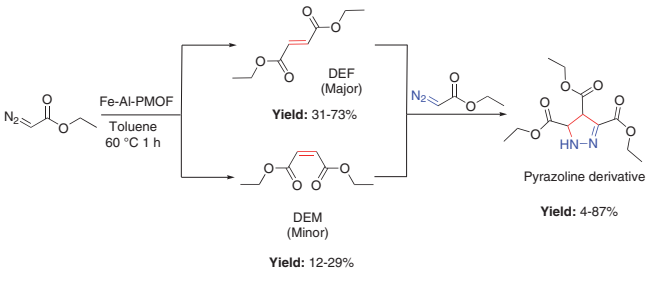
Floriano P. Silva Jr. received his PhD from the Federal University of Rio de Janeiro in 2005. His postdoctoral experiences were held at Oswaldo Cruz Institute (IOC) in 2006 and at the University of Kansas in 2008. Currently, he is the head of the Laboratory of Experimental and Computational Biochemistry of Drugs in IOC and his research efforts focus on structure and chemistry of proteins, molecular modeling, drug design, and structural molecular biology.

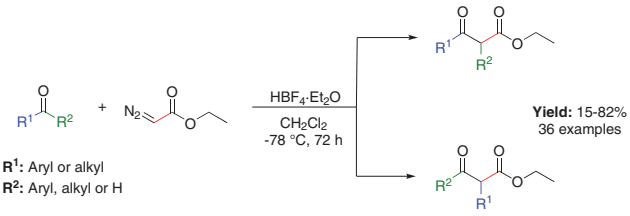
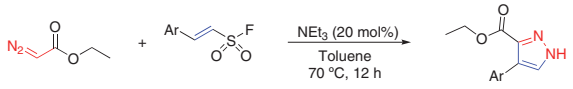
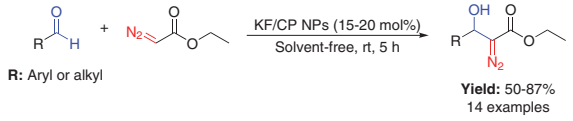
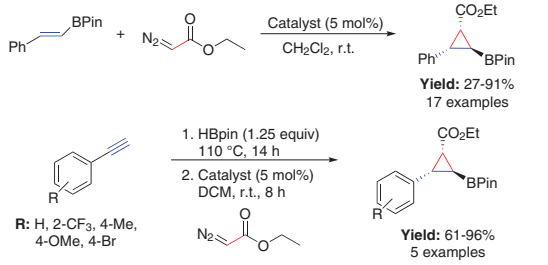
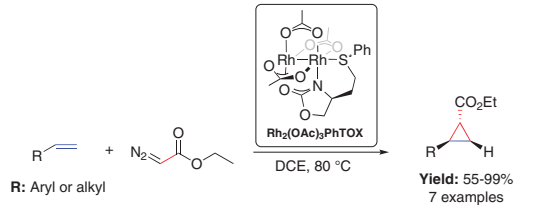
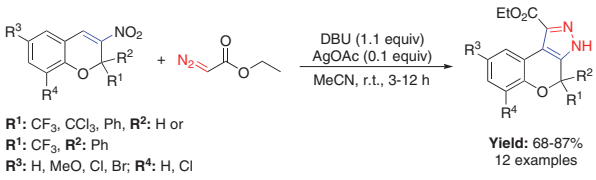
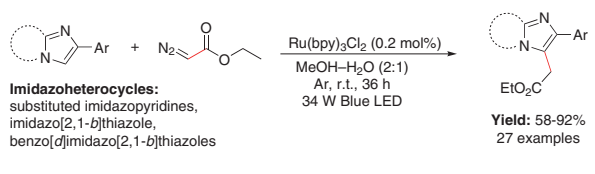
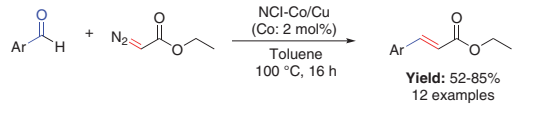
Sabrina B. Ferreira received her PhD from the Federal University of Rio de Janeiro in 2008 under the supervision of Prof. Carlos R. Kaiser and Prof. Vitor F. Ferreira. After her postdoctoral experience held at Fluminense Federal University (UFF) with Prof. Vitor F. Ferreira, she became a professor at UFRJ in 2010 where she is the head of the Laboratory of Organic Synthesis and Biological Prospecting. Her research efforts focus on organic synthesis, acting on the following subjects: heterocycles, carbohydrates, and natural products, and search for biologically active compounds.



Scheme 1 Ethyl diazoacetate preparation and some possible reactions

Table 1 Recent Applications of Ethyl Diazoacetate

(A) Cyclopropanes are a unique synthon within organic chemistry due to their properties such as high ring strain and geometry, which gives cyclopropanes an unusual structure with relatively shorter C–C and C–H bonds than in alkanes, and enhanced π-character of C–C bonds than normal.[5] Langletz and collaborators have recently reported the stereoconvergent synthesis of cyclopropanes using EDA and different styrenes in the presence of different photocatalysts under irradiation with blue LEDs. Using, *E*-, *Z*- or *E*-, and *Z*-β-styrenes mixture, they observed the formation of the same product, a single diastereomer with high yields.[6]	
(B) Olefination, i. e., obtention of C=C double bonds, is an important step for organic synthesis and it is chiefly achieved by using ylide compounds such as phosphorus reagents in the Wittig reaction. Zou and co-workers have performed different reactions to first investigate an olefination of aldehydes using EDA in the presence of triphenylphosphine (PPh_3) with iron(IV)–corrole complexes as catalysts. These complexes are analogues of porphyrin tetrapyrrolic macrocycle used mainly as catalysts for oxidation, epoxidation, hydroxylation, and insertion reactions. Their results showed an efficient method to afford *trans*-olefination products.[7]	
(C) Pyrazoline derivatives are important synthons used in medicinal chemistry due to their biological properties and also in the synthesis of fluorescent molecules due to their chromophoric properties. Abeykoon and co-workers studied the synthesis of pyrazolines from EDA using a metal porphyrin based metal-organic framework (Fe-Al-PMOF) and iron tetrakis(4-methoxycarbonylphenyl)porphyrin (FeP). Their results indicate the formation of diethyl maleate (DEM) and diethyl fumarate (DEF) with subsequent formation of the pyrazoline ring by the reaction of DEM and DEF with more EDA. The more the catalyst was washed, the more product was formed the next run, which is unusual for this type of reaction, and it can be explained by the activation of more inner catalytic sites in each wash.[8]	

(D) 1,2-Rearrangement is a usual reaction in organic synthesis, when a substituent moves from one atom to the next in an intramolecular reaction, forming different isomers. Rahaman and co-workers have synthesized a broad range of 3-oxo-esters by reacting EDA with different ketones and aliphatic aldehydes through a 1,2-shift using a Brønsted acid catalyst. Their results revealed that aryl methyl ketones produced only aryl-migrated products, while other ketones gave a mixture of products.[9]	
(E) The pyrazole core is an important aza-heterocycle present in natural and synthetic compounds, revealing different applications in synthetic and medicinal chemistry. The synthesis of this core using diazo compounds and alkynes/alkenes with transition metals as catalysts is well known and well established in the literature. Recently Sandeep and co-workers studied a new strategy of synthesis of this core through a metal-free reaction using β-aryl vinyl sulfonyl fluoride derivatives in a triethylamine-catalyzed [3+2] cycloaddition, obtaining good to high yields.[10]	
(F) Amino acids and amino alcohols can be obtained from β-hydroxy-α-diazo carbonyl derivatives, and, therefore, these molecules are important, mainly, when it comes to the synthesis of peptides and other macromolecules. Balou and co-workers presented the synthesis of different α-diazo carbonyl derivatives using a solvent-free and green protocol using potassium fluoride supported on nano clinoptilolite (KF/CP NPs) as catalyst. A variety of aliphatic and aromatic aldehydes were reacted with EDA to give compounds with moderate to high yields.[11]	
(G) Another strategy for the synthesis of highly enantio- and diastereoselective cyclopropanes was presented by Carreras and co-workers, where they synthesized different 1-boryl-2,3-disubstituted cyclopropanes from alkenylboronates with EDA in the presence of catalytic amounts of a chiral copper(I) complex. Besides the synthesis from alkenylboronates, the products can be obtained from alkynes through a sequence of hydroboration–cyclopropanation reactions. The yields varied from 27–96%.[12]	
(H) Cressy and co-workers synthesized a family of new Rh(II)-based catalysts containing tethered thioether ligands using microwave methods. These catalysts optimized cyclopropanation using EDA and different olefins, enhancing the yields. The catalyst with better results was the complex $Rh_2(OAc)_3PhTOX$, achieving 99% yield when styrene was used at 5 equivalents to EDA. Other substituted styrenes were reacted and the cyclopropanes were obtained with a 54–99% yield.[13]	
(I) Pyrazoles cores can be prepared by a 1,3-dipolar cycloaddition between an aliphatic diazo compound and nitroalkenes followed by aromatization of the cycloadducts. Bykova and co-workers used EDA to synthesize fused pyrazole from substituted 3-nitro-2*H*-chromenes in a new one-pot regioselective method, obtaining ethyl 3,4-dihydrochromeno[3,4-*c*]pyrazole-1-carboxylates with yields varying between 68–87%. This strategy uses silver acetate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as bases and catalysts, increasing the yield from 36–87%.[14]	
(J) Imidazopyridines are an important nitrogen-based core, which is found in a variety of natural products as alkaloids. Particularly, ethoxycarbonylmethylated imidazopyridines are present in several drugs, such as zolpidem, alpidem, saripidem, etc.[15] Bhattacharjee and co-workers demonstrated the synthesis of alkyl-substituted imidazopyridines by the reaction between imidazopyridines and EDA using $Ru(byp)_3Cl_2$ as photoredox catalyst under the irradiation of 34 W LED lamp. The best yield was obtained when a mixture of MeOH and H_2O (2:1) was used and the success of the methodology helped the authors to repeat the reaction with other imidazoheterocycles, such as substituted imidazopyridines, imidazo[2,1-*b*]thiazole, and benzo[*d*]imidazo[2,1-*b*]thiazoles with yield varying between 58–92%.[16]	
(K) Yasukawa and co-workers developed a methodology for the olefination of deactivated aromatic aldehydes with EDA. In the presence of a nitrogen-doped carbon-supported Co/Cu bimetallic catalyst (NCI) and triaryl phosphine, various aldehydes were converted into unsaturated esters in good yields, varying between 16–86%. The heterogeneous catalyst allows the recovery and the reuse of the catalyst and, even after several runs, there was no significant loss of reactivity.[17]	

Conflict of Interest

The authors declare no conflict of interest.

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