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Extended Abstract

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Multicomponent Strategies for Direct Synthesis of N-heterocycles from Diketene

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Diketene (DK) is a reactive and versatile commercially available compound. It is frequently used for the introduction of substituted C2, C3, and C4 parts into organic compounds. It is also best known as an agent for the construction of acetoacetic acids. Noticeably, DK is an ideal compound for chemical investigation, since it is easily available, cheap, and reactive.1 It possesses electrophilic and nucleophilic sites which are capable of undergoing numerous reactions. Because of the significance and unique reactivities of ketenes and DK, we have demonstrated the usages of ketenes and DK as the privileged synthons in the formation of heterocyclic derivatives.2,3 Our group has been pursuing different methods for diverse potential biological activity nitrogencontaining heterocycles syntheses using multicomponent reaction since the past few years. In continuation of our efforts on the applications of DK as an outstanding synthon in the synthesis of heterocyclic compounds, herein, we wish to report the efficient and simple methods for the synthesis of poly-substituted nitrogen-containing heterocycles through one-pot multicomponent reactions involving DK. All reactions are easily performed and proceed with high efficiency under very simple and mild conditions without any catalyst and give good yields avoiding time-consuming, costly syntheses, and tedious workup and purification of products. Diketene (4-methylene-oxetan-2-one or DK) consists of a four-membered lactone ring adjacent to a methylene function and it can be considered the anhydride of acetoacetic acid. DK is a reactive, readily available, and versatile molecule. Diketene also reacts with alcohols and amines to the corresponding acetoacetic acid derivative. DK appears to be an ideal molecule to be used in organic transformations. Diketene possesses electrophilic and nucleophilic sites which are capable of undergoing numerous reactions. In 1986 the chemistry of DK has been extensively and comprehensively reviewed by R.J Clemens. In the last decade, various interesting multicomponent reactions based on DK successfully achieved leading to the construction of a wide variety of heterocyclic systems. Very recently, we also published on the applications of DK as a privileged synthon in the synthesis of heterocyclic compounds as a chapter in Advances in Heterocyclic Chemistry. Continuing our efforts in the development of multicomponent reaction for the synthesis of potential biological activity nitrogen-containing heterocycles, in the present work, we describe the efficient synthesis of poly-substituted nitrogen-containing heterocycles, such as 1,4-dihydropyridines, pyrido[1,2-a] pyrimidines and spiro[indoline-3,4'-pyrano-pyrazole] derivatives via MCRs involving diketene. Heterocyclic compounds are backbone of drug design–about 80% of the known small molecule drugs belong to this type of substances and among them 60% relates to nitrogen containing heterocycles. On the other hand, heterocyclic compounds play important role in other branches of science and are the base of all living organisms. Therefore, study of the appropriate field of organic chemistry is a very important challenge that has been attracting attention of numerous scientific groups for last decades and stimulating for detailed study of the topic including the search for novel and development of known synthetic methods. One of the important pathways to nitrogen containing heterocycles is reactions of aminoazoles (two-component, one-pot, multicomponent, etc.) being efficient mono-, bi- and polynucleophiles with different electrophiles. The presence of several alternative reaction centers in aminoazoles often makes them useful reagents in controlled multidirectional interactions providing the possibility to synthesize diverse chemotypes of final products. Such approach is widely used in the modern heterocyclic chemistry and some books and reviews have been already published in this field, however, many of them deal with particular problems of aminoazole chemistry and actually during long period no comprehensive analysis of the problem has been made. Multicomponent reactions (MCRs) involving aminoazoles and aldehydes with cyclic CH-acids (different ketones, 1,3-diketones, Meldrum's acid etc.) are similar to the classic Hantzsch or Biginelly condensations. In early publications they had often resulted in the formation of mixtures of positional and regioisomers, therefore, some efficient methods for tuning chemo- and regioselectivity of such multicomponent heterocyclizations, including Condition-based divergence strategy to switch their directions by simple variation of the reaction conditions. Varying temperature and catalyst allowed authors to switch the heterocyclization of aromatic aldehydes 1**,** 1,3-cyclohexanedione or dimedone with 5-amino-3-arylpyrazoles between two directions with the formation of pyrazoloquinolinenones 6 (EtOH-Et_3N, MW, 150°C, 15 min) and pyrazoloquinazolinones being the products of thermodynamically and kinetically controlled reactions, respectively. Non-classical activation methods led to the reduction in time; moreover, applying microwave activation allowed to carry out the transformations at higher temperatures in comparison with standard heating, thus, additionally favoring reaction regioselectivity in case of thermodynamically controlled pathway. In the process of optimization, the new multicomponent reaction was found: *t*-BuOK being a stronger nucleophile then Et_3N attacked the carbonyl group of cyclic 1,3-diketone moiety in the intermediate which resulted in the ring opening and recyclization with the formation of quinolizinones. Later on the greener methodology of obtaining pyrazoloquinolinenones was elaborated using microwave synthesis in water.

Similar to compounds pyrazoloquinolinenones were synthesized even without solvent using L-proline as a catalyst. The analogous to heterocycles linear quinazolinones were obtained on the basis of 3-amino-1,2,4-triazole applying the great variety of conditions. It should be noted, that in all cases tetrahydroderivatives were formed. However, Petrov and Kasatochkin oxidized partially hydrogenated pyrimidine ring of to obtain compounds using ceric ammonium nitrate (CAN) in acetone. Later on the compounds were synthesized in the three-component reaction in water under microwave irradiation also with application of CAN. Linear tetrahydroquinazolinones of type had been also formed in condensations involving 5-amino-4-aryl-1,2,3-triazole and 5-amino-*N*-aryl-1,2,3-triazole-4-carboxamide, 5-aminotetrazole, 2-aminobenzimidazole, 2-aminoindazole moiety, methyl 5-amino-pyrazole-4-carboxylate and 5-amino-pyrazole-4-carbonitrile, 4-aryl-5-aminopyrazole. It should be noted, that *N*-unsubstituted 5-amino-1,2,3-triazole-4-carboxamide showed the same behavior and the products of reaction involving carboxamide aminogroup were not separated.

Bottom Note: *This work is partly presented at* 6th World Congress on NATURAL PRODUCT & SYNTHETIC CHEMISTRY June 24-25, 2019 | New York, USA.