



ONE POT MULTICOMPONENT REACTIONS USED IN THE SYNTHESIS OF NEW ORGANIC COMPOUNDS

Anil B. Chidrawar

*Department of Chemistry, Degloor College, Degloor - 431717, Dist: Nanded.
Swami Ramanand Teerth Marathwada University, Nanded, Maharashtra, India.
Email : anilchidrawar74@gmail.com*

Abstract :

Multicomponent reactions have emerged as useful methods because the combination of two or more components to generate new products in a single step is extremely economical. A green, simple, efficient, and cost-effective procedure has been carried out by this method. A mixture of 2-amino-6-substituted benzothiazole and bis methylthio methylene malononitrile on heating independently with aryl amines / phenols / heteryl amines/ compounds containing active methylene group would result in the formation of corresponding 2-substituted derivatives. The synthesized compounds were characterized by elemental analysis and spectral data.

Key Words :

2-amino-6-nitro benzothiazole, potassium carbonate, bis methylthio methylene malononitrile.

Introduction :

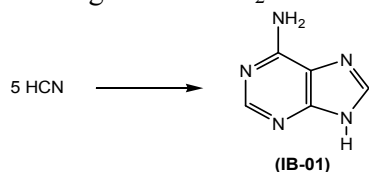
A multicomponent reaction (MCR) is a process in which three or more easily accessible compounds are combined together in a single reaction vessel to produce a final product displaying features of all inputs and thus offers greater possibilities for molecular diversity per step with a minimum of synthetic time and effort. A MCR is a domino process, a sequence of elementary steps according to a program in which subsequent transformations are determined by functionalities produced in the previous step. MCRs constitute an especially attractive synthetic strategy since they provide easy and rapid access to large libraries of organic compounds with diverse substitution patterns. As MCRs are one-pot reactions, they are easier to carry out than multi step syntheses. Coupled with high-throughput library screening, this strategy was an important development in the drug discovery in the context of rapid identification and optimization of biologically active lead compounds. Libraries of small molecule organic compounds are perhaps the most desired class of potential drug candidates, because standard peptides and oligonucleotides have limitations as bioavailable therapeutics. With a small set of starting materials, very large libraries can be buildup within a short time, which can then be used for research on medicinal substances.

Multicomponent reactions (MCR-s) have recently emerged as valuable tools in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds. The multicomponent reaction story began as far back as 1850 by the publication of the Strecker reaction arriving now a days at its apogee. During this one and a half century period, some notable achievements include the discovery of the Biginelli, the Mannich and the Passerini reactions culminating in 1959 when Ugi published probably the most versatile MCR based on the reactivity of isocyanides. In view of the increasing interest for the preparation of large heterocyclic compound libraries, the development of new and synthetically valuable multicomponent reactions remains a challenge for both academic and industrial research teams.

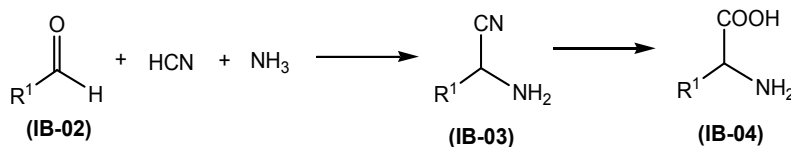
In spite of the significant useful attributes of MCRs for modern organic chemistry and their suitability for building up large compound libraries these reactions were of limited interest in the past fifty years. However, in the last decade, with introduction of high-throughput biological screening, the importance of MCRs for drug discovery has been recognized and considerable efforts from both academic and industrial researchers have been focused especially on the design and the development of multicomponent procedures for the generation of libraries of heterocyclic compounds. This growing interest is stimulated by the significant therapeutic potential that is associated with many heterocycles. Furthermore, the utility of rigid well defined structures of heterocycles was demonstrated in many detailed structure activity relationship (SAR) studies.

The “ideal synthesis” should lead to the desired product. In as few steps as possible, in good overall yield and by using environmentally compatible reagents. The synthetic variables that have to be optimized are time, costs, overall yield, simplicity of performance, safety, and environmental acceptability. In multistep syntheses the temporal and preparative complexity increases in proportion to the number of steps. It is reflected in many isolation and purification operations, such as crystallization, extraction, distillation, or chromatography.

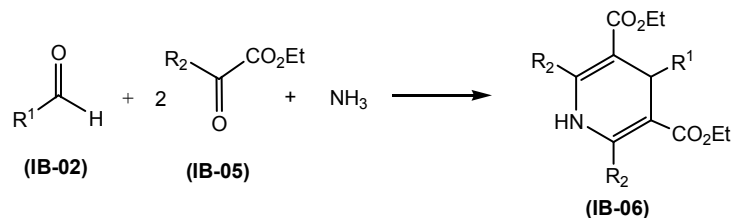
The concept of MCRs is not unknown in nature, it is important especially in evolution. It seems that adenine (IB-01) one of the major constituents of DNA and RNA, was prebiotically formed by the condensation of five molecules of HCN, a plentiful component of prebiotic atmosphere, in a reaction catalyzed by NH₃. The other nucleic bases have been generated in similar reactions involving HCN and H₂O.



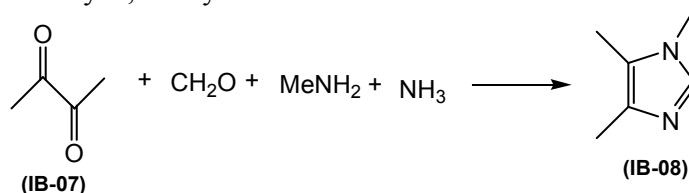
The first modern contribution to the development of multicomponent chemistry was made in 1850 by Strecker¹. The crucial step in the well-known Strecker synthesis of α -amino acids is the formation of α -amino nitriles (IB-03) from aldehyde (IB-02), HCN and NH₃ in one-pot. Subsequent hydrolysis of these synthetically valuable intermediates results in the amino acids (IB-04).



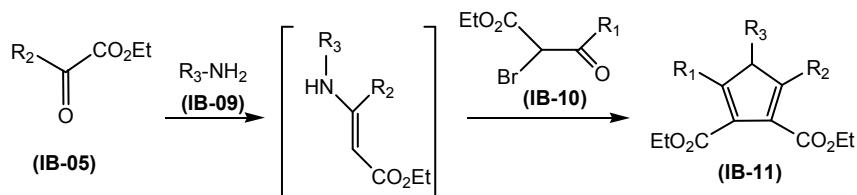
Further progress of multicomponent chemistry can be attributed to work of Hantzsch² in 1882. He synthesized symmetrically substituted dihydropyridines (IB-06) from NH₃, aldehyde (IB-02) and two equivalents of β -ketoesters (IB-05).



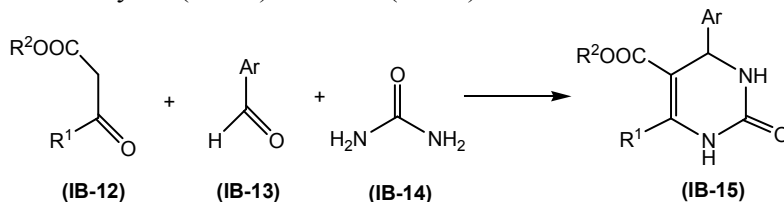
Radziszewski³ reported the multicomponent synthesis of imidazole (IB-08) by the reaction of diketone (IB-07), formaldehyde, methylamine and ammonia.



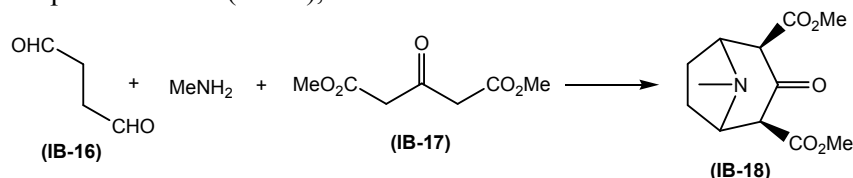
Another Contribution made by Hantzsch⁴ to MCRs was the synthesis of pyrroles (IB-11) by reacting primary amines (IB-09), β-ketonesters (IB-05) and α-halogenated β-ketoesters (IB-10).



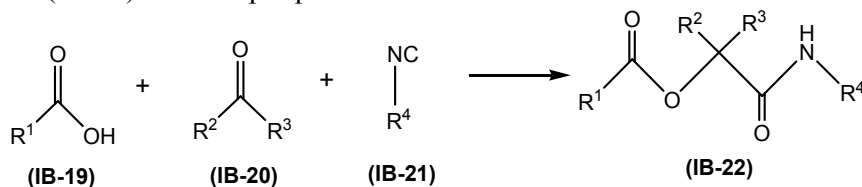
The Biginelli reaction⁵, first described in 1893, represents multicomponent synthesis of substituted dihydropyrimidines (IB-15) by acid-catalyzed cyclocondensation of β-ketoesters (IB-12), aromatic aldehydes (IB-13) and urea (IB-14).



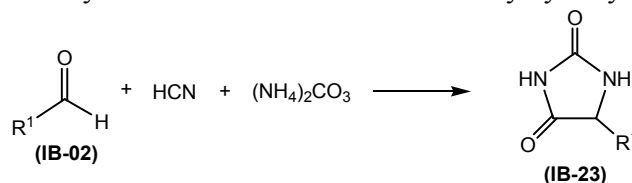
The first important application of MCRs in natural product synthesis was the Robinson⁶ synthesis of alkaloid tropinone (IB-18) from succinic dialdehyde (IB-16), methylamine and dimethyl 3-oxopentanedioate (IB-17), carried out in 1917.



The first MCR involving isocyanide was discovered in 1921 by Passerini⁷. Carboxylic acids (IB-19), carbonyl compounds (IB-20) and isocyanides (IB-21) afforded α-acyloxy carboxamides (IB-22) in a one-pot procedure.

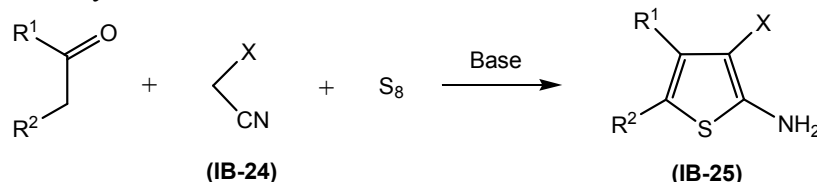


Bucherer and Bergs^{8,9} described a four-component reaction for the synthesis of hydantoin (IB-23). One-pot reaction of hydrogen cyanide, aldehyde (IB-02), NH₃ and CO₂ afforded hydantoin, which can be easily transformed into α -amino acids by hydrolysis.

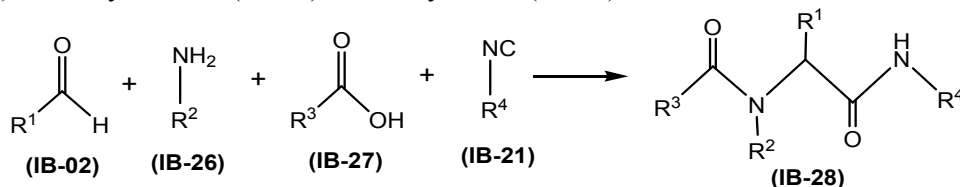


The chemistry of isocyanides is fundamentally different from the rest of organic chemistry, since they are the only chemical compounds with divalent carbon atoms C^{II} and all of their chemical reactions correspond to conversion of the divalent carbon atoms C^{II} into the tetravalent carbon atoms C^{IV}.

Gewald and co-workers¹⁰ described the synthesis of polysubstituted thiophenes (IB-25) with electron withdrawing substituents such as cyano, carboethoxy and carboxamido in the 3-positions and alkyl, aryl, cycloalkyl and hetaryl groups in the 4- and 5- positions. Three major modifications of this method are described in literatures which give access to various 2-aminothiophenes. The most elegant and simplest version consists of a one-pot procedure which includes the condensation of aldehydes, ketones or 1,3-dicarbonyl compounds with activated nitriles (IB-24) and sulfur in the presence of amine at room temperature. Ethanol, methanol, dimethyl formamide, dioxane, excess ketone such as methyl ethyl ketone or cyclohexanone are preferred solvents and the most often employed amines are diethylamine, morpholine or triethylamine.



Ugi *et.al.*¹¹ introduced the four-component reaction of the isocyanides, which is, since 1962, referred to as the Ugi reaction (U-4CR). The U-4CRs are one - pot reactions of amines, carbonyl compounds, acids, and isocyanides that form products from any educts. Synthesis of α -acylamino amides (IB-28) was achieved by reacting aldehydes (IB-02), primary amines (IB-26), carboxylic acids (IB-27) and isocyanides (IB-21).



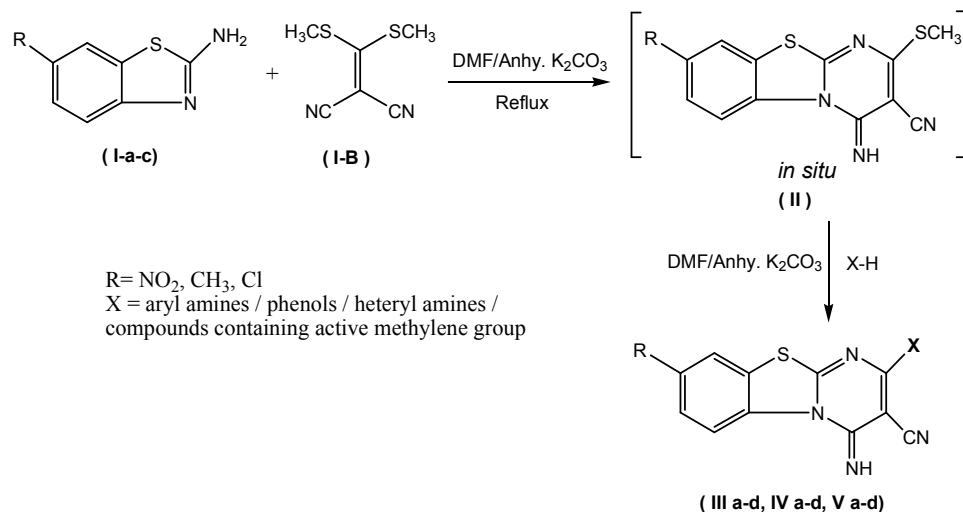
A mixture of a secondary amine (IB-29), cyclic keto compound (IB-30), hydrazoic acid and isocyanide (IB-31) on refluxing together undergoes U-4CR to form substituted tetrazole¹² (IB-32). A number of N-Containing heterocyclic compounds possess a wide spectrum of applications in various fields like medicine, industry, pharmacology and analytical chemistry¹³⁻¹⁵. Some of this derivatives also acts as antibacterial, anticancer, antimicrobial, antiviral, antihelmenthetic, insecticidal, and Herbicidal compounds¹⁶⁻¹⁷

Experimental Section:

All melting points were determined in open capillary tube and were uncorrected. IR spectra were recorded with potassium bromide pellets technique, ¹H NMR spectra were recorded on AVANCE 300 MHz Spectrometer in DMSO using TMS as internal standard. Mass spectra

were recorded on a FT VG-7070 H Mass Spectrometer using EI technique at 70 eV. All the reactions were monitored by thin layer chromatography.

Material and Methods :



General procedure :

Accordingly, a mixture of 2-amino-6-substituted benzothiazole (**I-a-c**) and bis methylthio methylene malononitrile (**I-B**) on heating independently with aryl amines / phenols / heteryl amines/ compounds containing active methylene group would result in the formation of corresponding 2-substituted derivatives (**III a-d**, **IV a-d**, **V a-d**)

Results and Discussion :

Multicomponent reactions which are one pot reactions constitute an especially attractive recent synthetic strategy since they provide easy and rapid access to large number of organic compounds with diverse substitution pattern. In present work, we report multicomponent synthesis of novel fused heterocyclic compound, 3-Cyano-4-imino-2-methylthio-8-substituted-4H-pyrimido [2,1-*b*] [1,3] benzothiazole and its 2-substituted derivatives.

Acknowledgements :

The authors are thankful to the Principal, Yeshwant Mahavidyalaya, Nanded for providing laboratory facilities and the Director, Indian Institute of Chemical Technology, Hyderabad for providing spectra.

References :

- i) A. Strecker, Ann.chem., 1850, 75, 27.
- ii) A. Hantzsch, Justus Liebigs Ann. Chem. 1882, 215, 1.
- iii) Radziszewski B., Ber. Dtsch. Chem. Ges., 1882, 15, 1499.
- iv) A. Hantzsch, Ber. Disch. Chem. Ges. 1890, 23, 1474.
- v) P-Biginelli, Ber. Disch. Chem. Ges. 1893, 26, 447.
- vi) R. Robinson, J. chem. Soc. (London) 1917, 111, 876.
- vii) Passerini M., Gazz. Chim. Ital. 1921, 51, 181.
- viii) H. Bergs, 1929, DE-B 566094.
- ix) T. Bucherer, H. Barsch, J.Prakt, chem. 1934, 140,151.
- x) Gewald, K. Angew. Chem. 1961, 73, 114.

- xi) I. Ugi, R. Meyr, U. Fetzer, C. Steinbruckner. *Angew. Chem.* 1962, 71, 386.
- xii) I.Ugi, F. Bodesheim, *Liebigs Ann.chem.*1963, 666, 61.
- xiii) Wu. X. Li. M. Yang. Q.W.Tang,Y.Zheng,J. Lian, J. Min, Xu. L. *Bioorg, Med. Chem.*, 2010, 18, 3812.
- xiv) M. E.D. Ibrahim, S.H.Lee, *Bioorg, Med. Chem.*, 2010, 18, 3860.
- xv) A.Olayinka O, O.Craig A, N.Obinna C, D. A. Akinpelu, *Bioorg. Med. Chem.*, 2010, 18, 214.
- xvi) J.B. Koepfly, J.F. Mead, Jr. Brockman, *J. Am. Chem. Soc.*, 1947, 69, 1836.
- xvii) C.S.J. Fu, F.Y. Wang, C.Y. Huang, K.C. Lu. G. Thou, T.C. Ch'ang Shan, *Chinese Science*, 1946, 103, 59.

Received on June 9, 2017.