

Exploring the Role of α -Dibromoketones in Organic Synthesis, with Emphasis on Heterocyclic Compound Formation

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ABSTRACT

α -Dibromoketones have emerged as versatile synthetic intermediates in organic chemistry, playing a crucial role in the construction of heterocyclic compounds. This review focuses on the application of α -dibromoketones in the synthesis of diverse heterocyclic frameworks and highlights their significance in the development of new methodologies. The introduction provides an overview of α -dibromoketones, their synthesis, and reactivity. The unique electrophilic nature of α -dibromoketones makes them ideal precursors for the formation of diverse heterocycles through nucleophilic addition, cyclization, or condensation reactions. Various synthetic strategies, including intramolecular cyclization, annulation, and multi-component reactions, utilizing α -dibromoketones as key intermediates, are discussed in detail. The synthetic methodologies presented encompass both traditional and modern approaches, highlighting the broad applicability of α -dibromoketones in heterocyclic compound synthesis. The scope and limitations of utilizing α -dibromoketones are addressed, emphasizing the importance of reaction conditions, substrate compatibility, and functional group tolerance. Additionally, the review discusses the mechanistic aspects of key transformations involving α -dibromoketones, shedding light on the intricate processes governing heterocycle formation.

INTRODUCTION

Heterocyclic compounds are ubiquitous in organic chemistry and possess diverse chemical and biological properties. Their synthesis is of great interest to synthetic chemists due to their potential applications in pharmaceuticals, agrochemicals, materials science, and other areas. α -Dibromoketones have emerged as valuable synthetic intermediates in the construction of heterocyclic compounds, offering versatile reactivity and enabling the rapid assembly of complex molecular frameworks.

α -Dibromoketones are α -bromo carbonyl compounds that feature a bromine atom attached to the α -position of a ketone functionality. This unique structural motif imparts distinct reactivity, making α -dibromoketones valuable building blocks for heterocyclic compound synthesis. The

presence of the α -bromo group enhances electrophilicity, rendering α -dibromoketones highly susceptible to nucleophilic attack and subsequent cyclization reactions.

Synthetic methodologies utilizing α -dibromoketones have been developed to access a wide range of heterocyclic systems, including but not limited to pyrroles, pyrazoles, indoles, furans, and thiophenes. The ability to introduce various substituents and functional groups during the synthesis allows for the tailored design of heterocyclic compounds with desired properties.

The strategic importance of α -dibromoketones lies in their ability to undergo diverse transformations leading to heterocyclic compound formation. These reactions can be classified into intramolecular cyclizations, annulations, and multi-component reactions, each providing distinct advantages for the synthesis of specific heterocyclic frameworks. The choice of reaction conditions, reagents, and catalysts plays a crucial role in controlling regioselectivity, stereoselectivity, and overall efficiency. The synthetic potential of α -dibromoketones in heterocyclic compound formation has attracted significant attention in recent years. Both traditional and modern synthetic approaches have been developed, showcasing the broad applicability of α -dibromoketones in organic synthesis. The development of novel methodologies and the exploration of mechanistic insights have further expanded the scope of α -dibromoketones, enabling the construction of complex heterocyclic scaffolds with high efficiency and precision. It discusses the synthetic strategies, reaction mechanisms, scope, limitations, and recent advances in the utilization of α -dibromoketones as versatile synthetic intermediates. By highlighting the importance of α -dibromoketones in the field of heterocyclic compound synthesis, this review aims to inspire further exploration and development in this exciting area of organic chemistry (Phillips, C. et al,1998).

SIGNIFICANCE OF THE STUDY

The significance of the study on the role of α -dibromoketones in organic synthesis, with an emphasis on heterocyclic compound formation, is multi-faceted and impactful in several ways. Heterocycles are essential components in numerous pharmaceuticals, agrochemicals, and functional materials. By understanding and harnessing the synthetic potential of α -dibromoketones, researchers can expedite the synthesis of these valuable compounds, accelerating the development of new drugs and materials the study provides valuable insights into reaction mechanisms and reactivity patterns associated with α -dibromoketones. Understanding the underlying mechanisms of these reactions allows chemists to fine-tune reaction conditions,

improve selectivity, and expand the scope of functional group compatibility. This knowledge contributes to the advancement of synthetic chemistry as a whole and facilitates the design of more efficient and sustainable synthetic routes (Al-juboory et al,2001).

Moreover, the exploration of α -dibromoketones in heterocyclic compound synthesis enables the creation of structurally diverse libraries of compounds. This diversity is crucial in drug discovery, as it allows for the screening of a broad range of compounds with varying activities and properties. It opens up new opportunities for discovering novel therapeutics and addressing unmet medical needs. Additionally, the study contributes to the expansion of synthetic methodologies and the development of new synthetic strategies. By showcasing the potential of α -dibromoketones as versatile building blocks, researchers can inspire further innovation and creativity in the synthesis of complex heterocyclic scaffolds. This expands the toolkit available to synthetic chemists and broadens the range of synthetic possibilities.

METHODOLOGY

SYNTHESIS

The reaction conditions will be standardized on trial basis.

Characterization Techniques:

- 1. Infrared Spectroscopy:** The functional groups of produced substances can be identified using this method. Infrared light interacting with an organic chemical may be used to measure the absorption, emission, and reflection.
- 2. NMR Spectroscopy:** An atom's physical and chemical characteristics can be determined through this sort of analysis. It uses the nuclear magnetic resonance phenomenon and can offer information on the structure, dynamics, reaction state, and chemical environment of molecules. By altering the resonance frequency, the intramolecular magnetic field surrounding an atom in a molecule can provide information about a molecule's electronic structure and its many functional groups.
- 3. Most Commonly:** NMR spectroscopy is employed in the study of organic compounds, although it may also be used to study any sample that has nuclei with spin, such as a

biological sample. NMR spectra of produced substances will be analysed using ^1H and ^{13}C NMR spectroscopy.

- 4. Mass Spectrometry:** Ionization and separation of chemical species by mass-to-charge ratio is accomplished using this method. Mass spectra, to put it another way, are plots that show the distribution of mass in a sample. When it comes to mass spectrometry, it may be used to analyse both pure materials and complicated mixtures.

Elemental Analysis: Organic compounds can be analysed using this method to determine the concentration of various elements. Inorganic compounds are made up of carbon, hydrogen, oxygen, and nitrogen, which are the four most frequent elements. Various polycyclic, nitrogen-containing, heterocyclic, polyhalogen-containing aromatic, including polyfluoroaromatic, organometallic, carbonaceous, etc. polyhalogen-containing aromatic including polyfluoroaromatic, organometallic, carbonaceous, etc. compounds and materials are characterised by their complex elemental composition and structure, a wide range of properties, thermal and acoustic properties, and a variety of thermal and acoustic characteristics. The determination of the compound's elemental composition by means of organic elemental analysis is still a pre-requisite for its accurate identification and purity verification. Its difficulties in the use of conventional and automated methods to determine the presence of carbon, hydrogen, and nitrogen in complex, barely degradable compounds are well-known. Some heterocyclic compounds, such as azide, nitrile, nitrogen, nitro, and nitrene, and amine groups at quantities more than 30% include nitrogen that cannot be completely converted to elemental nitrogen. As a consequence, findings were overestimated in the nitrogen determination. As a result, polyfluorinated substances, such as fluoropolymers, lubricants, fluorine-containing graphites, polyfluorocarbons and more, provide a substantial challenge for researchers. For example, certain fluorinated graphites contain intercalated halogen fluorides such as ClF_3 , ClF_5 , or BrF_3 or alkali fluorides, such as CF_3 or CF_4 . The aggressiveness of fluorine and HF generated during the breakdown process complicates the elemental analysis of these fluorides, leading to corrosion of analytical equipment. Because of their thermal stability and the need to remove fluorine from the combustion zone as an interfering element, many fluorine-containing compounds necessitate more severe breakdown conditions.

Interfering C, H, and N molecules were also absorbed using specific absorption reagents in the

reaction unit of automated elemental analysers. In the examination of compounds combining halogens and sulphur ($\text{Co}_3\text{O}_4 + \text{Ag}$, $\text{SnO}_2 + \text{Ag}$, AgVO_3 , and Ag with Al_2O_3), the combined reagent $3\text{MgO}\cdot\text{Al}_2\text{O}_3$ more strongly absorbs hydrogen fluoride than individual MgO . These chemicals are put either in the extra oxidation zone or in the reduction zone, depending on the temperature at which they are most efficient. In the case of complex multielement hardly degradable organic compounds, oxide additives proposed by the companies producing automated elemental analysers to provide complete decomposition are sometimes insufficiently efficient; therefore, substantial improvements are required, primarily at the step of substance decomposition, in order to get the best results.

LITERATURE REVIEW

Dömling, A. (2006). α,α - Dibromoketones (2) have been found to be a superior alternative to the conventionally used α - bromoketones (1) for performing the Hantzschthiazole synthesis.¹ These crystalline, nonlachrymatory compounds are more reactive than 1 as demonstrated by their reaction with 3,5- dimethyl- 1- thiocarboxamide (5).

Chebanov, V. A., et al (2005) The photochemical formation of oxetanes from different heterocycles have been investigated for many years in this laboratory. Thus far, only correlation between quenching effect of the heterocycles and capability of forming oxetanes have been established but no attempts have been made to elucidate from these data the different mechanistic pathways that lead from starting materials to product in various cases. In the light of kinetic as well as ionization potential information an attempt is made in this review to establish the mechanisms involved in these reactions. By means of the studies of the Stern-Volmer plots, the quenching constants of the reaction of Paternò-Büchi between substituted thiophene and selenophene with aromatic ketones and their relationship with the potentials of ionization of these heterocycles we can infer in the efficient synthesis of oxetanes.

Jasinski, M.(2007) A number of new synthetic methods are reviewed. Most of the methods are based on aluminum, boron, tin, silver Lewis acids and/ or Brønsted acid catalysts. Concepts of combined acid catalysis and super Brønsted acid catalysis are also summarized. These methods are useful for selective organic transformations including simple natural product synthesis. Although I am not a good Japanese chess (Shogi) player, I admire one famous professional player,

the late Kozo Masuda (1918–1991), the most gifted Shogi player of his era. He became a professional Shogi player while in his youth. After years of practice and dedication, he quickly climbed the ranks of the best and became the champion in 1957. His popularity did not derive from being an undefeatable champion; rather what was so special about his game was that he invented completely novel strategies and tactics in his matches. I was amazed by this and indeed I am sure it was not a simple task. Famous professional Shogi players today make use of the same conservative strategies in their games.

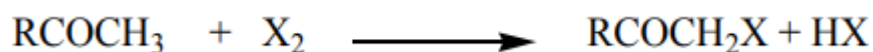
Ingle R.G. (2011) The present review article is concerned about the heterocyclic chemistry of benzimidazole synthesis and reactions with nucleophilic reagent, arynes and free radicals, oxidation; reduction in the review article emphasis is given on potential biological activities of benzimidazole derivatives. These exhibit many biological activities like antiulcer, antihelmintic, antipsychotic, antiprotozoal, antifungal. etc. Benzimidazole is important lead owing to its inherent properties and therapeutic action. Heterocyclic compounds are those cyclic compounds whose ring contain besides, carbon, one or more atoms of other elements. The non-carbon atoms such rings are referred to as hetero atoms. The most common hetero atoms are nitrogen, sulphur and oxygen. The heterocyclic compounds having lesser common atoms such phosphorus, tin, boron, silicon, bromine, etc. have been a subject of much investigation in recent years.

SYNTHESIS OF α -HALOKETONES

A well-written review by De Kimpe and Verhé described in detail the synthesis of α -halogenated ketones. We will list here the indications of new methods in addition to other common methods of operation.

GENERAL METHODS

Typically, the reaction of halogen-containing aliphatic ketones usually produces haloketones that are concentrated with certain side effects (Eq 1).



Direct fluorination, through F₂, usually triggers a separate reaction that leads to polyfluorinated and degraded products and consequently limited use. However, a number of reviews have been

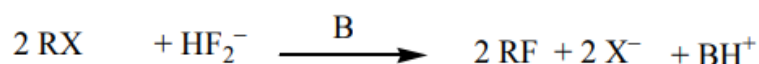
published by Erian and others regarding the preparation of α -fluoroketones.

During the monochlorination of acetone, small amounts of dichloroacetone remain isolated. However, the positive effects of monochlorination of acetone and high ketones are possible when exposure is made with an aqueous solution of calcium carbonate.

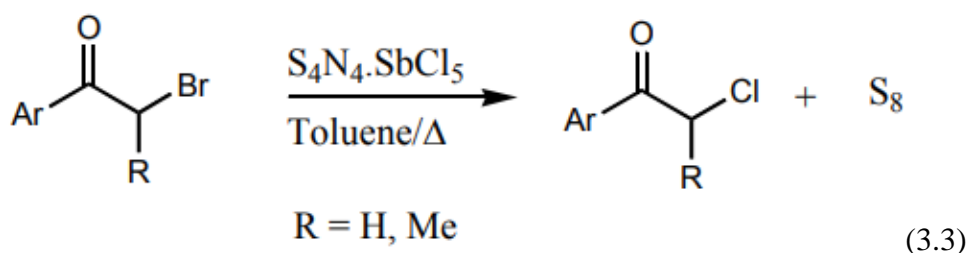
Bromine of ketones with bromine is a reversible process. In order to eliminate the balance in bromoketones, preparations should be continued with the removal of hydrogen bromide.

MISCELLANEOUS HALOGENATING AGENTS

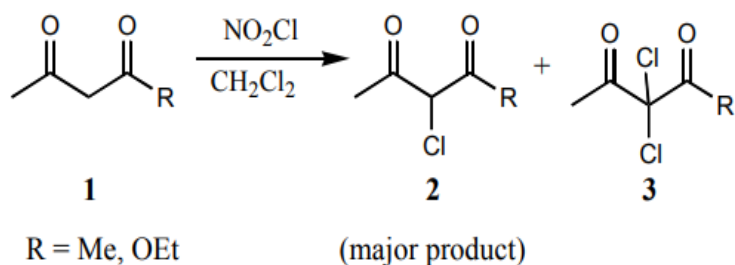
Nucleophilic fluorination of alkyl iodides, bromides and α -bromo- or α -chloroketones is effectively affected by tetrabutylammonium hydrogen difluoride in the presence of a catalytic amount of pyridine, dioxane, providing a good yield of fluorinated compound.



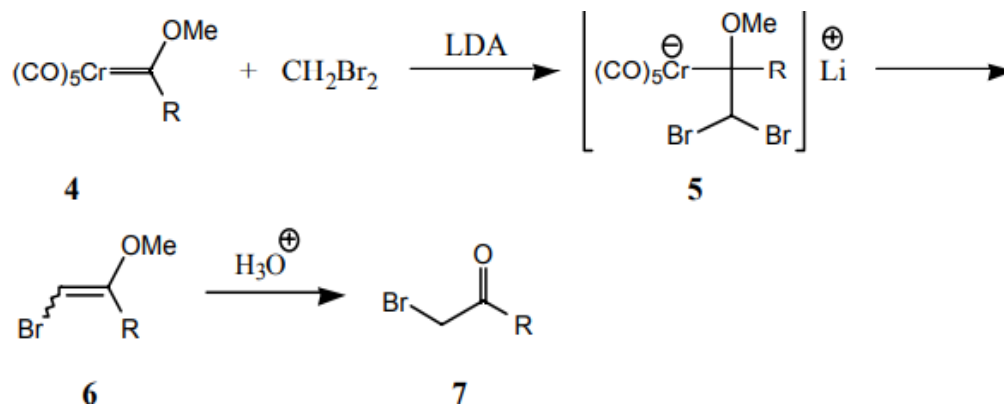
The reaction of α -bromoalkyl and arylketones inhibited by tetrasulfurtetranitride-antimony pentachloride complex ($\text{S}_4\text{N}_4\text{SbCl}_5$) in toluene to reflux provides α -chloroketones corresponding.



The reaction of 1,3-dicarbonyl compounds 1 with nitryl chloride induced the formation of α -chloro compounds with α , α -dichloro derivatives 2 and 3 by replacing the activated methylene group.

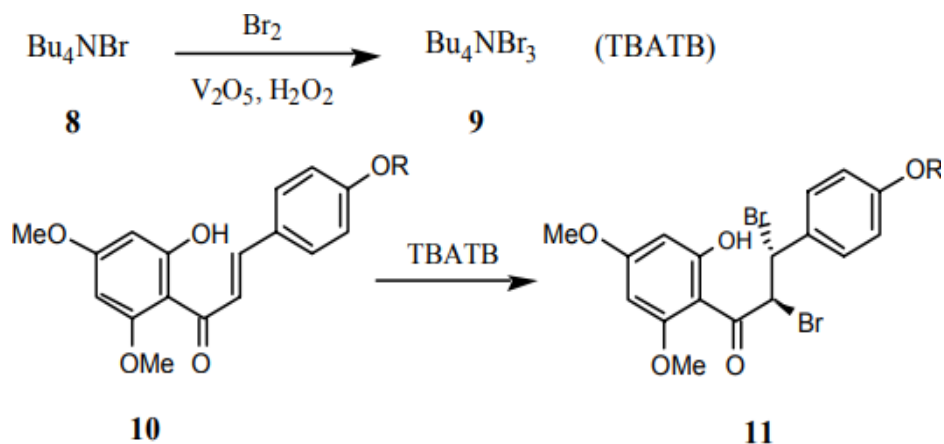


Fischer-type carbene complexes react with intermediate 5 and bromoenoether 6 and with the latest acid hydrolysis to purchase bromomethyl ketones 7.



R = Ar, 2-furyl, β -naphthyl, cyclopropyl

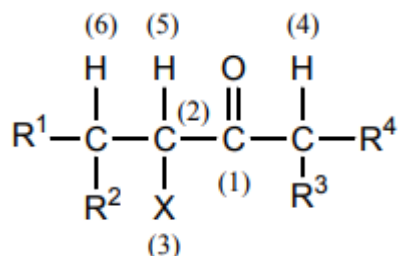
Tetrabutylammoniumtribromide (TBATB) (9), an agent that produces natural brominating, absorbs biodiversity easily under mild conditions. It is also useful as a selective agent for inhibiting α , β -unsaturated ketones, cf. 11 adjustments from 10.



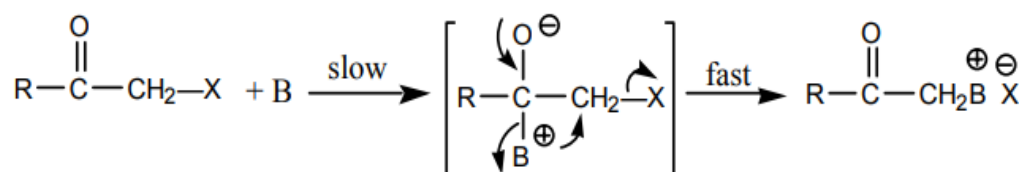
CHEMICAL REACTIVITY

In the treatment of α -haloketone with a variety of nucleophile, the attack is possible in six potentially electrophilic areas: the nucleophile is able to attack the carbonyl activity carbon (position 1), the carbon atom holding the halogen atom (zone 2) and halogen atom (location 3). Additionally, due to the presence of two electron-polar retraction groups, hydrogen atoms in α -

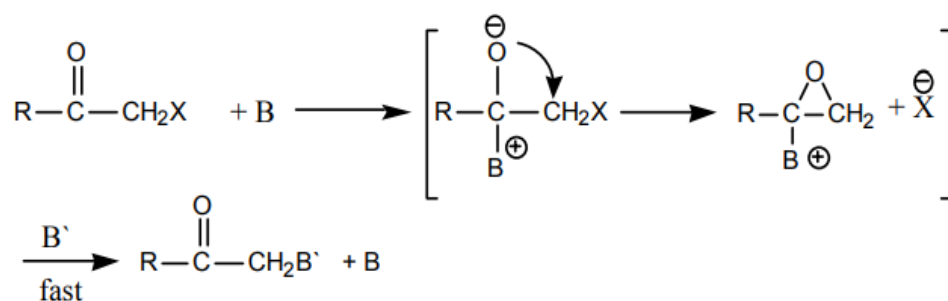
α' - and β -positions are also at risk of being attacked by nucleophiles or bases (positions 4, 5, and 6).



The interaction between the carbonyl and nucleophile group is primarily electrostatic and the reactivation of $\text{S}_{\text{N}}2$ is due to the polarization interaction caused by the low steric requirement of RCO compared to RCH_2



Separation of stable epoxides in response to α -haloketone-containing sodium methoxide and evidence that these active intermediate epoxides lead to other products provides further explanation for Pearson and others.



It is noteworthy that the reactivation of α -haloketones is due to the inductive effect of the carbonyl group which enhances the polarity of the carbon-halogen bond by increasing the electron deficiency in the α -carbon atom. Also, the brighter the $\text{C}\ddot{\text{X}}$ bond, the faster the nucleophile reaction. The data shown in Table 1 summarize the enhanced reactivation of α -halogenated ketones in relation to the corresponding alkyl halide in response to bimolecular nucleophilic changes.

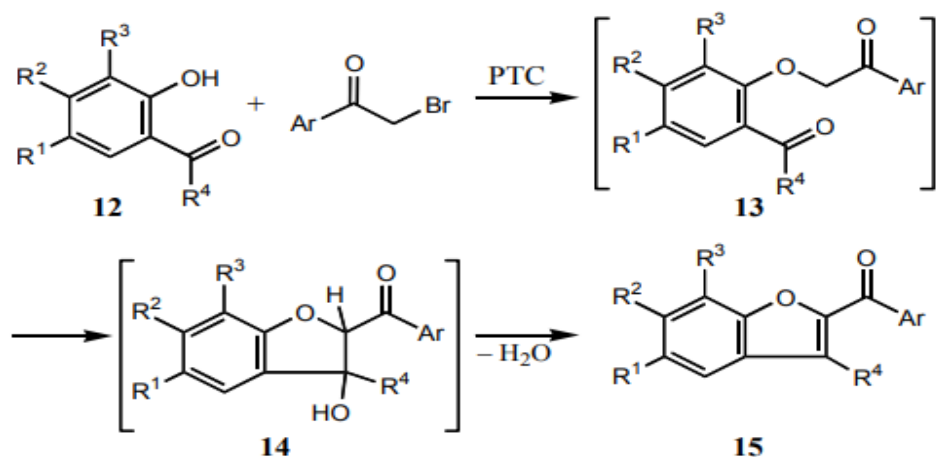
Table 1. Reactivity Relative to that of C₃H₇X of α -Halocarbonyl Compounds in Nucleophilic Substitutions

Reaction	<i>n</i> -C ₃ H ₇ X	PhCH ₂ X	CH ₃ COCH ₂ X	PhCOCH ₂ X
R-Cl + KI/acetone	1	197	35700	105000
R-Cl + S ₂ O ₃ ²⁻ /H ₂ O	1	—	1400	1600
R-Cl + ⁻ OAc/MeOH	1	—	198	228
R-Br + pyridine/MeOH	1	286	208	406
R-Br + thiourea/MeOH	1	300	—	10700
R-Cl + ⁻ SCN/MeOH	1	—	401	770

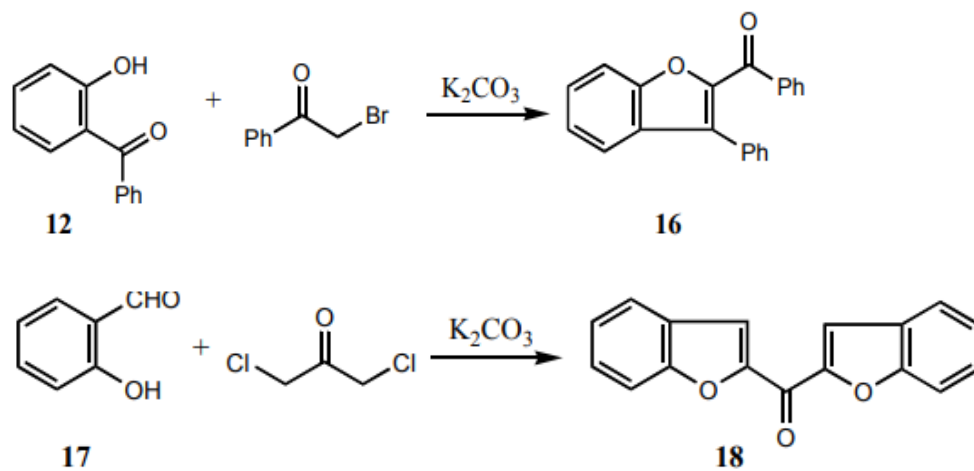
Reaction of α -Haloketones with Oxygen, Nitrogen and Sulfur Nucleophiles

The reactions of α -haloketones containing oxygen, nitrogen and sulfur nucleophiles are differentiated into one phase due to the large number of references. We classified this large amount of data in the form of built-in heterocycles, starting with rings of five and six members respectively of a growing number of heteroatoms. Such systematic treatment provides a clear idea of the possibilities for the procedure and may be helpful in choosing the direction of further research.

A. Fusion of Five-Ring Rings with One Heteroatom 1. Furan and Combined Outflow Concentration of *o*-hydroxyacetophenone 12 by phenacyl bromides under PTC (phase transfer catalysis) conditions in a two-phase system, using liquid K₂CO₃ (20)) as a base, dichloromethane or benzene as a solvent and tetrabutylammonium hydrogen sulfate as a phase transfer catalyst, supplied with 2-arylbenzofurans 15 with good yield and high purity as well.



The reaction of α -halo ketones with o-hydroxycarbonyl compounds gave the benzofuran a variety instead. Benzofuran compounds 16 and 18 were produced by cyclocondensation of α -halo ketones and o-hydroxybenzophenone and salicylaldehyde, respectively.



Difurano [2,3-a: 2', 3'-f] naphthalenes 21 is easily synthesized in two steps first with 1,5-dihydroxynaphthalene.

α -AMINO CARBONYL COMPOUNDS FOR THE SYNTHESIS OF AROMATIC THIOCYANATES

As a key structural unit, the α -amino carbonyl fragment is present in many natural products and chemical compounds, and is a flexible precursor for the synthesis of various heterocyclic

compounds. Glycine, a simple compound of α -amino carbonyl, is one of the most important amino acids in the human body. In addition, amoxicillin and clopidogrel demonstrate the therapeutic use of α -amino carbonyl compounds and provide resistance to certain diseases. α -Amino carbonyl compounds are involved in many reactions, the most important of which are the reaction of nucleophiles, which include alcohol, thiols, amines, phosphites, nitromethane, ketones, 1,3-dicarbonyl compounds, (hetero) arenes, and others.

To our best knowledge, there are no reports of thiocyanation of α -amino carbonyl compounds. Organic thiocyanates are well-known in the area of organosulfur chemistry and have become a hot field of biomass research, as they are not just substrates or building blocks of natural bioactive products but also flexible synthetic precursors for sulfur-containing compounds. such as thiols, thioethers, and disulfides. Therefore, it is appropriate to develop a simple and effective method of achieving thiocyanation of α -amino carbonyl compounds for the synthesis of organic thiocyanates

CONCLUSION

In conclusion, the exploration of the role of α -dibromoketones in organic synthesis, with an emphasis on heterocyclic compound formation, has demonstrated their significant value as versatile intermediates in the construction of diverse heterocyclic frameworks. Through this study, several key findings and insights have emerged. The study has highlighted the unique reactivity of α -dibromoketones, stemming from the electrophilic nature of the α -bromo carbonyl functionality. This reactivity allows for various synthetic strategies, including intramolecular cyclizations, annulations, and multi-component reactions, leading to the efficient formation of heterocyclic compounds. The synthetic methodologies developed using α -dibromoketones have provided rapid access to a wide range of heterocyclic systems, including pyrroles, pyrazoles, indoles, furans, and thiophenes. These methodologies offer flexibility in introducing functional groups and substituents, enabling the design and synthesis of tailor-made heterocyclic compounds with desired properties. The mechanistic understanding gained from studying α -dibromoketone-based reactions has provided valuable insights into the reaction pathways and factors influencing regioselectivity and stereoselectivity. This knowledge aids in the rational design of synthetic routes and the development of catalysts, enhancing control over reaction outcomes and enabling further optimization.

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