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Review

THE METHODS OF SYNTHESIS OF 2-AMINOBENZOPHENONES — KEY PRECURSORS OF 1,4-BENZODIAZEPINES

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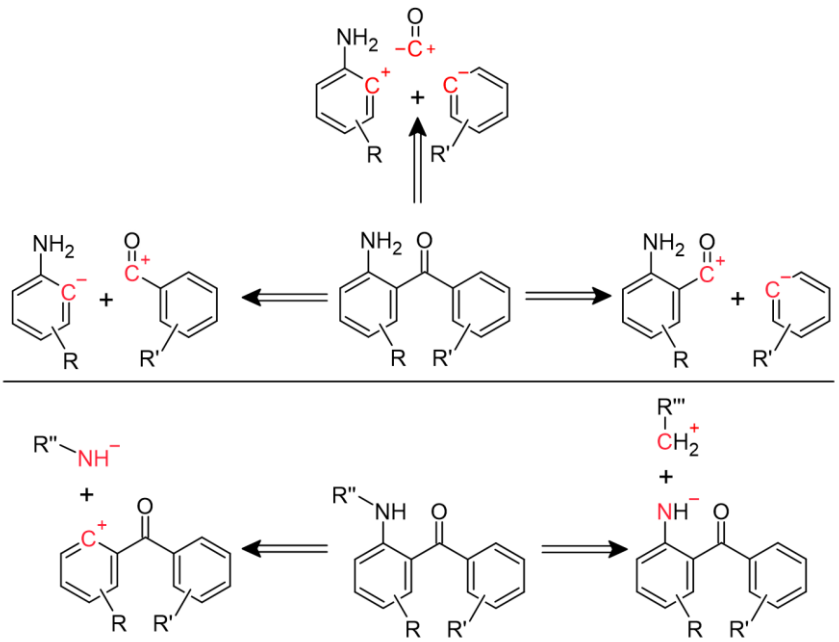
ABSTRACT

The review article briefly presents the pharmacological profile and mechanism of action of 1,4-dibenzodiazepines, and the structures of the most important drugs from this class of compounds. The strongest emphasis is placed on presentation of various methods for the synthesis of 2-aminobenzophenones — the most often used precursors in the synthesis of 1,4-benzodiazepines and numerous classes of azaarenes. The reactions or their sequences were grouped according to retrosynthetic strategies based on structural similarities and differences of the reagents used. There were presented not only the most classical methods like Friedel-Crafts acylation or Grignard reaction, but also more advanced transformations utilizing various catalysts and more sophisticated approaches involving the synthesis of heterocyclic systems followed by their reductive or oxidative cleavage. Selected nuances of the presented reactions were discussed, including fragments of mechanisms, limitations of the applicability of a given method, and the advantages of modern solutions over the oldest and more classical methods.

GRAPHICAL ABSTRACT



KEYWORDS: 2-aminobenzophenones, 1,4-benzodiazepines, drug synthesis, organic synthesis, disconnection approach.

1. Introduction

The first benzodiazepine derivative with an anxiolytic effect was chlordiazepoxide discovered in the 1950s by Sternbach [1]. Despite 70 years of their history, according to the World Health Organization (WHO), benzodiazepines are still among the most commonly prescribed medications [2].

The following article only briefly presents the mechanism of action of 1,4-dibenzodiazepines and the structures of the most important drugs from this class.

The main goal of this review is to present and systematize various methods, presented in the original articles, for the synthesis of 2-aminobenzophenones — the most often used precursors in the synthesis of 1,4-benzodiazepines. The reactions or their sequences were grouped according to retrosynthetic strategies based on structural similarities and differences of the reagents used.

2. 1,4-Benzodiazepines

2.1. Pharmacological profile and mechanism of action

The 1,4-benzodiazepine derivatives act on the central nervous system. They are used as psychotropic drugs, especially with anxiolytic, sedative and hypnotic, anticonvulsant and antiepileptic properties [3].

The action of benzodiazepines is related to the intensification of the inhibitory functions of GABAergic neurons. Specific binding sites for benzodiazepines have been identified within $GABA_A$ receptors distributed throughout the central nervous system, occurring mainly in the frontal and occipital cortex, hippocampus and cerebellum. Drugs from this group act as agonists at the binding sites. As a result of the interaction of benzodiazepines with the target, the affinity of γ-aminobutyric acid for the appropriate binding site, which is part of the chloride channel, increases. As a result of allosteric interaction, benzodiazepines increase the binding strength of GABA and therefore also increase the potency of γ-aminobutyric acid. This results in an increased likelihood of the chloride channel opening, allowing more chloride ions to flow into the cell. This leads to hyperpolarization of appropriate cells, with a subsequent decrease in their excitability [4].

2.2. Structures

Basically, the only invariable part of the structure of drugs based on diazepines is a seven-membered ring (B) with two nitrogen atoms arranged in positions 1,4 (less commonly 1,2) (Fig 1).

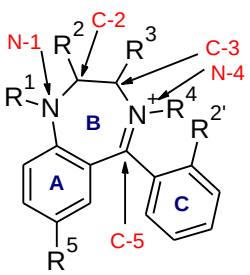


Fig 1. The structure of drugs based on diazepines.

There is attached an aromatic ring (A) — most often a benzene ring, usually containing an additional substituent R^5 — to the 1,4-diazepine system (B) in the [*d*] position. However, there are also known heteroaromatic derivatives in which e.g. thiophene, pyrazole, pyrrole or pyridine system is present. Carbon C-5 most often forms a bond with the second aromatic system (C) — usually a derivative of benzene, often containing substituents ($R^{2'}$) in the *ortho* position. Nevertheless, there are also examples of biologically active derivatives containing pyridine or even non-aromatic groups: piperazine or cyclohexene. The N-1 nitrogen atom is sometimes bearing various alkyl groups. There are also derivatives with an imidazole system attached in the 1,2 position or triazole. Among the other modifications there are also known derivatives in which the imine group at C-5 — N-4 has been modified. In such a case, the C-N bond is a substructure of an additional five or six-membered cyclic ether. Another common modification is the oxidation of nitrogen N-4 to form *N*-oxide.

Each structural modification is most often applied to enhance a specific activity and extend or shorten the duration of action of the active substance [3].

Selected examples of the most commonly used benzodiazepines [5, 6] are summarized in Table 1.

3. The application of 2-aminobenzophenones in organic synthesis

2-Aminobenzophenones (Fig 2) are the most typical precursors used not only in the synthesis of 1,4-benzodiazepines, but also in the preparation of: fluorenone, acridine, acridone, cinnoline, quinazoline, indazole, quinoline and 3-phenylindole derivatives [7].

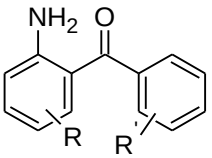
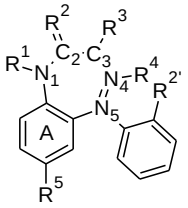


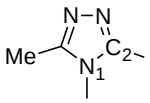
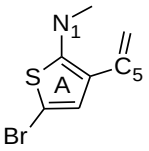
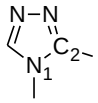
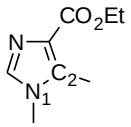
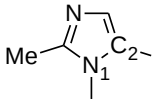
Fig 2. Structure of 2-aminobenzophenones.

Nevertheless, due to the thematic scope of the article, special attention was paid to derivatives of 2-aminobenzophenones used in the synthesis of both 1,4-benzodiazepine preparations already introduced to the market as well as many derivatives still in various stages of research and testing. Methods for synthesizing derivatives in which one or both benzene rings have been replaced by heterocyclic compounds were omitted, due to the fact that there are usually used different, specific reactions to obtain these systems

Table 2. contains derivatives of 2-aminobenzophenones that can be used to synthesize 1,4-benzodiazepines which have biological activity, listed in the appropriate table cells [5, 8].

Table 1. Selected examples of the most commonly used benzodiazepines.



Benzodiazepine	**-R^1**	**-R^2**	**-R^3**	**-R^4**	**-R^5**	**-R$^{2'}$**
Alprazolam			-H	-:	-Cl	-H
Brotizolam			-H	-:		-Cl
Triazolam			-H	-:	-Cl	-Cl
Chlordiazepoxide	-N_1=C_2(NHMe)-		-H	-O	-Cl	-H
Clobazam	-Me	=O	-H	=O*	-Cl	-H
Clonazepam	-H	=O	-H	-:	-NO_2	-Cl
Clorazepate	-H	=O	-CO_2^-	-:	-Cl	-H
Demoxepam	-H	=O	-H	-O	-Cl	-H
Diazepam	-Me	=O	-H	-:	-Cl	-H
Estazolam			-H	-:	-Cl	-H
Flumazenil			-H	-Me**	-F	=O***
Flurazepam	-$CH_2CH_2N(Et)_2$	=O	-H	-:	-Cl	-F
Lorazepam	-H	=O	-OH	-:	-Cl	-Cl
Midazolam			-H	-:	-Cl	-F
Nitrazepam	-H	=O	-H	-:	-NO_2	-H
Nordazepam	-H	=O	-H	-:	-Cl	-H
Oxazepam	-H	=O	-OH	-:	-Cl	-H
Prazepam		=O	-H	-:	-Cl	-H
Quazepam	-CH_2CF_3	=S	-H	-:	-Cl	-F
Temazepam	-Me	=O	-OH	-:	-Cl	-H

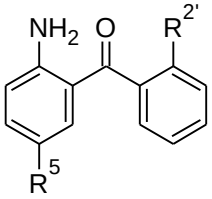
the symbol "-:" indicates the lack of a substituent and the presence of a lone pair of electrons

* at the position 4 - carbon; 5 – nitrogen

** single bond between the positions 4 and 5

***at position C-5

Table 2. The derivatives of 2-aminobenzophenones that can be used to synthesize 1,4-benzodiazepines with biological activity



-R^5	-$R^{2'}$			
	-H	-F	-Cl	-Br
-H	Devazepid	Trifluadom		
-F				Imidazenil
-Cl	Oxazepam Chlordiazepoxide Diazepam Prazepam Halazepam Temazepam Medazepam Clorazepate Ketazolam Oxazolam Alprazolam Estazolam Camazepam Cerburazepam Clorazepate Cyprazepam Demoxepam Fosazepam Iclazepam Privoxazepam Sulazepam Temazepam Nordazepam Adinazolam	Flurazepam Midazolam Cinolazepam Doxefazepam Elfazepam Ethyl Calfruzepate Ethyl Lofiazepate Fletazepam Fludiazepam Flutemazepam Flutroprazepam Proflazepam Quazepam Flutazolam	Delorazepam Lormetazepam Triazolam Ethyl Dirazepate Reclazepam Tolufazepam Tuclazepam Uldazepam Climazolam Cloxazolam Ro5-4864*	
-Br	Gidazepam	Flubromazolam Halaxazolam	Phenazepam Metaclazepam Mexazolam	
-NO_2	Motrazepam Nimetazepam Nitrazepam	Flunitrazepam	Meclonazepam Laprazolam Clonazepam	
-CF_3	Triflunordazepam			
-C≡CH	QH-II-66			

*chlorine in the position 4' instead of 2'

4. Methods for the synthesis of 2-aminobenzophenones

The general formula of 2-mono-alkyl-amino-benzophenones is shown below (Fig.3).

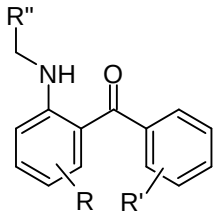


Fig 3. General formula of 2-mono-alkyl-amino-benzophenones.

Due to the fact that *N*-monoalkyl derivatives of aminobenzophenones are also often used in the synthesis of 1,4-benzodiazepines, and some of the methods presented in this chapter can also be successfully applied in their preparation, the issue has been extended.

The methods were grouped according to the rules of retrosynthetic analysis (Fig 4, 8, 15, 18, 20). Disconnections were carried out, resulting in the generation of actual or only potential chemical entities — synthons.

Donor synthons (d) have a negative charge, while acceptor synthons (a) have a positive charge. If they do not incorporate a functional group (or it is not strategic), they are marked with appropriate symbols, e.g. a^{alk} (alkylating), d^{Ar} (arylating). In the case of the presence of strategic functional groups (e.g. amino- or carbonyl-group), synthons are marked as a^n / d^n, where n means that the synthon incorporates a strategic functional group located on the n^{th} carbon atom in relation to the new bond formed [9].

4.1. Disconnection d^2 - a^1

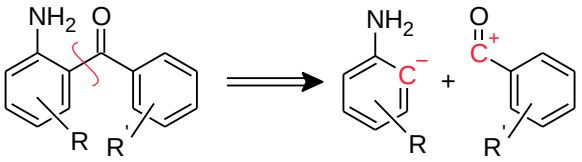


Fig 4. Disconnection d^2 - a^1.

4.1.1. Friedel-Crafts acylation

This reaction is mainly applied in the case of using *para*-substituted aniline derivatives [10]. However, this seemingly simple transformation is inherently complicated by the initial reaction of aroyl chloride with the amino group and the formation of an amide, which only then takes part in the actual aromatic electrophilic substitution reaction (Fig 5). What is more, as a result of subsequent condensation reactions, complex bicyclic systems are formed, which have to be hydrolyzed to release a product [7].

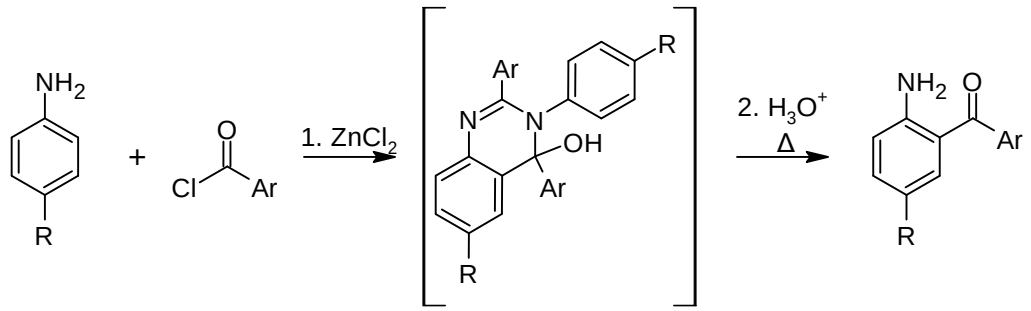


Fig 5. Friedel-Crafts acylation.

Although side reactions significantly reduce the overall yield, due to the availability and low price of appropriate amines and benzoic acids, used for the preparation of benzoyl chlorides, the Friedel-Crafts transformation is widely used.

Sometimes the reaction is even carried out with *meta*-substituted aniline derivatives. Even though in the example below the yield of the *ortho*-arylation product is only 6%, compared to 46% for the para isomer (Fig 6), this method is used due to the low cost of substrates and simplicity of synthesis [10].

The example (Fig 6) also illustrates the possibility of protecting the amino group by introducing an acetyl group [10], which helps avoid side condensation reactions. An alternative method involves converting aniline into a sulfonamide obtained in reaction with *p*-toluenesulfonyl chloride [11]. Due to two additional stages (introduction and removal of protection group), it is not always worth using them.

The presented reaction sequence also shows the usefulness of the electrophilic bromination reaction, which allows the introduction of a bromine atom into the aniline ring after the Friedel-Crafts reaction, using an amide moiety that reduces the nucleophilicity of the ring, thus limiting the possibility of di-bromination.

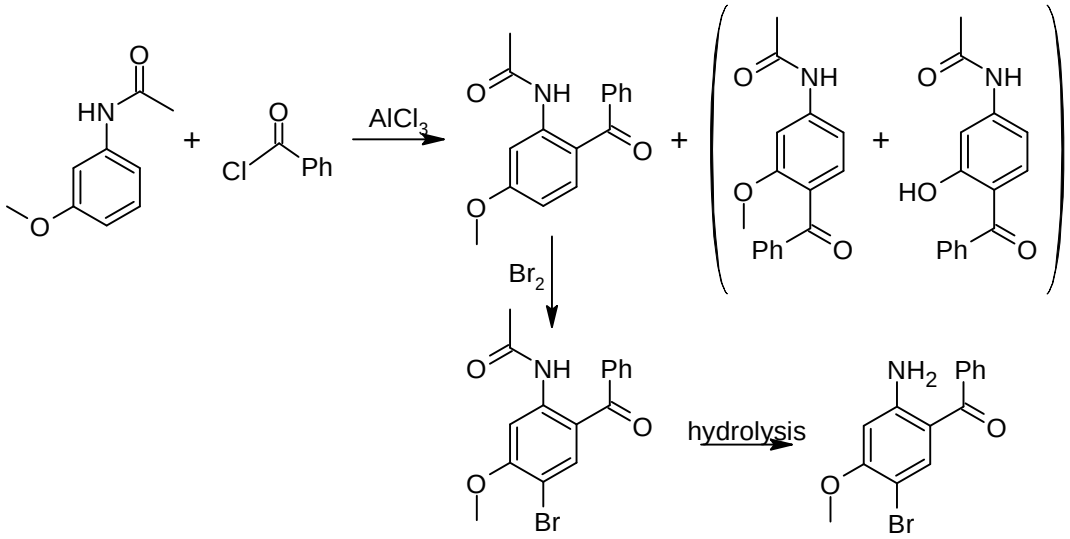


Fig 6. Friedel-Crafts and mono-bromination.

4.1.2. Sugasawa reaction

High regioselectivity towards the *ortho* position can be obtained by the Sugasawa reaction. The success of the transformation is related to the use of boron chloride, which is the coordination center for the electron pairs of nitrogen atoms from the amino and nitrile groups (Fig 6).

This mutual positioning favors obtaining the acylation product in the *ortho* position of the aniline ring, after hydrolysis of the resulting imine [7, 12]. The advantage of this method is also the possibility of obtaining nitro-derivatives.

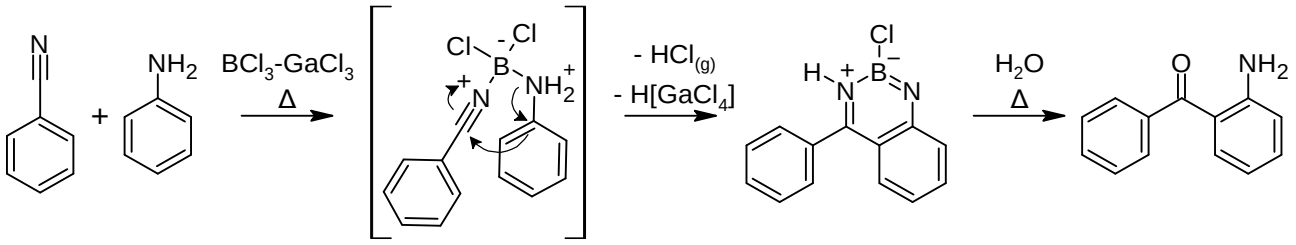


Fig 6. Sugasawa reaction.

4.1.3. *Ortho*-lithiation

The use of two equivalents of butyllithium allows for obtaining an *ortho*-metalized intermediate. It is stable due to the interaction of the electron pair of the highly nucleophilic, deprotonated amino group, which forms a complex with the lithium cation.

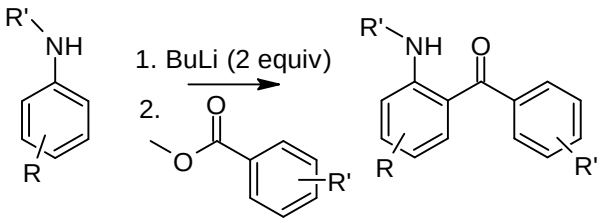


Fig 7. *Ortho*-lithiation.

Due to the steric bulk resulting from the presence of two aryl groups and the electronic effect of the negatively charged amino group conjugated to the carbonyl group, the resulting ketone does not react with the second equivalent of the organolithium compound. After lithiation aqueous workup, the corresponding 2-aminobenzophenone is formed (Fig 7) [13, 14].

Methods using very active lithium- and organo-magnesium compounds cannot be used if the substrates contain nitro functions that react under such conditions.

4.2. Disconnection d^{Ar} - $a^{1,3}$

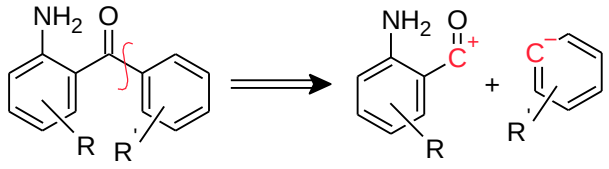


Fig 8. Disconnection d^{Ar} - $a^{1,3}$.

4.2.1. Grignard reaction

The use of organomagnesium compounds allows the desired reaction to be carried out with appropriate nitriles (Fig. 9) or aroyl halides.

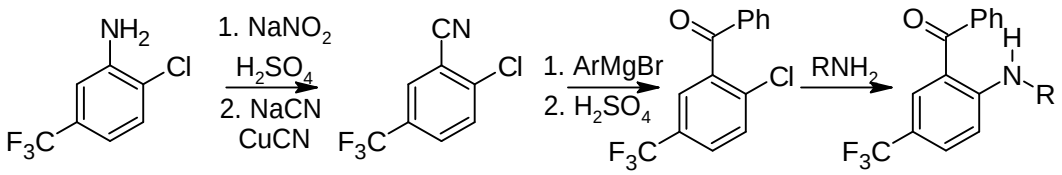


Fig 9. The sequence of Sandmeyer – Grignard – addition-elimination reactions.

The presented example also shows the possibility of using the Sandmeyer reaction, that enables to obtain appropriate benzonitriles easily. Acid chlorides are less frequently used as electrophilic reagents, due to the possibility of formation of carbinols.

The presence of an amino group in the molecule introduced into the reaction with the Grignard compound significantly complicates the transformation process. One equivalent of the organometallic compound is used for the initial deprotonation of the amine function, and the reinforced conjugation of its lone pair of electrons with the carbonyl group significantly reduces the electrophilicity of the substrate [15]. Therefore, in the example shown, the amine function was incorporated in the next step.

4.2.2. Lothrop-Goodwin method

In this method [10], unlike the previous one, the amine function may be present in the molecule being reacted with the organometallic compound. However, in this case it must be pre-protected by converting anthranilic acid into benzoxazinone. As a result of opening the heterocyclic compound, a deprotonated amide group is released. However, in this case, the conjugation of the amide group with the carbonyl group in the resulting negatively charged intermediate is beneficial due to the limitation of further transformations leading to carbinols (Fig 10).

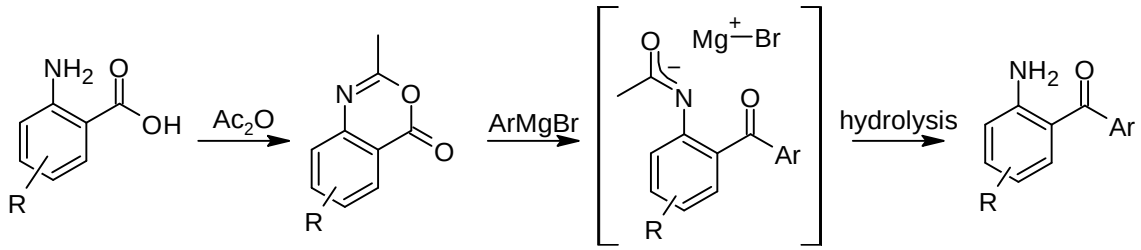


Fig 10. Lothrop-Goodwin method.

4.2.3. Weinreb ketone synthesis

In this approach, the first step is ring opening of commercially available isatoic anhydride or its previously synthesized derivative [16] using *N*-methoxy-*N*-methylamine [17, 18]. As a result of the addition of an organolithium compound, an adduct (stable chelate) is formed, which, after hydrolysis, decomposes into a carbonyl compound (Fig 11). The use of this method excludes the formation of carbinols.

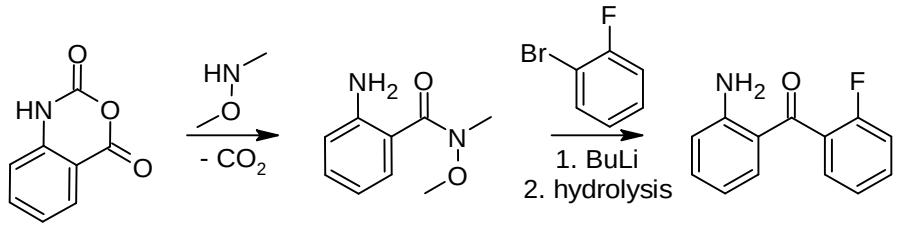


Fig 11. Weinreb ketone synthesis.

4.2.4. Addition of boronic acids to nitriles

The advantage of this method is the replacement of very active organometallic compounds with much milder substitutes — boronic acids (Fig 12), tolerated by a wider range of substituents. Unfortunately, the conjugation of the lone pair of electrons of the amino group with the nitrile group weakens the electrophilic nature of the sp-hybridized carbon, what makes the reaction yields moderate [19].

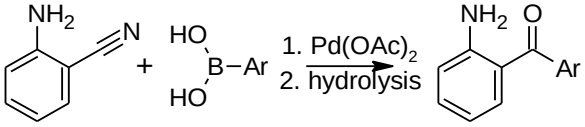


Fig 12. Addition of boronic acids to nitriles.

4.2.5. Hoesch reaction

In the classic case, to carry out the acylation reaction with the nitrilium cation, it is necessary to use very active aromatic compounds, such as polyhydroxybenzenes [20]. However, when using *orto*-cyanoaniline derivatives, it is possible to even take advantage of the presence of the amino group to carry out the reaction even with inactive partners such as chlorobenzene. For this purpose, the capabilities of strongly acidic agents — superacids — can be used (Fig 13). It allows the amino group to be protonated, transforming it into a group with a very strong inductive effect and simultaneously eliminates the coupling between the electron pair of nitrogen and the nitrile group, what destabilizes the nitrilium cation generated in the same molecule, and thus significantly increases its electrophilicity and activity [21].

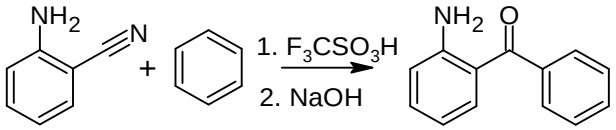


Fig 13. Hoesch reaction utilizing superacid.

A similar phenomenon is used to modify the Friedel-Crafts reaction (Fig. 14) by generating a highly active acyl cation from anthranilic acid using polyphosphoric acid [22].

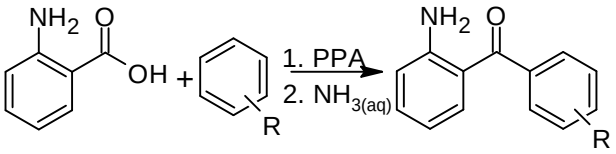


Fig 14. Friedel-Crafts reaction utilizing polyphosphoric acid.

4.3. Disconnection d^2 - a^1

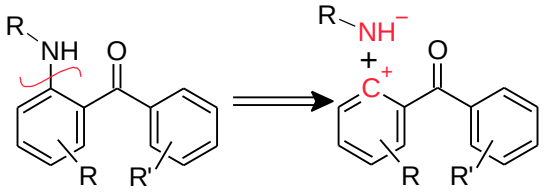


Fig 15. Disconnection d^2 - a^{1d}.

4.3.1. Addition-elimination reaction

The sequence of addition and elimination reactions allows the incorporation of amino groups into benzophenones [15]. The reaction proceeds particularly easily in the presence of an additional electron withdrawing group located in the *para* position relative to the halogen (Fig 16).

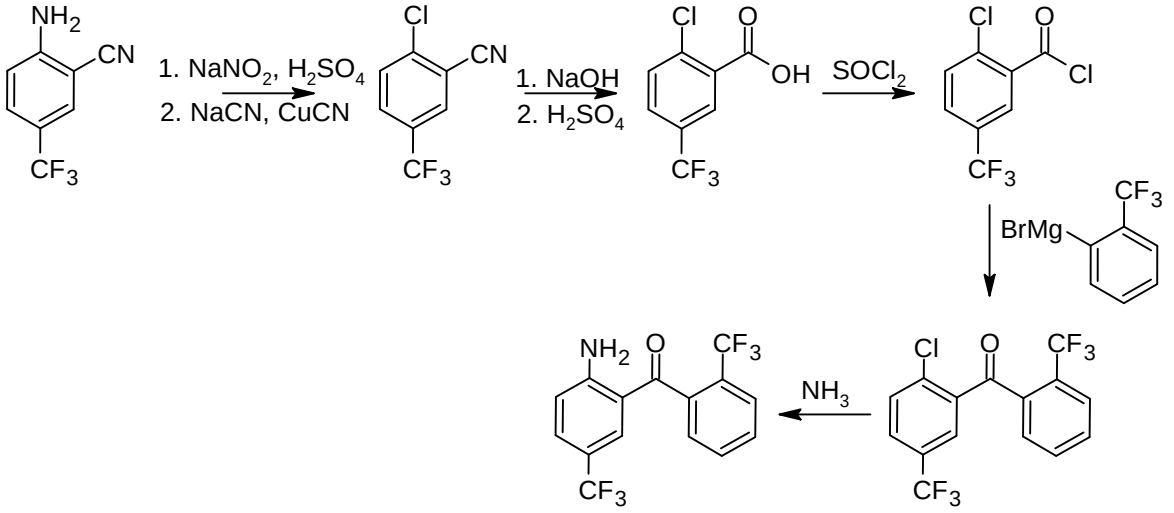


Fig 16. Addition-elimination reaction facilitated by the presence of trifluoromethyl group.

4.3.2. Transition-metal-catalyzed halogen substitution in aryl halides

The process (Fig. 17) involves the oxidative insertion of a metal into a carbon-halogen bond (oxidative-addition), the exchange of the ligand (halogen anion) with a nucleophile — an amino group, and the reductive-elimination with the formation of a new carbon-nitrogen bond [23].

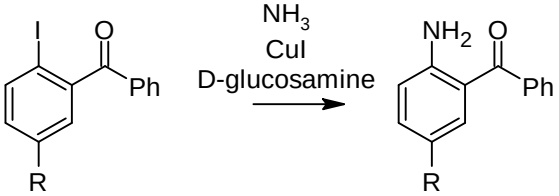


Fig 17. Transition-metal-catalyzed iodine substitution.

4.4. Disconnection a^2 - d^1/a^1 - d^{Ar}

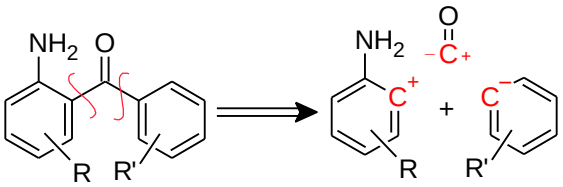


Fig 18. Disconnection a^2 - d^1/a^1 - d^{Ar}.

4.4.1. Suzuki reaction

The three-component Suzuki reaction (Fig. 19) catalyzed by palladium complexes involves the coupling of o-iodoaniline with carbon monoxide and phenylboronic acid [24, 25].

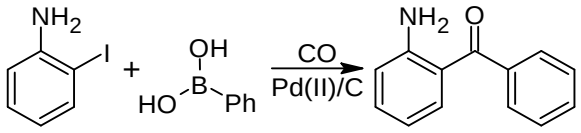


Fig 19. Three-component Suzuki coupling.

4.5. Disconnection d^0 - a^{alk}

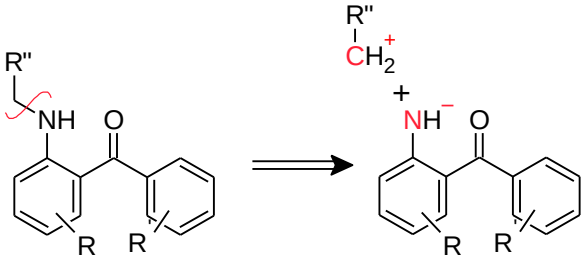


Fig 20. Disconnection d^0 - a^{alk}.

4.5.1. Monoalkylation of 2-aminobenzophenones

In order to enable selective *N*-alkylation, 2-aminobenzophenones are converted into sulfonamides (Fig 21). The introduction of *p*-toluenesulfonyl group not only facilitates deprotonation of NH moiety but also prevents from polyalkylation. Hydrolysis — deprotection of the tosyl group leads to the formation of secondary amines that are substrates in the synthesis of numerous 1,4-benzodiazepines [10].

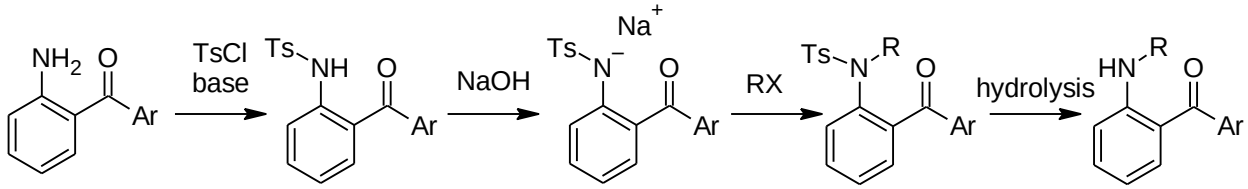


Fig 21. Monoalkylation of 2-aminobenzophenones utilizing *p*-toluenosulfonyl auxiliary group.

4.6. Methods involving the cleavage of heterocyclic systems

4.6.1. Oxidative cleavage

This method involves the use of ozonolysis of appropriately decorated indole derivatives that can be easily obtained using Fischer indole synthesis, based on the pericyclic rearrangement of phenylhydrazone (Fig 22). Despite the complexity of the sequence of reactions, the overall yield is around 60% [10].

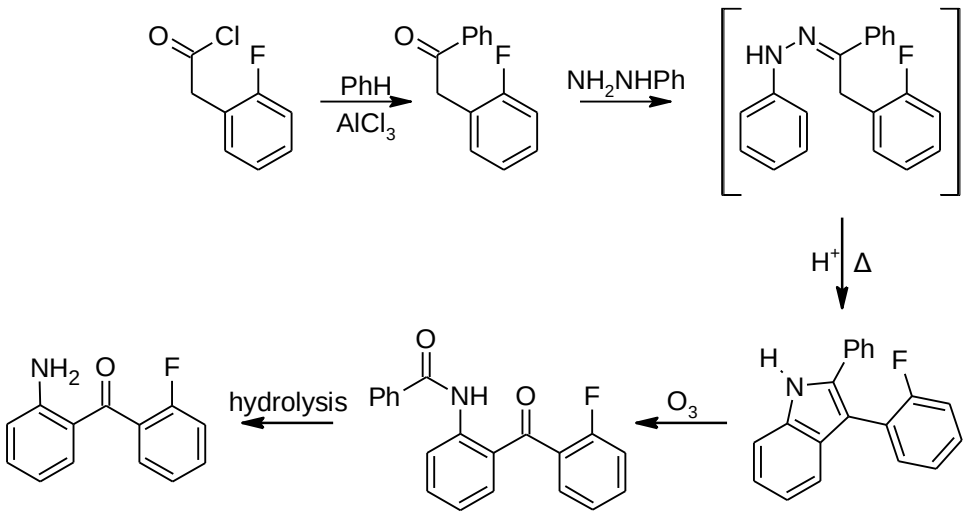


Fig 22. The sequence of reactions: Friedel-Crafts – Fischer-indole-synthesis – ozonolysis - hydrolysis.

4.6.2. Reductive cleavage

Similarly to the previous method, 'reductive' approach (Fig. 23) uses the transformation of a heterocyclic compound.

The first step is the addition of a carbanion (generated from benzyl cyanide) to the *ortho* position of halogeno nitroarene to form a σ^H adduct. In water-alcohol solutions, a multi-stage Davis reaction [26] takes place, its last stage is a cyclization with the elimination

of the cyanide ion leading to anthranile derivatives. A more modern variant of this transformation is Wróbel method [27].

The obtained 1,2-benzoizoksazoles are reduced using various methods [28-30] to 2-aminobenzophenone derivatives.

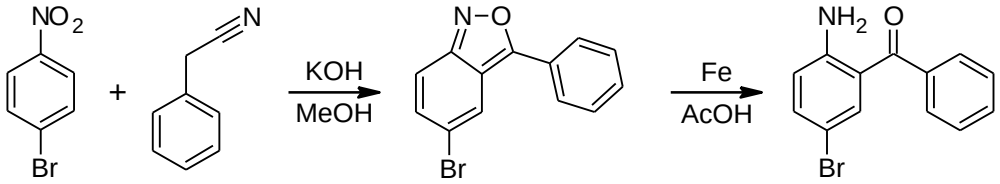


Fig 23. The sequence of Davis reactions and reductive cleavage.

5. Conclusion

This review article could be concluded by paraphrasing the well-known among organic chemists saying: 'there are never too many methods for the synthesis of…' 2-methylaminobenzophenones.

The use of a particular one of them depends primarily on the substituents (and their resistance to reaction conditions) that are to be introduced into the aromatic rings of 2-aminobenzophenones, the availability and price of substrates, the ease of purification and isolation, and finally, the individual preferences of chemists.

The search and design of new, improved, shorter and effective methods for the synthesis of 2-aminobenzophenones is still a current challenge due to their usability in the synthesis of biologically active compounds, especially benzodiazepines.

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