Microwave-assisted Hirao reaction: recent developments

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Abstract Organic molecules containing phosphorus, now, constitute a major branch of chemistry, and offer fascinating possibilities for their structural, synthetic, and mechanistic study as well as promising biological activities. Organophosphorus compounds find numerous potential applications in the areas of industrial, agricultural, and medicinal chemistry. Aryl- and vinyl-phosphonates are an important class of organophosphorus compounds with potential biological relevance. The Hirao reaction offers a way to access these compounds through phosphorus-carbon (P–C) cross-coupling of aryl and vinyl halides with *O,O*-dialkyl phosphites, and this reaction has attained a commendable development in many ways in regard to the diversity in the substrates, >P(O)H species, catalysts, and reaction conditions. The present article deals with such developments that occurred under the influence of microwave irradiation.

Keywords The Hirao reaction · Microwaves · Phosphorous–carbon cross-coupling · Aryl/vinyl-phosphonates · Phosphine oxides

Abbreviations

DIEA	<i>N,N</i> -Diisopropylethylamine
DMF	<i>N,N</i> -dimethylformamide
DMSO	Dimethyl sulfoxide

dppp	1,3-Bis(diphenylphosphino)propane
Et ₃ N	Triethylamine
GR	Glucocorticoid receptor
MMP-2	Matrix metalloproteinase-2
MTB-GS	<i>Mycobacterium tuberculosis</i> glutamine synthetase
MW	Microwave
Pd(PPh ₃) ₄	Tetrakis(triphenylphosphine)palladium
PTC	Phase-transfer catalysis

Introduction

The chemistry of organophosphorus compounds is rich enough, and such chemical entities occupy a significant position among the plethora of organic compounds as far as their properties and applications are concerned [1]. Organophosphorus compounds find a wide range of applications in the areas of industrial, agricultural, and medicinal chemistry owing to their inherent biological and physical properties [2, 3]. Phosphorus-carbon (P–C) bond formation, thus, remains a valid and active exercise in chemical research as a result of which new reactions are continuously being developed for the preparation of organophosphorus compounds such as substituted phosphonates and related derivatives of potential multifaceted interests [4–6]. The synthesis of arylphosphonates and related derivatives is a focus of interest these days [5]. Aryl phosphonates can be prepared by the Arbuzov reaction of trialkyl phosphites and aryl halides only under special conditions due to the lower reactivity of aryl halides [7, 8]. Later on, the Hirao reaction has appeared as the most suitable method for the synthesis of arylphosphonate derivatives [51]. Since the first report in 1980s, there has

This article is dedicated to Professor Srinivasan Chandrasekaran.

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been a commendable development on this reaction, and the present article is restricted only to focus on the synthesis of diverse aryl- and vinyl-phosphonates and related derivatives by means of the microwave-assisted Hirao reaction. Microwave technique is regarded as one of the 'green tools' in organic synthesis [9], and the key benefit of using this technique is to accelerate reaction rate.

The Hirao reaction

In the early 1980s, Hirao and coworkers reported a phosphorus-carbon cross-coupling reaction of aryl- and vinyl halides with *O,O*-dialkyl phosphites in the presence of triethylamine (Et_3N) and catalytic amount of tetrakis(triphenylphosphine)palladium [$\text{Pd}(\text{PPh}_3)_4$] to synthesize a variety of dialkyl aryl- and vinyl-phosphonates in good yields [10–12]. This reaction is now known as the Hirao reaction after the name of the inventor. The general representation of the Hirao reaction is shown in Scheme 1.

The Hirao reaction has now become an important P–C bond forming method since its discovery about 35 years ago. On further development and modifications, this method constitutes the current state of the art in the synthesis of P–C(sp²) bonds as documented in a number of reviews [13–15]. The Hirao reaction has been gradually extended to more aryl and vinyl derivatives and to variety of >P(O)H species, thus making available phosphonic, phosphinic and phosphine oxide derivatives as well [5].

Mechanistic aspect of the Hirao reaction

In their following report, Hirao and his group [12] also proposed a mechanism for the reaction. Palladium(0) is supposed to undergo oxidative addition with aryl-/vinyl halide to generate a palladium(II)-complex as the key intermediate. The dialkyl phosphite molecule then attacks the aryl-/vinyl-palladium(II) halide complex to afford the desired product, dialkyl aryl-/vinyl phosphonate, along with the formation of palladium(II) halide hydride. In the next step, this palladium(II) halide hydride reacts with triethylamine to regenerate palladium(0) species, thus, making itself available for another reaction cycle. The overall mechanistic path is delineated in Scheme 2.

Application of microwave in the Hirao reaction: the benefits

In recent years, application of microwaves to synthetic organic chemistry has become increasingly popular and attracted considerable practical [16–19] and theoretical attention [20]. The most common benefits from microwave irradiation are the considerable shortening of reaction times, thereby accelerating reaction rates, and the increase in the selectivities. However, the most valuable benefit is when a reaction can be carried out that is otherwise impossible under traditional thermal conditions. This may be the consequence of a so-called special microwave effect

Scheme 1 The Hirao reaction

Scheme 2 Proposed mechanism for the Hirao reaction

Scheme 3 Synthesis of diethyl arylphosphonates by palladium-catalyzed phosphonation of aryl halides

[21]. Microwave irradiation technique is also regarded as a ‘green tool’ to save energy consumption [22]. As part of ongoing development of various synthetically important reactions using this technique, the Hirao reaction has also attained quite significant advancement so far. The present article is aimed to offer an up-to-date overview of such developments in synthesizing diverse and functionalized aryl- and vinyl-phosphonates and related derivatives through P–C cross-coupling via the microwave-assisted Hirao reaction.

The microwave-assisted Hirao reaction: recent developments

Like many other significant reactions in organic chemistry, the Hirao reaction has also been studied under the influence of microwave irradiation as reported so far. In 1997, Villemain et al. [23] carried out the coupling reaction between aryl halides (**1**) and diethylphosphite (**2**) in the presence of bis(triphenylphosphine)palladium dichloride as catalyst in triethyl amine (Et_3N) and toluene under argon atmosphere using microwave irradiation to prepare a variety of diethyl arylphosphonates (**3**) in moderate to good yields (Scheme 3). The lowest yield (13 %) was observed with 4-iodobenzoic acid and the highest yield (96 %) was isolated in case of 4-iodoanisole. The reactions with aryl

iodides gave generally good yields except for the hindered *ortho*-substituted aryl iodides. C–Cl bond activation under the reaction conditions was not observed at all with chlorobenzene, but such activation in case of chlorobenzene-tricarbonylchromium was so pronounced that phosphonation of this complex took place feasibly yielding 80 % of the product just at 8 min without its decomposition. The key advantages of this present protocol over the classical heating methods are the dramatic rate acceleration and easy workup procedure. For example, phosphonation reaction of this complex can also be accomplished via an Arbuzov-type reaction under classical heating with the same yield (81 %) but after 7 h at reflux [24]. Earlier in 1982, Hirao and his group observed that reaction between aryl halide and dialkylphosphite, catalyzed by palladium(0) complexes, is efficient but requires long time in hours (on average 10 h) [12].

In 2006, Jiang and coworkers [25] utilized a modified Pd-catalyzed microwave-assisted Hirao reaction for P–C cross-coupling between synthetic 11 β -4-(((trifluoromethyl)sulfonyl)oxy)phenyl-substituted steroid (**4**) and disubstituted phosphates/phosphine oxides (**5**) in the presence of $\text{Pd}(\text{OAc})_2/\text{dppp}/\text{DIEA}/\text{dioxane}$ to produce a new series of phosphorus-functionalized 11 β -aryl-substituted steroids (**6**) (Scheme 4) with promising progesterone receptor antagonist activity. The stereochemical features of the substrate molecule remained intact within the product.

The investigators evaluated their progesterone receptor (PR) antagonist activity in a T47D cell-based assay and glucocorticoid receptor (GR) antagonist activity in an A549 cell-based assay. Most of the compounds were potent PR antagonists (nanomolar range), with some showing better selectivity than mifepristone used as a standard. Moreover, some selected compounds showed modest oral progestin antagonist activity in rat uterus. From the viewpoint of structure–activity relationship, it was evident that when R^1 and R^2 are both alkoxy groups, the change in their size did not affect potencies, while a change in the electronics reduced the potency with a more electron-withdrawing group. It was also observed that substitution at the phenyl ring did not significantly change the potency.

In the same year, Beletskaya et al. [26] introduced a phase-transfer catalysis (PTC) method for the arylation of

phosphorylated monosaccharides (**8**) of pyranose and furanose series bearing $>P(O)H$ moiety in the presence of $PdCl_2(PPh_3)_2$, and microwave irradiation was found to be useful over conventional heating in shortening reaction-time (viz. 3 h to 14 min) (Scheme 5). Conventional heating, in some cases, decomposed the substrate molecules as well. Introduction of PTC technique coupled with the utilization of MW irradiation, thus, successfully offered a facile path for synthesizing these biologically relevant compounds.

In the next year, Gaumont and his group [27] reported the synthesis of a series of vinylphosphine-borane complexes (**12**) via palladium-catalyzed C–P cross-coupling of diverse vinyl triflates (**10**) with secondary diaryl-, dialkyl- and alkylarylphosphine-boranes (**11**) mainly under heating conditions. However, in some cases they carried out the same reactions using microwave irradiation, and observed

Scheme 4 Palladium-catalyzed synthesis of phosphorus-functionalized 11β-aryl-substituted steroids (**6**)

Scheme 5 Palladium-catalyzed P-arylation of hydrophosphoryl derivatives of protected monosaccharides (**9**)

Scheme 6 Palladium-catalyzed synthesis of vinylphosphine-borane complexes

that those reactions undergo smoothly with comparable yields but with shortened reaction times. The overall reactions and effect of microwave irradiation in shortening the reaction-time are exemplified in Scheme 6. Vinylphosphine boranes find useful applications in organophosphorus chemistry as synthetic intermediates for the preparation of polyphosphines and ligands for organometallic catalysis.

In 2008, Stawinski and co-workers [28] developed a general and efficient microwave-assisted method for the preparation of a broad spectrum of aryl- and vinylphosphonates (**15** and **17**, respectively) based on a Pd-catalyzed cross-coupling of aryl/vinyl halides (**13/16**) with H-phosphonate diesters (**14**) using Pd(PPh₃)₄ as a prevalent palladium catalyst and either cesium carbonate or triethylamine as base in THF; the reaction was completed within 10 min furnishing good yields (Scheme 7). It is also noteworthy that the reaction is completely stereospecific with retention of configuration at the phosphorus center and at the same time, the configuration in the vinyl moiety remains unaltered.

Using this protocol, the investigators [28] also synthesized few more complex compounds bearing nucleoside and cholesteryl moieties with high yields, viz. **19** and **21**

(Scheme 8). This is to mention herein that microwave heating did not affect the stereochemistry of the substrate molecules and remained unchanged in the products as well.

Larhed and his group [29] first time used palladium acetate for the Pd(II)-catalyzed P–C coupling reaction between aryl/vinyl boronic acids or trifluoroborates (**22**) and dialkyl phosphites (**2**) in the presence of a rigid bidentate ligand dmphen (dmphen = 2,9-dimethyl-1,10-phenanthroline) and *p*-benzoquinone as oxidant without the addition of base or acid under microwave irradiation in DMF solvent (Scheme 9). The reaction was found to proceed rapidly, just within 30 min, with high chemoselectivity under non-inert conditions. The present investigators extended their protocol to synthesize a *Mycobacterium tuberculosis* glutamine synthetase (MTB-GS) inhibitor (**26**). However, the mechanism of this reaction was believed to be different from that of the Hirao reaction; Pd(II) is the active form of the catalyst, which is regenerated from the Pd(0) species by the oxidant. Contrary to the Pd(0)-catalyzed P-arylation reactions, this P–C coupling can be carried out under neutral to acidic conditions, thereby substantially contributing to the versatility of transition metal-mediated P–C bond formations [48].

Scheme 7 Palladium-catalyzed synthesis of aryl- and vinylphosphonate diesters

Later on, Rummelt et al. [30] developed a green, simple, and novel protocol for cross-coupling of various iodo- and bromobenzoic acids (**27**) with diphenylphosphine oxide (**5**) catalyzed by heterogeneous and recyclable Pd/C catalytic system in water without the addition of any ligand and additive under microwave irradiation (Scheme 10). The novel series of phosphine oxides can be of further use as ligands for biphasic and water-soluble metal catalysis and organocatalysis. The investigators first performed the reaction with 4-iodobenzoic acid upon conventional heating at 100 °C (99 % yield at 1 h), but different halogenated benzoic acids (viz. 4-bromo and 2-iodobenzoic acid) did not yield the desired product under conventional heating. To overcome such a limited scope of the reaction, they used microwave (MW) heating, instead of conventional heating, and became successful in their endeavor. The operational simplicity, fastness of the process, simple workup, and high purity of the desired compounds (**28**) are some of the key features of the present protocol, which make it a good candidate for application in both laboratory and large-scale synthesis.

Recently, Jablonkai and Keglevich have made a considerable modification of the Hirao reaction [31]; they have observed that the Pd-catalyzed reaction can undergo

smoothly under the influence of microwave irradiation in the presence of palladium acetate without any *P*-ligand under solvent-free conditions (Scheme 11). The investigators used a variety of >P(O)H species, such as dialkyl phosphites, ethyl *H*-phenylphosphinate, diphenylphosphine oxide, and dibenzo[*c,e*] [1, 2] oxaphosphorine oxide, and a series of aryl bromides in the P–C cross coupling reaction. In most of these cases, the corresponding products **30** were obtained in high yields (73–95 %). The investigators also compared the MW-assisted reactions with those carried out under thermal conditions and the results revealed the specific influence of MW irradiation in accelerating rate of the reaction; better yields were isolated with shorter reaction-time (from hours to minutes) compared to those carried out under conventional heating.

In the very next year, Keglevich group have extended the same reaction with more variety of both the substrates, thereby offering the reaction a general value [32]. Thus such a *P*-ligand-free variation of the microwave-assisted Hirao reaction proves to be a generally useful and eco-friendly method. In their very recent report, Jablonkai and Keglevich have demonstrated an environmentally friendly, catalyst-free and microwave-assisted variation of Hirao

Scheme 8 Palladium-catalyzed synthesis of phosphonate diesters linked with nucleoside and cholesteryl moieties

Scheme 9 Pd(II)-catalyzed synthesis of aryl/vinylphosphonate diesters (**23** and **25**)

Representatives

Scheme 10 Pd/C-catalyzed synthesis of aryl diphenylphosphine oxides (**28**) in water

Representatives

Scheme 11 Ligand-free synthesis of arylphosphonates/phosphine oxides (**30**)

reaction, which allowed the synthesis of new phosphinoylbenzoic acid derivatives **33** in water [33]. 4-Bromo and 3-bromobenzoic acids along with 4-iodobenzoic acid underwent P–C coupling reactions with diarylphosphine oxides in the absence of any catalyst in water as a solvent under microwave irradiation, and the phosphinoylbenzoic acids obtained were directly converted into their corresponding ethyl esters **33** in good yields (Scheme 12).

Applications of the Hirao products

The Hirao products (i.e. aryl- and vinyl-phosphonates, phosphine oxides and related derivatives) are compounds of practical importance in industry, agriculture, and medicine as well as in everyday life [34–39]. In addition to their applications as pesticides, detergents, or anticorrosive agents, these phosphorus-containing synthetic compounds

Representatives

Scheme 12 Catalyst-free synthesis of phosphinoylbenzoate esters (**33**) in water**Scheme 13** A tree-diagram indicating applications of the Hirao products

have received a lot of attention both in drug research and in medicinal chemistry due to their great potential in combating diseases and pathological conditions, and curing parasitic infections [40].

Arylphosphonate scaffolds are used in designing fuel cell membranes [39] and materials with special optical properties [41–43]. Arylphosphonates are the phosphonic acids precursors, which can be used for their water-soluble properties and for the synthesis of mixed organic–inorganic materials [44, 45]. Vinylphosphonates are a well-known class of organophosphorus compounds that are very useful intermediates for the construction of many synthetically and pharmaceutically important compounds including acyclic, carbocyclic, and especially heterocyclic compounds, β -aminophosphonates and 1,2-epoxyalkylphosphonates [46, 47]. Terminal vinylphosphonates (1-aryl or 1-alkyl ethenylphosphonates) are used as precursors for the

synthesis of optically active 1-aryl- or 1-alkyl-substituted ethylphosphonates by asymmetric reduction [48]. They are also useful for the synthesis of 2-(aryl)vinylphosphonates through direct Heck coupling reactions with aryl halides [49]. Vinylphosphonates are involved in the preparation of flame-retardants or polymers, fuels, lubricant additives, as well as intermediates for drugs and agrochemical compounds [50, 51]. Nucleotide- or polyisoprenoid-derived vinylphosphonates possess promising medicinal properties [52, 53]. A series of substituted vinylphosphonates has been recognized as excellent matrix metalloproteinase (MMP-2) inhibitors in vitro, with potential anti-cancer implications [54]. It has, thus, been demonstrated that a P–C bond may offer different kinds of biological activities and in accordance to this fact, there has been a growing interest in these classes of organophosphorous compounds in medicinal [25, 52, 54, 55] and nucleic acid chemistry

[53, 56–60]. A tree-diagram (Scheme 13) summarizes major applications of Hirao products.

Conclusions

Organic molecules containing phosphorus, now, constitute a major branch of chemistry, and offer fascinating possibilities for their structural, synthetic, and mechanistic study. Organophosphorus compounds find numerous potential applications in the areas of industrial, agricultural, and medicinal chemistry owing to their inherent biological and physical properties. Among a variety of organophosphorus compounds, functionalized aryl- and vinyl-phosphonates and related derivatives show a broad spectrum of applications. The Hirao reaction offers a way to access these compounds, and this reaction has been developed in many folds during the last 35 years. The present article is devoted to offer an insight into the recent developments in the synthesis of diversely functionalized aryl- and vinyl-phosphonates and related derivatives via the Hirao reaction under the influence of microwave irradiation. Microwave irradiation results in rapid rate acceleration of the reaction with excellent stereoselectivity. Application of this ‘green tool’ for smooth going of the Hirao and Hirao-type reactions has accomplished a considerable advancement in the synthesis of diverse kinds of phosphonate derivatives, and the author hopes this article would be helpful to target readers at large.

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