Zárójelentés

"*The utilization of microwaves in organophosphorus chemistry*" (K119202 NKFI)

1.) The synthesis of bisphosphonic derivatives and related tasks

Phosphorous acid could be added on the C=O group of benzaldehydes in strongly acidic medium. Using hydrochloric acid, the corresponding α-chlorophosphonate was also formed together with the expected α-hydroxyphosphonate [1]. The dronic acid syntheses starting from carboxylic acids and different P-reagents were surveyed, and critically evaluated [2]. In the field of the synthesis of dronic acid derivatives from substituted carboxylic acids, the preparation of pamidronic acid was improved [3], and MW irradiation was not found useful, however, a catalytic amount of [bmim][BF_4], either without any solvent, or in sulfolane, greatly enhanced the efficiency of the reactions. The syntheses of alendronate [4], zoledronic acid [5], ibandronate [6] and risedronic acid [7] were optimized to have the best outcomes ever reported. The results were also summarized in a proceedings [8], in a review article [9] and in an invited book chapter [10]. A new method was developed for the synthesis of zoledronic acid in diethyl carbonate as a green solvent [11]. Aminomethylene-bisphosphonates, analogous to hydroxymethylene bisphosphonates were also synthesized [12]. Within this group of tasks, in the subtopic of "MW-promoted acylation of CH-acidic compounds", we found that C-acylation took place in the reaction of acetoacetic ester with benzoyl chloride, while using diethylphosphoryl chloride, the enol form was phosphorylated (meaning *O*-acylation). Interaction of malonic ester with benzoyl chloride led to the formation of a by-product. In the field of "Arbuzov reactions promoted by MW irradiation", the $NiCl_2$-catalyzed reaction of different bromoarenes with triethyl phosphite was investigated. The optimum reaction conditions (regarding temperature and molar ratio) were explored, the side reactions identified, and it was pointed out that, in this case, the presence of an ionic liquid additive is not really useful.

2.) Microwave-assisted reactions: theory and application in organophosphorus chemistry

A significant advance was achieved in the exploration of the theoretical aspects of MW chemistry. The distribution of the local overheatings was modeled mathematically, and the accelerating effect was predicted by the Arrhenius equation [13,14]. The scope and limitations of the application of MW irradiation in organic reactions were summarized in an invited book chapter [15]. The scope and limitations of the MWs [16] and the modelling of the effect of MWs [17] was further popularized. Most model compounds in the MW-assisted esterifications were ring phosphinic acids. From among these species, the conformation of 1-hydroxyphospholane oxides and 1-hydroxy-1,2,3,4,5,6-hexahydrophsosphinine oxide was evaluated by high level theoretical calculations. A novel energy surface diagram was introduced [18]. It was experienced that the esterification of phosphinic acids is more efficient (lower temperature, shorter reaction time and higher yields) in the presence of a catalytic amount of a suitable ionic liquid [19]. The cyclic propylphosphonic anhydride (T3P® reagent) was also utilized in esterifications [20]. The T3P® reagent is an efficient "coupling" agent, however, it is rather expensive, and its use is not atom efficient. The different methods of esterification were compared and evaluated in a case study [21]. Our protocol developed was also useful for the esterification of phosphinic acids with phenols [22]. Continuous (flow) direct esterification of a *H*-phosphonic acid was also elaborated [23]. Regarding the MW-assisted esterification of phosphonic derivatives, it was found that phosphonic acids are more reactive than phosphonic acid-monoesters, and also that ionic liquid additives may promote the esterification [24]. For the esterification of the second hydroxy group of phosphonic ester-acid derivatives, alkylating esterification seemed to be the method of choice [25]. The MW-promoted direct esterification of phosphoric acid derivatives with one or two free hydroxy groups remains a difficult challenge. The preliminary results on the direct esterification of benzenesulfonic acid under MW irradiation are encouraging, however, we are far from the solution. Transesterification of dibenzyl-*H*-phosphonates were accomplished under flow MW conditions [23]. The use of ILs as additives was surveyed in a comprehensive way [26]. An optimized method for the acid-catalyzed hydrolysis of a few ring phosphinates was developed. However, the hydrolyses did not require MW assistance [27]. Hydrolysis of a few phosphonic esters were also investigated, kinetic studies were performed, and the reactivity of the substrates was mapped [28]. On the invitation of the Editor-in-Chief of Synthesis, two invited reviews and a book chapter were published on our recent results in MW chemistry [29–31]. The possible applications of MWs, especially from the point of view of the simplification of catalytic reactions under MW were surveyed [32–34].

3.) Theoretical study and practical application of the Hirao P–C coupling reaction

The "P-ligand-free" Hirao reaction was further investigated. On the one hand, the mechanism of the $Pd(OAc)_2$-version was evaluated by high level quantum chemical calculations, on the other hand, it was proved experimentally that the optimum quantity of the >P(O)H reagent, in case of 10% of $Pd(OAc)_2$ catalyst, is a portion of 1.3 equivalents. Hence, 0.1 equivalents of the P-reagent may act as a reducing agent, while 0.2 equivalents provide the two P-ligands via the trivalent tautomeric form. The theory and practice were in accord [35]. The activity and formation of different “PdP_2” catalysts incorporating different Ar_2POH ligands were also evaluated [36]. Changing for the $NiCl_2$-catalyzed cases, it was surprising to find that the unexpected Ni(II) → Ni(IV) protocol governed the P–C couplings, no matter if the ligand was 2,2′-bipyridyl, or if there was a reducing agent or not [37,38]. The role of the halo-substituent was clarified as compared to mezilates and triflates [39]. Hetaryl bromides could also be involved in the P–C coupling [40]. As the Hirao reaction still represents a hot topic, recent developments of this field (especially from “green” point of view) were reviewed in a book chapter and paper [41,42]. In respect of the Suzuki reaction, the initial experiments showed that the “P-ligand-free” accomplishment may work, but the C–C coupling is not so efficient. Tautomerizm of the >P(O)H reagents has been evaluated by quantum chemical calculations [43].

4.) Investigations in the field of α-aminophosphonic derivatives

In the topic of MW-assisted Kabachnik–Fields reactions, the variation of the >P(O)H reagents led to new α-aminophosphonates [44,45] and α-aminophosphine oxides [46]. According to another approach, the aza-Pudovik reaction of imines also led to similar type of products [47]. Optically active α-aminophosphine oxides were also synthesized [48]. New results were obtained on the synthesis of α-aminophosphonates with sterically demanding α-aryl substituents [49], and on the preparation α-aminophosphine oxides applying carboxylic amides as the “amine” components [50]. In connection with the mechanism of the Kabachnik–Fields reaction, the reversibility of the α-hydroxyphosphonate intermediates was proved [51]. Several other papers containing new results on the use of aminoalcohols as the starting material [52], on the preparation of bis- and tris aminophosphonates [53], or just conference proceedings [54,55] were also published. Regarding flow synthesis, as a simple model, first the direct esterification was translated into the continuous flow accomplishment [56]. This was followed by the elaboration of the continuous flow synthesis of α-aminophosphonates [57,58]. The use of α-aminophosphine ligands in complexes was surveyed [59]. Possibilities for the preparation of secondary phosphine oxides were also summarized [60]. The flow MW-assisted alcoholysis of dialkyl phosphites was also studied in detail [61,62]. We summarized our experiences in MW-assisted flow chemical accomplishments in an invited paper [63]. Alcoholysis and aminolyses of P-amides under MW irradiation have not been successful.

5.) Investigations in the field of α-hydroxyphosphonic derivatives

Newer results were attained in the synthesis and modification of α-hydroxyphosphonates (HPs). On the one hand, for the time being, the greenest protocol was elaborated for the preparations of α-HPs (the product is crystallized from the reaction mixture) [64], on the other hand, the HPs were converted to aminophosphonates [65,66]. New α-HPs [67,68], along with a series of phosphorylated α-HPs were synthesized [69]. The HPs could be converted to the corresponding benzylphosphates by a rearrangement reaction [70]. In respect of the optical resolution of α-HPs, we have attained interesting results on diastereomeric associates obtained during the treatment of racemates with dibenzyl D-tartaric acid (DBDTA) (that is much better than TADDOL). We could isolate a series of HP-DBDTA associates that were characterized by X-ray study [71]. The bioactivity studies on a part of the HPs synthesized revealed interesting anticancer activity [67,72,73]. We surveyed the preparation and reactions of α-HPs [74–76]. A method has been elaborated for the optical resolution of 1-isopentyl-3-methyl-3-phospholene 1-oxide [77]. An interesting bis(Rh) complex was also prepared [78].

6.) A study on the deoxygenation of phosphine oxides

In the field of the deoxygenation of phosphine oxides a series of silanes were tried out, and the order of reactivity was established [79]. The reduction of a series of tertiary phosphine oxides was investigated under MW irradiation applying user-friendly silanes, such as polymethylhydrosilane and tetramethyldisiloxane. The reactivity of the phosphine oxides was also mapped [80,81]. The deoxygenation of phosphole oxide dimers (7-phosphanorbornene derivatives) was accomplished by dimethylsulfideborane. The method may be applied, but is not entirely selective [82]. Recent results of the P=O deoxygenations were summarized in a book chapter [83]. The possibilities for the deoxygenation of phosphine oxides were surveyed in a review article [84]. Deoxigenation of phosphinates and phosphinic amides have not yet been successful. New P-alkyl 2,3-oxaphosphabicyclo[2.2.2]octane derivatives were synthesized, and the bridged P-heterocycles were used in the fragmentation-related phosphorylation of nucleophiles [85,86].

The results of the Keglevich group were summarized for the Gy. Oláh special issue of Structural Chemistry [87]. The heterocyclic segments were reviewed separately [88]. Newer achievements in the synthesis of phosphine oxides were surveyed in a book chapter [89].

In summary it can be said that the undertaken job was fulfilled. In some respects, the work has been completed in advance. Practically, most of the tasks was realized. The 90 papers published during the four years might indicate our input. To close the project, an invited minireview was published on the connection of MW irradiation at catalysis in the journal Molecules [90].

Irodalom

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