Review Article

An overview of solvent-free and solvent/s-involved phosphorylation to synthesize Zoledronic acid

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ABSTRACT

This work provides a complete overview of solvent-free and solvent-involved phosphorylation strategies employed to synthesize the renowned biphosphonate drug, Zoledronic acid. In this regard, all the disclosed patents and journal publications were considered and reviewed as per the yearly chronology towards the use of solvent/s or in the absence of it for the phosphorylation. Interestingly, a prolonged reaction time, sticky lump formation, exothermicity, enormous HCl release, tedious workup, etc had allowed the researchers to venture various synthetic and isolation approaches to overcome the process-specific setbacks. In line to this context, various solvent/s were used alone or in combination with another solvent to synthesize Zoledronic acid in varied yields. A few attempts were also reported under solvent-free conditions in reasonably good yields. Moreover, along with the above variations, a few different *p*-reagent/s are also reported towards the synthesis of Zoledronic acid.

***Key words*:** Biphosphonates, Zoledronic acid, Phosphorylation, *P*-reagents, Hydrolysis, Green-solvent.

Synthesis of Zoledronic acid ***Z*** involves the reaction of an acid derivative (**2**) or its salt (**3**) with selective *p*-reagent/s {phosphoric acid (H_3PO_4), phosphorous acid (H_3PO_3), phosphorous trichloride (PCl_3), phosphorous oxychloride ($POCl_3$), triphosgene, mesyl chloride, etc} in the presence of suitable solvent/s or in the absence of solvent at a suitable temperature. After the phosphorylation, the reaction mixture was hydrolyzed by refluxing in water or HCl solution and further workup processes will lead to the isolation of ***Z*** (**Scheme 1**).

Numerous synthetic strategies were adopted by various researchers and are reported in various publications (patents/journals). The present review attempt will provide a distinct sectorial overview of the solvent-free or solvent/s-involved phosphorylation approaches disclosed in patents and journal publications to synthesize ***Z***.

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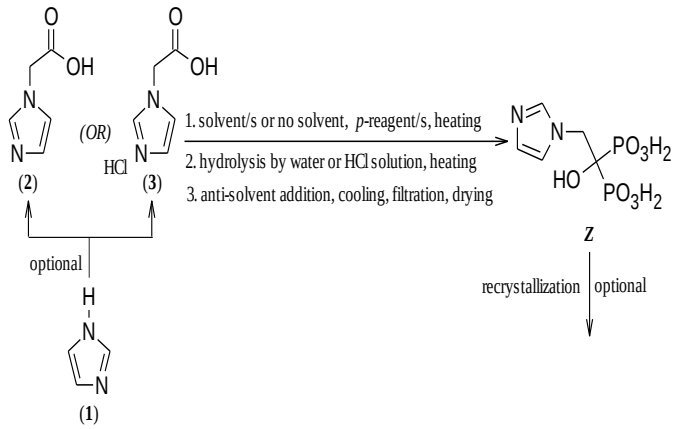

Scheme 1. A renowned pathway to synthesize Zoledronic acid via phosphorylation and hydrolysis of (**2**) or (**3**).

Details gathered from patent publications

Numerous patents were published/filed comprising a lot of information on the synthesis and biological activities of ***Z***.

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To the context, a critical examination of disclosed processes was done to identify the solvent-free and solvent/s-based strategies employed to isolate ***Z***. Jaeggi KA & Widler L., in 1989, had reported the phosphorylation of key starting material 1-*H*-imidazol-1-ylacetic acid hydrochloride (**3**) by the renowned *p*-reagents like H_3PO_4 (85%) and PCl_3 in the presence of chlorobenzene to isolate ***Z*** (yield: 41.0%) [1]. Hu W., *et al*, in 2002, had illustrated the condensation of key starting material 1-*H*-imidazole (**1**) with ethyl-chloroacetate (**4**) and then hydrolyzed to isolate (**3**). Phosphorylation of (**3**) using the *p*-reagents like H_3PO_3 and PCl_3 in chlorobenzene to get ***Z*** (yield: 48.1%) [2]. De FL., *et al*, in 2002, had reported the use of tributyl ammonium chloride (TBAC) as the solvent instead of hydrocarbon-based solvents. Phosphorylation of 1-*H*-imidazol-1-ylacetic acid (**2**) was done by using H_3PO_3 and PCl_3 in the TBAC medium to get ***Z*** (yield: 25.95%) [3]. Lidor HR., *et al*, in 2003, had illustrated the phosphorylation of key starting material (**2**)/(**3**) in silicon oil alone or with toluene using the *p*-reagents H_3PO_3 and phosphorous oxychloride ($POCl_3$) to isolate ***Z*** (yield: 38.0-79.0%) [4].

Aronhime J & Lifshitz LR., in 2004, had disclosed the phosphorylation of (**2**)/(**3**) in solvents like silicon oil, chlorobenzene, toluene, and PEG-400 in distinct experiments using H_3PO_3 and $POCl_3$ to get ***Z*** (yield: 13.4-100%). Interestingly, the use of chlorobenzene or silicon oil for phosphorylation gave a better yield compared to other solvents [5]. Patel VM., *et al*, in 2004, had reported the phosphorylation of (**2**) in sulfolane using H_3PO_3 and PCl_3 to isolate ***Z*** (yield: 70.7%). A similar attempt was done using 1, 2-dimethoxyethane as the solvent to isolate ***Z*** (yield: not mentioned) [6]. Patel VM., *et al*, in 2004, had disclosed the condensation of (**1**) with chloroacetyl chloride (**5**) and benzyl alcohol (**6**) to isolate the intermediate benzyl-1-*H*-imidazol-1-ylacetate (**7**). It was then reduced by Pd/C or hydrolyzed by 10% HCl to isolate (**2**). It was subjected to phosphorylation using H_3PO_3 and PCl_3 in sulfolane to get ***Z*** (yield: 70.7%) [7].

Pulla RM., *et al*, in 2004, had illustrated the condensation of (**1**) with methyl chloroacetate (**8**) to get (**2**), it was then converted to (**3**) by the treatment with isopropanol-HCl. Phosphorylation of (**3**) using H_3PO_4 and PCl_3 in the presence of various solvents like ethylene dichloride, cyclohexane, and chlorobenzene gave ***Z*** (crude yield: 79.0-85.0%). A better yield was obtained in an experiment performed using ethylene dichloride as the diluent for phosphorylation [8]. Grassi S & Volante A,. *et al*, in 2004, had reported the phosphorylation of (**3**) using H_3PO_3 and $POCl_3$ in the absence of solvent to isolate ***Z*** (yield: 62.0%) [9]. Cai WZ., in 2005, had illustrated a one-step process to condense (**1**) with (**4**) in 1, 4-dioxane using 60% sodium hydride (NaH), and an in situ phosphorylation was done using H_3PO_4 and PCl_3 to get ***Z*** (yield: 32.0%). Similarly, (**1**) was reacted with chloroacetonitrile (**9**) in 1, 4-dioxane using potassium carbonate (K_2CO_3) and phosphorylation was done using H_3PO_4 and PCl_3 to isolate ***Z*** (yield: 29.9%) [10].

Pandey SC., *et al*, in 2005, had disclosed the phosphorylation of (**2**) in *n*-octane using H_3PO_3 and PCl_3 to get ***Z*** (yield: 64.89%). A similar attempt of phosphorylation in 1, 4-dioxane for (**2**) gave ***Z*** (yield: 51.91%) [11]. Vecchioli A., *et al*, in 2006, had illustrated the phosphorylation of (**2**) in methanesulfonic acid (MSA) using PCl_3 to isolate ***Z*** (crude yield: 83.0%). The process efficiently avoids the use of H_3PO_4 or H_3PO_3 for the reaction [12]. Deshpande PB & Luthra PK., in 2006, had reported an efficient phosphorylation of (**2**) in diphenyl ether (DPE) using H_3PO_3 and PCl_3 to isolate ***Z*** (crude yield: 75.0%) [13].

Yadav RP., *et al*, in 2006, had disclosed the condensation of (**1**) with (**8**) to isolate the intermediate methyl 1-*H*-imidazol-1-ylacetate (**10**). It was hydrolyzed to (**2**) and then subjected to phosphorylation in the absence of solvent using H_3PO_3 and PCl_3 or $POCl_3$ to isolate ***Z*** (crude yield: 74.62-78.79%) [14]. Samsel EG & Wu TC., in 2007, had illustrated the condensation of (**1**) with *t*-butyl chloroacetate (**11**) to get (**2**). It was then phosphorylated in the presence of diglyme using H_3PO_4 and PCl_3 to isolate ***Z*** (crude yield: 28.0%). An experiment was also conducted in PEG-400 instead of diglyme to isolate ***Z*** (yield: 7.0%) [15]. Baptista J & Mendes Z., in 2007, had reported the phosphorylation of (**2**) in the presence of an aprotic polar solvent *N, N'*-dimethylethyleneurea (DMEU) using H_3PO_3 and PCl_3 to obtain ***Z*** (crude yield: 85.6%) [16]. Liu Y & Delaup AJ., in 2008, illustrated the phosphorylation of (**2**) in sulfolane using H_3PO_3 and the PCl_3 to isolate ***Z*** (crude yield: 53.0-64.0%). The experiments were done by the modulated mode of addition of *p*-reagents (co-addition/alternate addition etc) [17].

Nazarenko AB & Fedorov VE., in 2009, had demonstrated the phosphorylation of 1-*H*-imidazol-1-ylacetonitrile (**12**) in MSA using alone PCl_3 to isolate ***Z*** (yield: 85.0-92.0%). A few experiments were conducted using different equivalents (1.25, 2.5, and 3.0) of MSA for phosphorylation [18]. Dembkowski L., *et al*, in 2009, disclosed the conversion of (**2**) to (**3**) by the addition of HCl solution and immediate phosphorylation in the absence of solvents/diluents using PCl_3 alone to isolate ***Z*** (crude yield: 41.0-49.0%). Initially added water itself will act as the diluent for the process. Moreover, it avoids the

use of H_3PO_4 or H_3PO_3 for phosphorylation [19]. Kas M., *et al*, in 2009, had reported a few pathways to convert (**1**) to (**2**) by the condensation with (**8**). Moreover, (**2**) was phosphorylated in a PEG-400 medium using H_3PO_3, PCl_3, or $POCl_3$ to isolate ***Z*** (yield: 31.3-32.9%). Instead of PEG-400, diethyl carbonate (DEC) was used to convert (**2**) to ***Z*** (yield: 59.0%). Interestingly, the combination of diluents like PEG-400 and DEC for phosphorylation gave a better atom economy of ***Z*** (crude yield: 75.0-84.0%). Furthermore, propylene carbonate (PC) was used along with PEG-400 / PEG-600 / PEG-1000 as the solvent combination in distinct experiments to isolate ***Z*** (crude yield: 97.0-99.0%) [20].

Hu Y., *et al*, in 2010, had disclosed a one-pot synthetic strategy to condense (**1**) with (**4**) using 1, 4-dioxane or tetrahydrofuran (THF) and the in situ phosphorylation using H_3PO_3 and PCl_3 to isolate ***Z*** (crude yield: 55.0-58.3%) [21]. Lanxiang S., *et al*, in 2011, had disclosed the phase transfer reagent mediated condensation of (**1**) with (**4**) and its further hydrolysis to isolate (**3**). It was phosphorylated in trifluoroacetic acid (TFA) or sulfuric acid (H_2SO_4) using H_3PO_4 and PCl_3 to get ***Z*** (crude yield: 57.0-58.8%) [22]. Yinchuan Z., *et al*. in 2011, had reported the phosphorylation of (**2**) or (**3**) in liquid paraffin medium using H_3PO_4 and PCl_3 to get ***Z*** (crude yield: 56.6-81.1%) [23]. Keglevich G., *et al*, in 2012, had reported the phosphorylation of (**2**) in an MSA medium using a different set of *p*-reagents like triphosgene, mesyl chloride, PCl_3, etc to get ***Z*** (crude yield: 59.0-74.0%). The process avoids the use of routine *p*-reagents like H_3PO_4 or H_3PO_3 for phosphorylation [24]. Kai S., *et al*, in 2012, had illustrated the phosphorylation of (**2**) in commercially affordable aliphatic hydrocarbon-based solvents like *n*-hexane, *n*-decane, *n*-tetradecane along with water using PCl_3 alone to isolate ***Z*** (crude yield: 81.0-91.0%) [25].

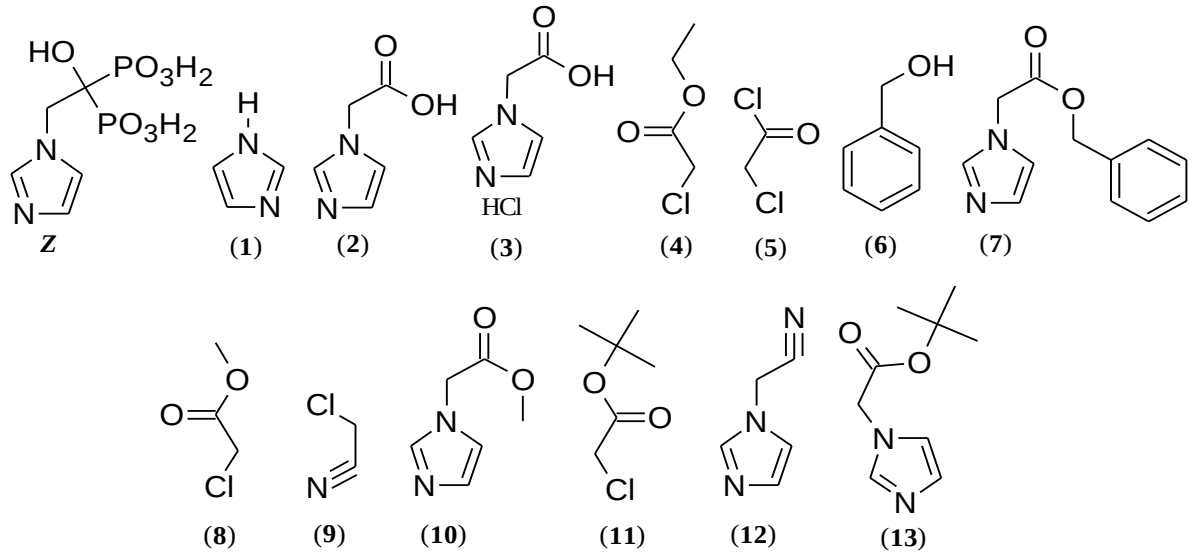

Figure 1. List of various key reactants and intermediates featuring in different synthetic strategies of Zoledronic acid

Hao E., *et al*, in 2015, had illustrated the condensation of (**1**) with (**3**) in the presence of ionic liquid ([bmim]BF_4) to get (**3**). Phosphorylation of (**3**) in the presence of ionic liquid ([bmim]BF_4) using H_3PO_4 (85%) and PCl_3 gave the sodium salt of ***Z*** monohydrate (yield: 60.0%). Numerous experiments were done to optimize the process using different ionic liquids, variations in reaction temperature, and changes in PCl_3 addition duration. Different ionic liquid {*N*-ethylpyridine tetrafluoroborate [EPy][BF_4], [bmim][PF_6], LOH, LCN, LOOH} was used in distinct experiments to obtain ***Z*** (yield: 90.0-92.0%). Meanwhile, the ionic liquid facilitated the phosphorylation as an effective reaction mixture diluent [26]. Wu Y., *et al*, in 2016, had disclosed the phosphorylation of (**2**) in chlorobenzene and also in sulfolane using H_3PO_3 along with PCl_3 in high scale to isolate ***Z*** (crude yield: 78.1% and 65.0% respectively). A few experiments were also done by conducting the phosphorylation of (**2**) in the absence of solvent using H_3PO_3 along with PCl_3 or $POCl_3$ to isolate ***Z*** (crude yield: 83.7-87.3%) [27].

Details gathered from journal publications

Many researchers had reported their work on ***Z*** in numerous national/international journals.. In all those, the synthetic method part was examined critically to tabulate the disclosures about solvent-free and solvent/s-based strategies to isolate ***Z***.

Widler L., *et al*, in 2002, had reported the phosphorylation of (**2**) in chlorobenzene using H_3PO_4 (85%) and PCl_3 to isolate ***Z*** (yield: 67.0%) [28]. Srinivasa RDVN., *et al*, in

2007, had reported the phosphorylation of (**2**) in *p*-cresol using H_3PO_3 along with PCl_3 to get ***Z*** (crude yield: 80.0%) [29]. Keglevich G., *et al*, in 2011 and 2012, had illustrated and explained the mechanistic aspects behind the phosphorylation of (**2**) in MSA using PCl_3 and with/without H_3PO_3 to obtain ***Z*** (crude yield: 0-71.0%). The work proved that, in the presence of MSA as the medium for reaction, alone PCl_3 can induce the phosphorylation and hence there is no requirement of H_3PO_3 to obtain ***Z*** (crude yield: 23.0-71.0%) [30, 31].

Mustafa DA., *et al*, in 2011, had disclosed the phosphorylation of (**2**) in sulfolane medium using H_3PO_3 along with PCl_3 under the assistance of microwave irradiation (3-4 min) to isolate ***Z*** (yield: 70.0%). Interestingly, the same experiment when conducted in a conventional pathway resulted in the formation of ***Z*** (yield: 67.0%) with not much deviation in outcome. But the conventional process takes more reaction time than the microwave irradiation pathway [32]. Lenin R., *et al*, in 2013, had reported the phosphorylation of (**2**) using H_3PO_3 and PCl_3 in the presence of silica gel under microwave irradiation (3-4 min) to isolate sodium salt of ***Z*** (yield: 80.0%) [33]. Kovács R., *et al*, in 2014, had reported a review article regarding the use of greener solvent MSA for the phosphorylation of (**2**) requiring alone PCl_3 [34]. Ratrout SS., *et al*, in 2015, had reported the phosphorylation of *t*-butyl-imidazol-1-yl acetate (**13**) in the presence of MSA and chlorobenzene using H_3PO_4 and $POCl_3$ to isolate sodium salt of ***Z*** (yield: 85.0%). It was later converted to ***Z*** (yield: 79.0%) by the treatment with concentrated HCl (37.0%). The work also disclosed the route of synthesis of (**13**) by condensation of (**1**) with (**11**) in acetonitrile using NaH [35].

Keglevich G., *et al*, in 2015, had disclosed the phosphorylation of (**2**) in MSA using PCl_3 to isolate sodium salt of ***Z*** and then to ***Z*** (yield: 49.0%) using 1 N HCl solution [36]. Nagy DI., *et al*, in 2016, had reported a review article regarding the use of different solvents for the synthesis of hydroxymethylenebisphosphonic acids. The work covers the synthesis of ***Z*** (yield: 31.0-53.0%) using MSA to phosphorylate (**2**) using PCl_3 and with/without H_3PO_3. Similarly, the use of chlorobenzene in various disclosures using H_3PO_4 or H_3PO_3 and PCl_3 gave ***Z*** (yield: 41.0-100%). Furthermore, the use of sulfolane for phosphorylation gave ***Z*** (yield: 67.0-71.0%). Attempts of solvent-free conditions for phosphorylation of (**2**) using H_3PO_3 and PCl_3 / $POCl_3$ gave ***Z*** (yield: 61.0-81.0%). Use of different ionic liquids as the diluent also gave ***Z*** or its sodium salt (yield: 26.0-92.0%). Similarly, the use of *p*-cresol as the solvent gave ***Z*** (yield: 80.0%). Additionally, phosphorylation of (**2**) in *n*-octane gave ***Z*** (yield: 65.0%). The work covers the use of other solvents like cyclohexane, 1, 4- dioxane, diphenyl ether, propylene carbonate, a mixture of propylene carbonate and PEG 600, PEG 400, dimethoxymethane, dimethoxyethane, diglyme, 1, 2-dichloroethane, *N*, *N*-dimethylurea, and silicon oil [37].

Nagy DI., *et al*, in 2017, had reported a review article covering the vital role of PCl_3 and H_3PO_3 in specific molar equivalents for the formation of hydroxymethy lenebisp hosphonic acids from the corresponding carboxylic acids. The work disclosed the impact of *p*-reagent/s for the phosphorylation of (**2**) in MSA or sulfolane medium to isolate ***Z*** [38]. Nagy DI., *et al*, in 2018, had illustrated the phosphorylation of (**2**) in sulfolane using H_3PO_3 and PCl_3 to isolate ***Z*** dihydrate (yield: 74.0%). The use of ionic liquid [bmim][BF_4] as the reaction medium gave ***Z*** dihydrate (yield: 75.0%). Similarly, the use of sulfolane and [bmim][BF_4] for phosphorylation resulted in the formation of ***Z*** dihydrate (yield: 93.0%) [39]. Nagy DI., *et al*, in 2018, had emphasized the phosphorylation of (**2**) in MSA using the *p*-reagent PCl_3 alone to isolate ***Z*** (yield: 53.0%) [40]. Grün A., *et al*, in 2019, had reported the phosphorylation of (**2**) in sulfolane, or the presence of an ionic liquid, or both together as the medium for the reaction using PCl_3 and H_3PO_3 to obtain ***Z*** (yield: 74.0-93.0%). The combination of solvent sulfolane and the ionic liquid [bmim][BF_4] gave a promising output of ***Z*** (yield: 93.0%) [41].

Ábrányi BP., *et al*, in 2021, had reported a review article covering the phosphorylation of (**2**) using only PCl_3 using MSA to isolate ***Z*** (yield: 46.0-53.0%). Similarly, the use of H_3PO_3 and PCl_3 in sulfolane gave ***Z*** (yield: 63.0-74.0%) [42]. Grün A., *et al*, in 2021, had disclosed the phosphorylation of (**2**) using different equivalents of H_3PO_3 and PCl_3 in diethyl carbonate (DEC) as a green solvent medium to isolate ***Z*** (0-61.0%). The work extends to cover the use of MSA and DEC, alone or in different combination ratios to synthesize ***Z*** (yield: 0-53.0%). This approach was observed to be less efficient as compared to the use of sulfolane for phosphorylation. But, found reasonably better as compared to the use of MSA for phosphorylation to isolate ***Z***. [43]. Sanjay SS., in 2023, had reported a review article regarding the synthesis and purification of ***Z***. It covers the disclosures provided in various patents regarding the till date adopted synthetic strategies in detail to isolate ***Z*** and its few forms [44].

Summary

As per the prior arts, phosphorylation in MSA medium requires only PCl_3. If the same was performed in solvents other than MSA, then both PCl_3 and H_3PO_3 are required in

optimum equivalents. Numerous solvents are being used for the phosphorylation to isolate ***Z*** and its salt, all those were tabulated in **Table 1**.

Table 1 List of solvent-free and solvent-based strategies employed for the phosphorylation to synthesize *Z*.

Solvent/s based synthetic strategies	
Solvent/s for phosphorylation	**References**
Chlorobenzene	[1], [2], [5], [8], [27], [28], [35]
Tributylammoniumchloride	[3]
Silicon oil	[4], [5]
Toluene	[5]
PEG-400	[5], [15], [20]
Sulfolane	[6], [7], [17], [27], [32], [39], [41]
1, 2-Dimethoxyethane	[6]
Cyclohexane	[8]
Ethylene dichloride	[8]
1, 4-Dioxane	[10], [21]
n-Octane	[11]
Methanesulfonic acid	[12], [18], [24], [30], [31], [34], [35], [36], [40], [43]
Diphenyl ether	[13]
Diglyme	[15]
N, N'-dimethylethyleneurea	[16]
Diethyl carbonate	[20], [43]
Diethyl carbonate & PEG-400	[20]
Propylene carbonate & PEG-400	[20]
Propylene carbonate & PEG-600	[20]
Propylene carbonate & PEG-1000	[20]
Tetrahydrofuran	[21]
Trifluoroacetic acid	[22]
Sulfuric acid	[22]
Liquid paraffin	[23]
n-Hexane	[25]
n-Decane	[25]
n-Tetradecane	[25]
Ionic liquid/s	[26], [39], [41]
p-Cresol	[29]
Silica gel	[33]
Sulfolane & Ionic liquid	[39], [41]
Methanesulfonic acid & Diethyl carbonate	[43]
Solvent-free synthetic strategies	
Phosphorylation in the absence of solvent/s	[9], [14], [19], [27]

CONCLUSION

An exceptionally complex phosphorylation forms a crucial step to synthesize ***Z***. To ensure the scalability and the industrial adaptability of phosphorylation, numerous reaction optimization experiments were reported by many researchers. As a part of it, solvent-free and different solvent/s involved phosphorylation reactions were demonstrated with varied purity and yields of ***Z***. This work primarily focused to give an overview of all the solvents used and the solvent-free synthetic strategies adopted for the phosphorylation to prepare ***Z***. The supportive details were extracted separately from the filed patents and the journal publications, comprising the specific illustrations towards the synthesis of ***Z***.

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