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Synthetic Utility of Propylphosphonic Anhydride–DMSO Media: An Efficient One-pot Three-component Synthesis of 2-Arylquinolines

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Propylphosphonic anhydride (T3P®)–DMSO-mediated one-pot three-component synthesis which provides 2-arylquinolines in a single step from benzyl alcohols, anilines, and ethyl vinyl ether by the modified Povarov reaction has been demonstrated. T3P®–DMSO is a mild and low-toxic peptide coupling agent and an easy to handle reagent for bulk reactions at room temperature.

Quinolines, as a leading pharmaceutically important compound, are present in many biologically active alkaloids and exhibit a number of interesting biological activities, such as antibacterial,[1] anti-inflammatory,[2] antifungal and analgesic properties.[3] Since the basic skeleton of quinolines is widespread in natural products, numerous approaches including the Conrad–Limpach–Knorr synthesis,[4] the Skraup–Doebner–Von Miller synthesis,[5] and the Friedlander synthesis,[6] have been developed for the synthesis of quinolines. Recently, reports concerning transition-metal-mediated synthesis of quinolines have also appeared,[7] and many transition metals like rhodium,[7a] iron,[7b] zinc,[7c] and iridium,[7d] are being used.

Cyclocondensation and cycloaddition reactions are the most effective methods for the construction of *N*-heterocycles. Among these, the acid-catalyzed imino Diels–Alder Povarov reaction[8a] has been widely used to build substituted quinoline core from anilines, aldehydes, and electron-rich alkenes by asymmetric,[8b] enantioselective,[8c] and diastereoselective[8d] synthesis by the Povarov reaction.

Although a variety of methods for the synthesis of these quinoline frameworks have been developed, most of the preparations involve stepwise processes, decrease in yield, and tedious workup and harsh reaction conditions, and to overcome all these cumbersome processes new synthetic methods are being explored. From a literature survey it was evident that quinolines were not synthesized from alcohols through the Povarov reaction, in this reaction media that utilizes oxidation of alcohols to carbonyl compounds, and then cyclocondensation with anilines followed by the Diels–Alder [4 + 2] cycloaddition with electron-rich alkenes, through the Povarov reaction gave quinolines in high yields. One-pot synthetic sequences have been now recognized as more a sustainable approach to target molecules as they minimize the number of steps as well as the reaction time and waste. Therefore, development and search for new procedures with novel substrate scope is continuing and is in great demand.

Propylphosphonic anhydride (Figure 1) is a prevailing peptide coupling reagent with low toxicity.[9] Its versatility as a reagent in organic synthesis has generated innovative uses beyond peptide synthesis.[10] T3P® has been utilized in molecular rearrangements,[11] dehydration chemistry,[12] and in the preparation of a range of functionalized heterocycles.[13a,13b] T3P® has also been used in the synthesis of quinolines.[14a–14c] Recently, we have reported a one-pot tandem approach for the synthesis of benzimidazoles, benzothiazoles,[15] and 4-thiazolidinones,[16] from alcohols using DMSO–propylphosphonic anhydride (T3P®) media as an oxidizing as well as cyclodehydrating agent, in continuation of our work on the development of new synthetic methodologies toward pharmaceutically important heterocyclic compounds.

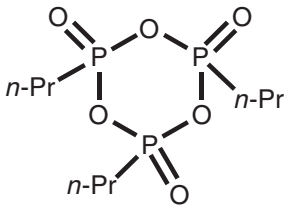
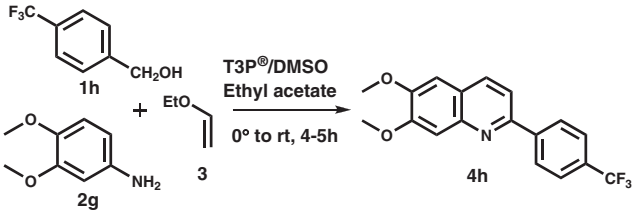


Figure 1. Structure of propylphosphonic anhydride (T3P®).



Scheme 1. General approach for the synthesis of 2-arylquinolines.

We attempted T3P®–DMSO-mediated one-pot three-component synthesis of 2-arylquinolines directly from various alcohols, involving oxidation, condensation followed by cyclization under mild reaction conditions (Scheme 1) and the results are presented in Table 1. Initially, a model reaction was conducted between benzyl alcohol (**1a**) (1.1 mmol), aniline (1.0 mmol) (**2a**) and ethyl vinyl ether (1.0 mmol) (**3**) in the presence of T3P® (1.0 mmol) in a mixture of solvents containing EtOAc:DMSO in 2:1 ratio at 25 °C for 8 h, which afforded 2-arylquinolines in 20% yield. We then monitored the reaction by increasing the equivalence of T3P® and we observed that 2.0 mmol of T3P® gave maximum yield 93% of the desired 2-arylquinoline **4a** (Table 1, Entry 3). These results suggested that the stoichiometry of T3P® plays an important role in the progress of the reaction. Next we studied the effect of solvent on reaction. Initially the reaction was carried out in DMSO and we did not get considerable yield of the required compound of 2-arylquinoline. Subsequently we tried various solvent mixtures like THF, toluene, CH_2Cl_2, $CHCl_3$, dioxane, and CH_3CN with

Table 1. Synthesis of **4a** under different reaction condition

Entry	Solvent[a]	T3P[b] /equiv	Temp /°C	Time /h	Yield /%[c]
1	EtOAc	1.0	0–25	8	20
2	EtOAc	1.5	0–25	8	55
3	EtOAc	2.0	0–25	4	93
4	EtOAc	3.0	0–25	4	89
5	THF	2.0	0–25	4	70
6	Toluene	2.0	0–25	4	25
7	CH_2Cl_2	2.0	0–25	4	35
8	$CHCl_3$	2.0	0–25	4	43
9	Dioxane	2.0	0–25	4	40
10	CH_3CN	2.0	0–25	4	45
11	EtOAc	2.0	40	3	81
12	EtOAc	2.0	50	2.5	76
13	EtOAc	2.0	60	2	72
14	EtOAc	2.0	70	1	68

[a]Solvent and DMSO were taken in 2:1 volume ratio. [b]T3P® 50% solution in ethyl acetate. [c]Isolated yield.

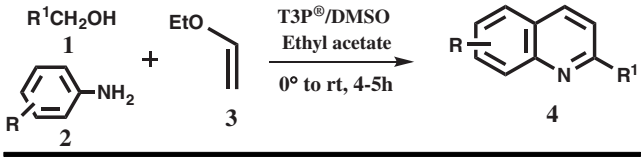
DMSO, but none of the solvent systems gave significant yield (Table 1, Entries 5–10). Hence ethyl acetate with DMSO proved to be the best solvent mixture for this reaction. Optimization of temperature for the reaction was carried out at temperature of 40, 50, 60, and 70 °C (Table 1, Entries 11–14), it was observed that increase in temperature resulted in gradual decrease in yield and reaction time.

Hence room temperature was chosen as the optimum temperature for this reaction. The scope of this method was extended by the study of the reaction of different substituted benzyl alcohols and anilines for the transformation. It was observed that diverse functional groups played significant roles in providing the product yields. Benzyl alcohols with electron-donating as well as electron-withdrawing groups at the 4-position reacted well with aniline derivatives and gave almost equal product yields. In the case of 2-substituted benzyl alcohols yields were less due to steric hindrance associated with the substituent (Table 2, Entries 4, 6, 10, and 12). In the case of 3-substituted anilines mixtures of 5- and 7-substituted quinoline regioisomers were obtained as products in considerable yield. It is noteworthy that both benzyl alcohol and aniline bearing various functionalities such as nitro, methyl, halogen, methoxy, ester, trifluoromethyl, and hydroxy groups survived the reaction and the relevant results are presented in Table 2.

The possible mechanism involves the reaction of DMSO with T3P® followed by substitution reaction of alcohol and results in the cleavage of phosphoester bond to form intermediate **5**. Elimination of dimethyl sulfide gives carbonyl compound **6** which undergoes condensation and cyclization by the [4 + 2] Diels–Alder cycloaddition with vinyl ethyl ether through the modified Povarov reaction to afford 2-arylquinolines **4** as shown in Scheme 2.

A convenient and versatile method has been developed and optimized for the synthesis of 2-arylquinolines mediated by T3P®–DMSO, a mild and low-toxic peptide coupling agent. The method not only employs readily accessible T3P®, but also tolerates diverse benzyl alcohols and various anilines giving access to distinctively substituted 2-arylquinolines in good yields. Further, it is an easy to handle reagent for bulk reactions, and the reaction conditions are sufficiently mild that sensitive functional groups are tolerated making the process more practical for 2-arylquinolines synthesis.

Table 2. Scope of the propylphosphonic anhydride in three-component Povarov reaction



Entry[a]	R^1 (**1**)	Ar (**2**)	**4**	Time /h	Yield /%[b]
1	C_6H_5 (**1a**)	C_6H_5 (**2a**)	**4a**	4	93[17a,17b]
2	4-ClC_6H_4 (**1b**)	4-$MeOC_6H_4$ (**2b**)	**4b**	4	90[17e]
3	4-FC_6H_4 (**1c**)	4-$MeOC_6H_4$ (**2b**)	**4c**	4	91[17d]
4	2-ClC_6H_4 (**1d**)	3-$MeOC_6H_4$ (**2c**)	**4d**	5	80
5	4-HOC_6H_4 (**1e**)	4-$NO_2C_6H_4$ (**2d**)	**4e**	5	86[17g]
6	2-$NO_2C_6H_4$ (**1f**)	2-Me-3-BrC_6H_3 (**2e**)	**4f**	5	75
7	2,4-$Me_2C_6H_3$ (**1g**)	3-FC_6H_4 (**2f**)	**4g**	4	87
8	4-$CF_3C_6H_4$ (**1h**)	2,4-$(MeO)_2C_6H_3$ (**2g**)	**4h**	4	90
9	4-$MeOC_6H_4$ (**1i**)	3-$MeOC_6H_4$ (**2c**)	**4i**	4	92
10	2-ClC_6H_4 (**1d**)	2,4-$(MeO)_2C_6H_3$ (**2g**)	**4j**	4	82
11	4-FC_6H_4 (**1c**)	4-FC_6H_4 (**2h**)	**4k**	4	91[17f]
12	2-MeO-4-FC_6H_3 (**1j**)	2-$MeOC_6H_4$ (**2i**)	**4l**	4.5	78
13	4-COOMe-2-$MeOC_6H_3$ (**1k**)	2-naphthyl (**2j**)	**4m**	5	90
14	3-FC_6H_4 (**1l**)	4-FC_6H_4 (**2h**)	**4n**	4	95
15	C_6H_5 (**1a**)	4-FC_6H_4 (**2h**)	**4o**	4	90[17c]
16	C_6H_5 (**1a**)	4-$MeOC_6H_4$ (**2b**)	**4p**	4	88[17d]

[a]Benzyl alcohol (**1a**) (1.1 mmol), aniline (1.0 mmol) (**2a**), ethyl vinyl ether (1.0 mmol) (**3**), T3P® (2.0 mmol).[18] See Supporting Information for experimental detail.[19] [b]Literature reported compounds.

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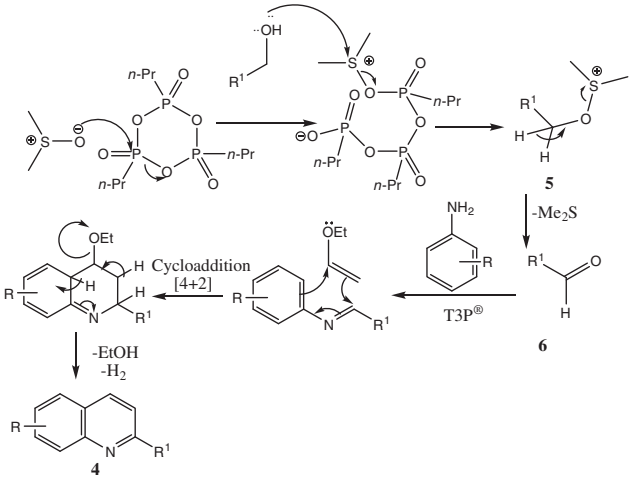

Scheme 2. Possible mechanism of the T3P®–DMSO-mediated 2-arylquinolines synthesis.

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18 Procedure for the preparation of 2-arylquinoline **4**: To a suspension of benzyl alcohol (1.1 g, 0.0101 mol), aniline (0.94 g, 0.0101 mol), and ethyl vinyl ether (0.728 g, 0.0101 mol) in a mixture of EtOAc:DMSO (8.0:2.0 mL) was added T3P® (2.0 mmol, 50% solution in ethyl acetate) at 0 °C, and the resulting mixture was stirred at room temperature for 4–5 h. Progress of the reaction was monitored by TLC. The reaction mass was concentrated, the obtained residue was neutralized with 10% $NaHCO_3$ solution, and then extracted with ethyl acetate (2 × 20 mL), the combined organic phase was washed with water and brine solution, and dried over anhydrous sodium sulfate. The organic phase was evaporated and the crude product was purified by column chromatography using silica gel mesh 100–200 (15% EtOAc in hexanes).

19 Supporting Information is available electronically on the CSJ Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

