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An efficient synthesis of nitrile, tetrazole and urea from carbonyl compounds†

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An efficient conversion of carbonyl compounds (aldehydes and ketones) to nitrile, tetrazole, and urea was developed with the use of a $POCl_3$ and sodium azide mixture using a convergent and microwave method. This is the first report on the direct conversion of ketone to urea. The synthesized compounds were characterized by ^1H NMR, ^{13}C NMR, mass and IR spectroscopies and were found to be in agreement with reported compounds.

Introduction

Carbonyl conversions are important processes in organic syntheses/preparations. They have been used to synthesize various effective intermediates such as amides,[1] oximes,[2] imines,[3] alcohols[4] and tetrazoles.[5] Many scientists have developed various synthetic methods starting from carbonyl precursors.[6] The Schmidt reaction is one of the well-known methods for carbonyl conversions.[7] In this process, carbonyl compounds were converted into carboxamides in the presence of an acid/Lewis acid catalyst and an azide source.[8,9] Further, the carboxamides can be converted into tetrazoles with the use of sodium azide and a halogenating agent.[10] In our previous report, we developed the methodology for direct conversion of amide to tetrazole with the use of $POCl_3$ and NaN_3.[11] Phosphoryl chloride is a well-known halogenating agent which can also act as an acid catalyst. So the direct conversion of carbonyl to tetrazole can be achieved with the use of $POCl_3$ and sodium azide *via* amide formation.

The actual research is planned to synthesize tetrazole from carbonyl compounds because tetrazole has numerous applications in the field of chemistry.[12–15] Three different precursors such as benzaldehyde, acetophenone, and benzophenone have been chosen and the reaction methodology has been followed as per Sribalan *et al.*[11] As expected, acetophenone converted into tetrazole and the other precursors gave different unexpected products. The unexpected products were isolated and identified as benzonitrile and diphenylurea. These products are valuable intermediates having various synthetic applications. Nitrile compounds are very good precursors for synthesizing various functional groups such as carboxylic acids,[16] oximes,[17] tetrazoles,[18] amines,[19] imidazoles[20] and carboxamides.[21] Similarly, urea can be used as a precursor for synthesizing various functionalities such as amines,[22] carbamates,[23] isocyanates[24] and imides.[25] Urea derivatives have also shown many applications in the fields of materials chemistry,[26] electrochemistry,[27] crystallography,[28] catalyses,[29] photochemistry,[30] polymer chemistry[31] and medicinal chemistry.[32] In particular, in the medicinal chemistry field, urea-based compounds have shown various bioactivities such as antibacterial,[33] anti-inflammatory,[34] anticancer,[35] antidiabetic,[36] and anti-HIV[37] activities. Urea denatures nucleobases[38] and proteins[39] and has been reported as a Rho kinase inhibitor.[40] To the best of our knowledge, there are no reports available on these conversions (nitrile, tetrazole, and urea) with $POCl_3$ and NaN_3 mixtures. Few reports are available on the synthesis of urea by Curtius rearrangement,[41] and the reaction of isocyanates/phosgenes with an amine.[42,43] But there are no reports available on the conversion of carbonyl compounds to urea. In particular, this is the first report on the direct conversion of ketone to urea. The conversion of an aldehyde to nitrile has been reported with a long reaction time.[44–49] But there are no reports available on the conversion of an aldehyde to nitrile within a minute at room temperature. Thus the research is continued to develop the conversion of carbonyls to nitrile, tetrazole, and urea with the use of a $POCl_3$ and NaN_3 mixture. Furthermore, these conversions were developed in a microwave synthesizer for reducing the reaction time. The merits of this method include less reaction time, low-cost reagents, easily available precursors, single step conversion, reagents as solvents and good yields. Overall, the conversion of carbonyls to various functionalities is presented in Scheme 1.

Experimental section

General consideration

All the reactions were carried out with the use of a guard tube set-up and nitrogen gas was purged into the reaction set-up

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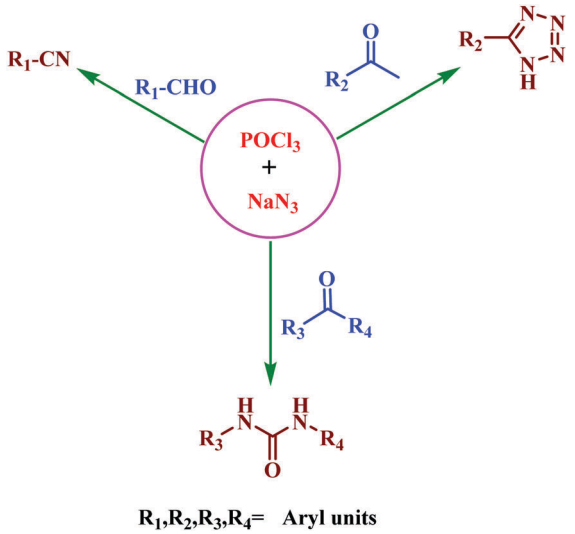


Scheme 1 Schematic representation of various carbonyl conversions.

before starting the reaction (to avoid moisture contact). All the reagents were purchased from Sigma-Aldrich/Spectrochem. Phosphoryl chloride was used from a freshly opened bottle or a distilled one (to avoid moisture contact in the reaction). The reactions were tested up to a 5 g scale in the thermal method and a 3 g scale in the microwave method (for safety purposes). (**Caution**: Generally, azides are explosives. So the personal protective equipment (PPE) like face shields has to be worn before starting the reactions.) IR spectra were recorded on a JASCO FT-IR410 using the KBr pellet method. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 300 MHz and 75 MHz instruments in $CDCl_3$ with TMS as an internal standard. Chemical shift values are mentioned in δ (ppm) and coupling constants are given in Hz. Mass spectra were recorded on an AB SCIEX 3000 LC-MS. The progress of all reactions was monitored by TLC on 2 × 5 cm pre-coated silica gel 60 F254 plates with a thickness of 0.25 mm (Merck). The chromatograms were visualized under UV 254–366 nm and iodine. All the reactions (both thermal and microwave reactions) were carried out in an open vessel with a guard tube set-up for the safer method.

Chemistry

General procedure for the conversion of aldehydes to nitriles (2a–n). To a stirred mixture of aldehyde (1 mmol) and sodium azide (1 mmol), phosphorus oxychloride was added (in the open vessel with a guard tube) and the reaction mixture was quenched with crushed ice. Then the reaction mixture was extracted with ethyl acetate (50 mL), and washed with sodium bicarbonate solution (50 mL), water (50 mL) and brine solution (50 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. The evaporation of the solvent afforded the product.

General procedure for the conversion of acetophenones to 5-methyltetrazoles (4a–j)

Thermal method. To acetophenone (1 mmol), sodium azide (2 mmol) and phosphorus oxychloride were added (in the open vessel with a guard tube). Before starting the reaction, nitrogen gas was purged into the reaction mixture for 5 min. The reaction mixture was heated to 80 °C for 9 h. The completion of the reaction was monitored by TLC. Then the reaction mixture was allowed to attain room temperature and carefully quenched with crushed ice. Then the reaction mixture was extracted with ethyl acetate, and washed with sodium bicarbonate solution (50 mL), water (50 mL) and brine solution (50 mL). The organic layer was separated and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and finally, the product was purified by column chromatography with ethyl acetate and petroleum ether as an eluent.

Microwave method. In a 10 mL double neck RB flask, acetophenone (1 mmol), phosphorus oxychloride (2 mmol) and sodium azide (2 mmol) were added and one neck is connected to a reflux condenser with a guard tube and the other neck is connected to a nitrogen inlet. The nitrogen gas is purged into the reaction mixture for 10 min. Then the nitrogen inlet was removed and immediately closed with a stopper. The reaction setup was fixed in a microwave synthesizer (better to avoid sealed tube microwave irradiation). The reaction mixture was subjected to microwave irradiation at 120 W at 90 °C for 20 min. Then the reaction mixture was allowed to attain room temperature. Then the reaction mixture was quenched with crushed ice. The mixture was neutralized with sodium bicarbonate solution. The product was extracted with ethyl acetate (50 mL), and washed with water (50 mL) and brine solution (50 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Finally, the product was purified by column chromatography petether and ethlyl acetate with as an eluent.

General procedure for the conversion of benzophenones to diphenyl urea derivatives (6a–l)

Thermal method. To benzophenone (1 mmol), sodium azide (2 mmol) and phosphorus oxychloride (5 mmol) were added (in the open vessel with a guard tube). Before starting the reaction, nitrogen gas was purged into the reaction mixture for 5 min. The reaction mixture was heated to 80 °C for 24 h. The completion of the reaction was monitored by TLC. Then the reaction mixture was allowed to attain room temperature and carefully quenched with crushed ice. Then the reaction mixture was extracted with ethyl acetate and washed with sodium bicarbonate solution (50 mL), water (50 mL) and brine solution (50 mL). The organic layer was separated and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and finally, the product was purified by column chromatography with ethyl acetate and petroleum ether as an eluent.

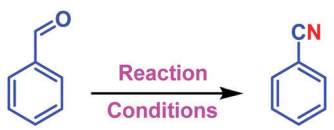
Microwave method. In a 10 mL double neck RB flask, benzophenones (1 mmol), phosphorus oxychloride (5 mmol) and sodium azide (2 mmol) were added and one neck is connected to a reflux condenser with a guard tube and the other neck is connected to a nitrogen inlet. The nitrogen gas is purged into the reaction mixture for 10 min. Then the nitrogen inlet was removed and immediately closed with a stopper. The reaction setup was fixed in a microwave synthesizer (better to avoid sealed tube microwave irradiation). The reaction mixture

was subjected to microwave irradiation at 120 W at 90 °C for 30 min. Then the reaction mixture was allowed to attain room temperature. Then the reaction mixture was quenched with crushed ice. The mixture was neutralized with sodium bicarbonate solution. The product was extracted with ethyl acetate (50 mL), and washed with water (50 mL) and brine solution (50 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Finally, the product was purified by column chromatography with pet etheracetate as an eluent.

Results and discussion

Initially, the conversion of an aldehyde to nitrile was carried out in the presence of a $POCl_3$ and NaN_3 mixture and benzaldehyde was chosen as a model substrate for optimization. The best solvents for dissolving sodium azide were water, DMF, and DMSO. The selection of these solvents was not advisable for our reaction conditions, because these solvents readily react with $POCl_3$ and generate by-products such as phosphoric acid, Vilsmeier formulating agents and Swern oxidizing agents.[50,51] So the reaction was started with toluene, THF, 1,4-dioxane, and acetonitrile and carried out with equimolar amounts of $POCl_3$ and NaN_3 at room temperature. Depending on the polarity of the solvents, the reaction time was varied and yields achieved were from moderate to good (Table 1, entries 1–4). The preliminary results suggested that acetonitrile is a good solvent because its reaction time and yields are better than those of the others. When temperature was increased to 80 °C the reaction time was reduced to 30 min and the yield of the reaction was increased to 86% (Table 1, entry 5). Even though the reaction was complete in 30 minutes with a good solvent, the research was continued to develop better optimization. Since our previous report suggested that only $POCl_3$ and NaN_3 were better than solvent used methodologies, optimization was continued with excessive $POCl_3$ (5 eq.) and equimolar sodium azide at room temperature (Table 1, entry 6). Unexpectedly, the reaction was complete within a minute and the reaction yield was increased to 92%. Furthermore, the reaction was repeated for its development

Table 1 Optimization of the reaction conditions for conversion of an aldehyde to nitrile



1a 2a

S. No.	Solvent	$POCl_3$ (eq.)	NaN_3 (eq.)	Temp. (°C)	Time	Yield (%)
1	Toluene	1.0	1.0	RT	8 h	70
2	THF	1.0	1.0	RT	6 h	75
3	1,4-Dioxane	1.0	1.0	RT	5 h	79
4	ACN	1.0	1.0	RT	4.5 h	81
5	ACN	1.0	1.0	80 °C	30 min	86
6	$POCl_3$	5.0	1.0	RT	<1 min	92
7	Nil	1.0	1.0	RT	<1 min	95

Table 2 Optimization of the reaction conditions for conversion of acetophenone to 5-methyltetrazole

S. No.	$POCl_3$ (eq.)	NaN_3 (eq.)	Temperature (°C)	Time (h)	Yield (%)
1	1.0	2.0	60	12	50
2	2.0	2.0	60	11	82
3	2.0	2.0	80	9	87
4	2.0	2.0	95	8	75
5	2.0	3.0	80	9	80
6	5.0	2.0	80	10	84
7	10.0	2.0	80	10	75

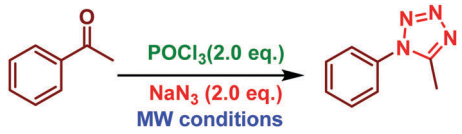
from the previous optimization with equimolar $POCl_3$ and NaN_3 (Table 1, entry 7). The same results were obtained with 95% yield. Thus, the optimized results revealed that equimolar sodium azide and $POCl_3$ were the best conditions for the conversion of an aldehyde to nitrile. The list of these optimized conditions for this conversion is presented in Table 1.

Based on the above-optimized results, the conversion of acetophenone to tetrazole was started with neat $POCl_3$ and sodium azide. The first reaction was carried out with equimolar $POCl_3$ and NaN_3 at 60 °C (Table 2, entry 1). The reaction was complete in 12 h and the yield was 50% correspondingly. Furthermore, for improving the yield of the reaction, the quantity of $POCl_3$ was increased to 2 eq. and the reaction was repeated at 60 °C. The reaction was complete in 11 h and its yield was improved to 82% (Table 2, entry 2). To identify the best optimized conditions the reaction was repeated under several reaction conditions and reagent quantities (Table 2, entries 3–7). Among the various conditions, 2 eq. of $POCl_3$ with equimolar sodium azide (2 eq.) at 80 °C for 9 h with 87% yield were identified as the best optimized conditions (Table 2, entry 3). Upon continuation, the same method was developed in the microwave synthesizer (open vessel method).

The best conditions in the thermal method (Table 2, entry 3) were chosen for optimization in a microwave synthesizer for the conversion of acetophenone to tetrazole. To optimize the best reaction conditions different microwave powers (80 to 120 W), temperatures (80 to 100 °C) and reaction times (5 to 30 min) were applied (Table 3, entries 1–7). Among these conditions, 2 eq. of $POCl_3$, 2 eq. of NaN_3 at 90 °C, and 120 W for 20 min were identified as the best optimized conditions with 82% yield of the product (Table 3, entry 6). The list of optimized conditions for the conversion of acetophenone to 5-methyltetrazole using both thermal and microwave methods is presented in Tables 2 and 3.

Similarly, neat $POCl_3$ and NaN_3 were chosen for the conversion of benzophenone to diphenylurea. Initially, the reaction was carried out with 1–2 eq. of $POCl_3$ and 1–2 eq. of NaN_3 for 12 h at 60 °C. The reactions yielded a trace amount of diphenylurea (Table 4, entries 1 and 2). To optimize the best conditions, the reaction was repeated with different equivalents of reagents, reaction times and temperatures (Table 4, entries 3–10). Finally, the optimized reaction conditions were identified as 5 eq. of

Table 3 Optimization of the reaction conditions for conversion of acetophenone to 5-methyltetrazole using the microwave method



S. No.	MW power (W)	Temperature (°C)	Reaction time (min)	Yield (%)
1	80	80	5	<5
2	80	80	20	22
3	80	80	30	28
4	100	80	20	35
5	100	90	20	43
6	120	90	20	82
7	120	100	20	74

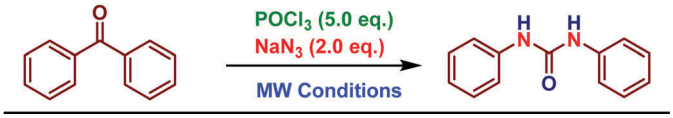
Table 4 Optimization of the reaction conditions for conversion of benzophenone to diphenylurea using the thermal method

S. No.	$POCl_3$ (eq.)	NaN_3 (eq.)	Temperature (°C)	Time (h)	Yield (%)
1	1.0	2.0	60	12	Trace
2	2.0	2.0	60	12	Trace
3	2.0	2.0	80	12	<5
4	2.0	2.0	95	12	<5
5	2.0	3.0	80	15	<5
6	5.0	2.0	80	15	25
7	5.0	2.0	80	20	52
8	5.0	2.0	80	24	75
9	5.0	2.0	80	36	70
10	10.0	2.0	80	24	68

$POCl_3$, 2 eq. of NaN_3 at 80 °C for 24 h with 75% yield of diphenylurea. During the course of the reaction, there was the formation of diphenyltetrazole as a by-product (15%) which was inevitable. When the quantity of NaN_3 was high, tetrazole formation also increased. The usage of 2 eq. of NaN_3 resulted in a maximum yield of urea. Furthermore, the same reaction was developed in a microwave synthesizer (open vessel method). The best conditions in the thermal method were chosen for the microwave synthetic method during the conversion of benzophenone to diphenylurea. To optimize the best reaction conditions, the microwave power (80 to 120 W), temperature (80 to 90 °C) and reaction time (10 to 40 min) were changed (Table 5, entries 1–9). Among these conditions, 5 eq. of $POCl_3$, 2 eq. of NaN_3 at 90 °C, and 120 W for 30 min were identified as the best optimized conditions with 82% yield of the product (Table 5, entry 8). The list of optimized conditions for the conversion of benzophenone to diphenylurea by both thermal and microwave methods is presented in Tables 4 and 5.

The scope of these conversions was examined with various substrates like electron withdrawing, electron donating and sterically hindered precursors. Negligible yield variations were identified in the conversion of an aldehyde to nitrile (84–96%). In the case of conversion of acetophenones to 5-methyltetrazoles,

Table 5 Optimization of the reaction conditions for conversion of benzophenone to diphenyl urea using the microwave method



S. No.	MW power (W)	Temperature (°C)	Reaction time (min)	Yield (%)
1	80	80	10	Trace
3	80	80	20	10
4	100	80	20	15
5	100	90	20	53
6	110	90	20	59
7	120	90	20	64
8	120	90	30	73
9	120	90	40	66

electron donating groups like methoxy and methyl on the *para* positions gave good yields when compared to the parent substrate (85–88%). Similarly, a chloro substituent on the *para* position gave 84% tetrazole. But an electron withdrawing group (–NO_2) on the *para* position affected the yield of the reaction, which afforded 62–63% of the product. Similarly, *ortho* substituents also affect the yield of the reaction. For instance, *ortho* methoxy acetophenone gave 53–55% tetrazole. The *meta* substituent gave a moderate yield (73–75%). Bulky substituents like naphthalene and biphenyl and

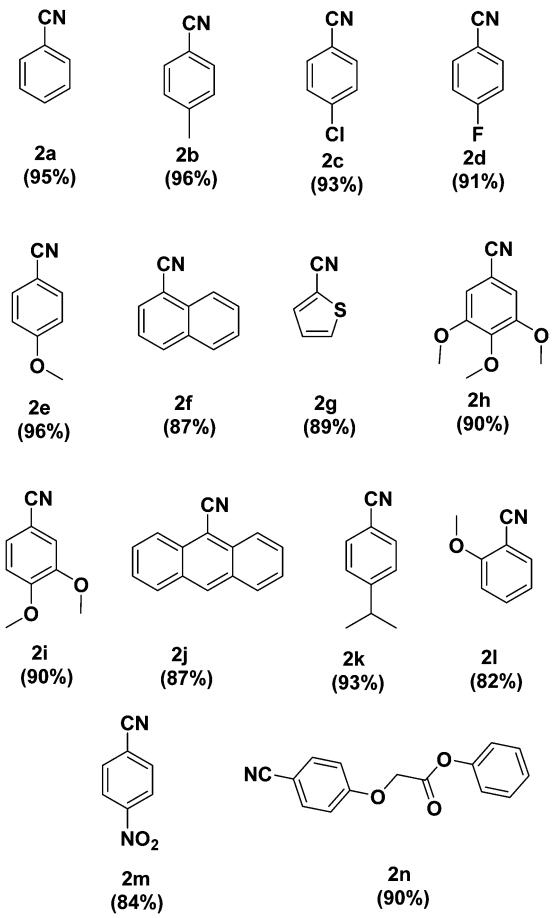


Fig. 1 List of synthesized nitriles.

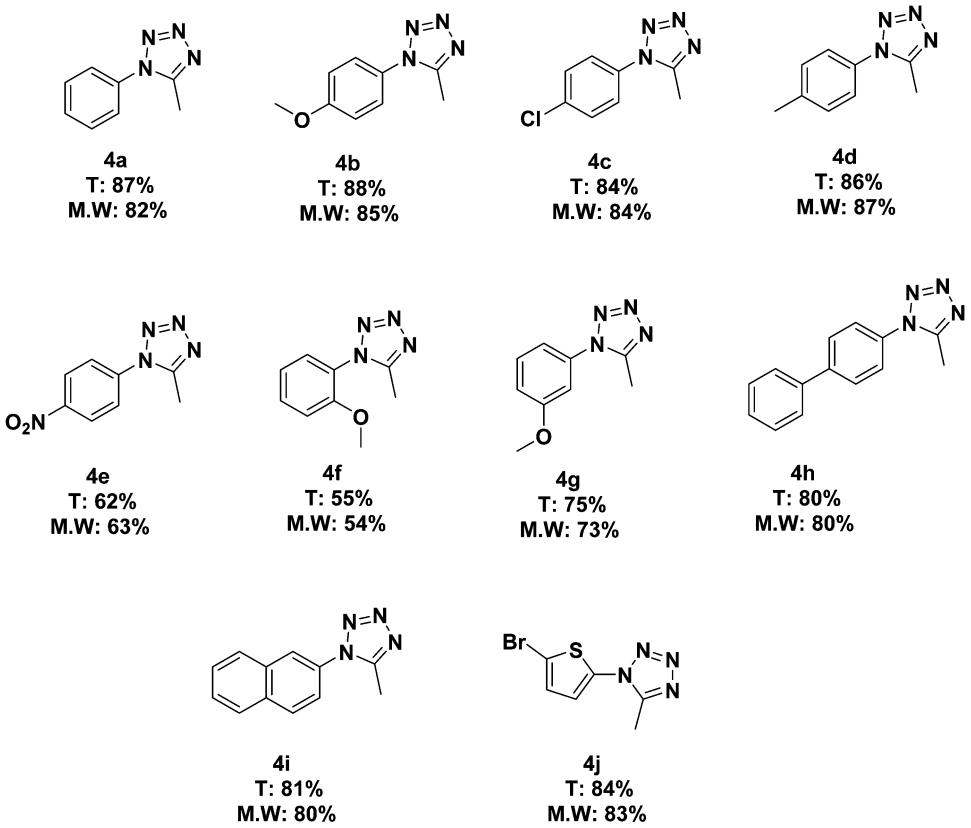


Fig. 2 List of synthesized tetrazoles.

heterocycles like thiophene also gave a good yield of products (80–84%).

Similar to acetophenone conversion, the substrate scope affects the conversion of benzophenones to diphenylureas. Substituents like methyl and chloro on the *para* position gave 70–73% yields of urea. An electron withdrawing group like nitro on the *para* position gave a very poor yield (50–52%). Similarly, substituents on the *ortho* position gave a poor yield of the product (54–56%). The *meta* substitution and bulky units such as phenoxyphenyl and naphthalene gave 60–69% of products. Aliphatic substituents containing substrate *tert*-butyl phenyl ketone gave their corresponding urea with 61–62% yield. The little yield variations were identified between thermal and microwave conversions. The list of synthesized products and their yields is presented in Fig. 1–3.

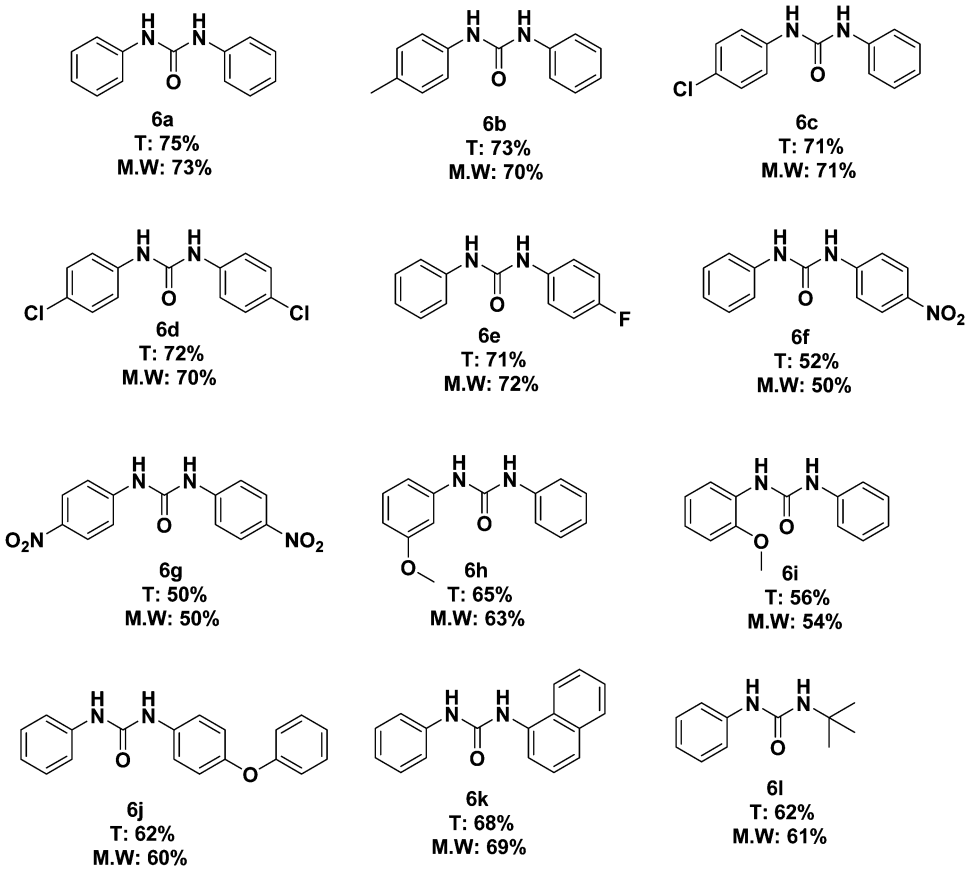
Plausible mechanisms for the formation of products were proposed from their corresponding precursors (Fig. 4). For proposing the mechanism for these conversions, the intermediates were isolated (intermediates **IV** and **XII**, which are presented in the ESI†). Based on the intermediate and product formation, the plausible mechanism for these conversions was proposed.

In the conversion of an aldehyde to nitrile, the lone pair of oxygen of carbonyl attacks the phosphoryl chloride, giving intermediate **I**. Intermediate **I** gave intermediate **II**. The final product **III** was obtained from intermediate **II** *via* the elimination of H^+ and nitrogen molecules.

In the conversion of acetophenone to tetrazole, the addition of carbonyl to phosphoryl chloride gives vinyl chloride **IV**. The nucleophilic addition of an azide anion to vinyl chloride gave vinyl azide **V**. Furthermore, nucleophilic addition of an azide anion to vinyl azide gave intermediate **VII** *via* intermediate **VI**. Finally, tetrazole **VIII** was obtained *via* internal cyclization of intermediate **VII**.

In the conversion of benzophenone to urea, the intramolecular rearrangement of R_2 in intermediate **II** gave intermediate **IX**. The nucleophilic addition of an azide anion to intermediate **IX** gave intermediate **X**. **X** gave carbodiimide **XII** with the elimination of nitrogen molecules followed by the rearrangement.[11] The carbodiimide gave the corresponding urea **XIII** upon the addition of water (while quenching).[11] During this conversion, the minor product tetrazole is formed from the internal cyclization of intermediate **X**. The tetrazole and intermediate **X** are in equilibrium with each other and lead to tetrazole formation.[52] Upon increasing the sodium azide quantity, the equilibrium is shifted towards tetrazole formation.

From the above conversions, it is clear that the carbonyl compounds containing the α-hydrogen are ready to convert into vinyl chloride with phosphoryl chloride. It further reacts with sodium azide and gives tetrazoles.[53] But the benzophenone based compound does not have α-hydrogen and follow a different reaction pathway with the same reagents and conditions. So it



T: Thermal yield; M.W: Microwave yield

Fig. 3 List of synthesized diphenyl urea derivatives.

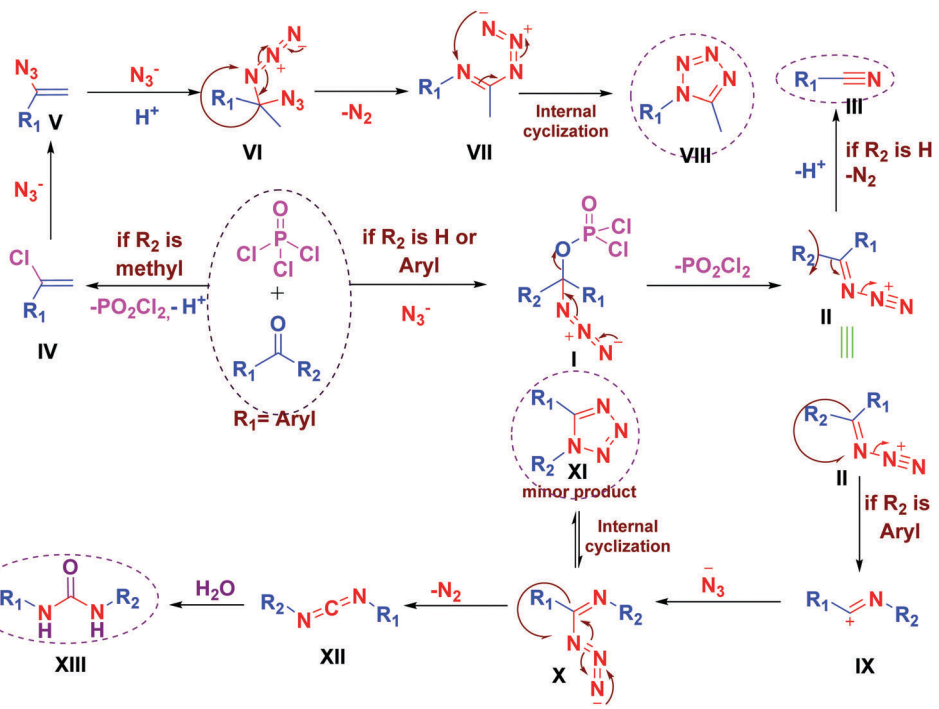


Fig. 4 Plausible mechanism for the formation of nitrile, tetrazole, and urea.

afforded urea as the major product. The NMR spectra of intermediates **IV** and **XII** and minor product **XI** are presented in the ESI.†

All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, mass and IR spectroscopies. The compounds were matched with previously reported compounds which clearly confirm the product formations. The model spectra are provided in the ESI.†

Conclusion

New efficient synthetic methods were developed from the unprecedented conversion of carbonyl compounds with economically cheaper reagents. A plausible mechanism for the formation of their corresponding products was proposed and explained. The ongoing research is on synthesizing biologically active nitrile, tetrazole, and urea based derivatives.

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