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Microwave-Assisted One-Pot Tandem Reactions for Direct Conversion of Primary Alcohols and Aldehydes to Triazines and Tetrazoles in Aqueous Media

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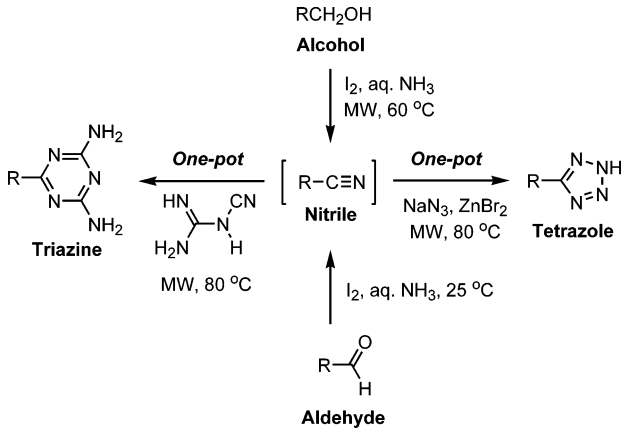

A series of primary alcohols and aldehydes were treated with iodine in ammonia water under microwave irradiation to give the intermediate nitriles, which without isolation underwent [2 + 3] cycloadditions with dicyandiamide and sodium azide to afford high yields of the corresponding triazines and tetrazoles, including the α-amino- and dipeptidyl tetrazoles in high optical purity.

Using water as a safe medium for various organic reactions has been reviewed.[1] We have previously shown that a variety of aldehydes are converted to their corresponding nitriles using iodine as an appropriate oxidant in ammonia water.[2] In comparison with similar reactions using liquid ammonia or ammonia gas saturated in alcohol solvents,[3] operation in ammonia water is simpler and more efficient, giving the nitriles in high yields at room temperature within a short reaction time (<1 h). Nitrile compounds are viable precursors for preparation of nitrogen-containing functional compounds.[4] We have previously demonstrated the tandem reactions of various aldehydes in aqueous media to furnish the corresponding amides, triazines, and tetrazoles via the intermediate nitriles by additions of H_2O_2, dicyandiamide/KOH, and $NaN_3/ZnBr_2$ in one-pot procedures.[5] Though the reaction of the intermediate nitriles with H_2O_2 was carried out smoothly at room temperature, the formation of triazines and tetrazoles still required refluxing (e.g., ≥100 °C) for a prolonged period (12−48 h). In order to improve these preparation protocols, we considered using microwave irradiation, which has become a powerful technique to accelerate thermally driven chemical reactions.[6] It has been shown that aryl halides are converted to the aryl nitriles and further to the aryl tetrazoles in a tandem reaction with sodium azide under microwave irradiation in DMF solution or on solid support.[7] We anticipated that the similar cycloaddition reactions of nitriles would be enhanced by microwave irradiation, especially in the above-mentioned salt-containing aqueous media that may take microwave energy effectively.

Our study began with the direct conversion of an aldehyde with iodine in ammonia water to a nitrile intermediate, which without isolation was heated with dicyandiamide, using a focused microwave reactor (power of 80−100 W), to furnish the [2 + 3] cycloaddition product 2,6-diamino-1,3,5-triazine in a one-pot operation (Scheme 1 and Table 1). The 1,3-dipolar cycloaddition of nitrile compounds **2a**−**e** (generated in situ from aldehydes **1a**−**e**) with dicyandiamide proceeded smoothly at 80 °C under microwave irradiation.[8] The reaction time was shortened to 15−30 min, even without using KOH as an external base, which is often utilized as a promoter in conventional heating methods.[5,9] Diamino-1,3,5-triazines such as **3a**−**e** are a class of compounds possessing diverse bioactivities[10] and widely used in material design via assembly of the multiple hydrogen-bonded complexes.[11]

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SCHEME 1. Microwave-Assisted One-Pot Tandem Reactions for Direct Conversion of Alcohols and Aldehydes to Triazines and Tetrazoles in Aqueous Media

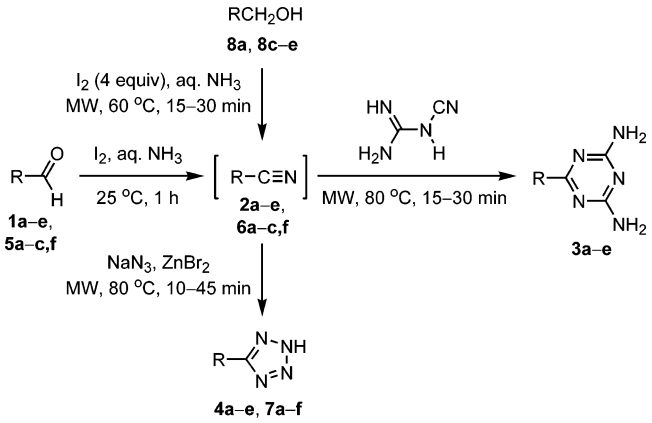
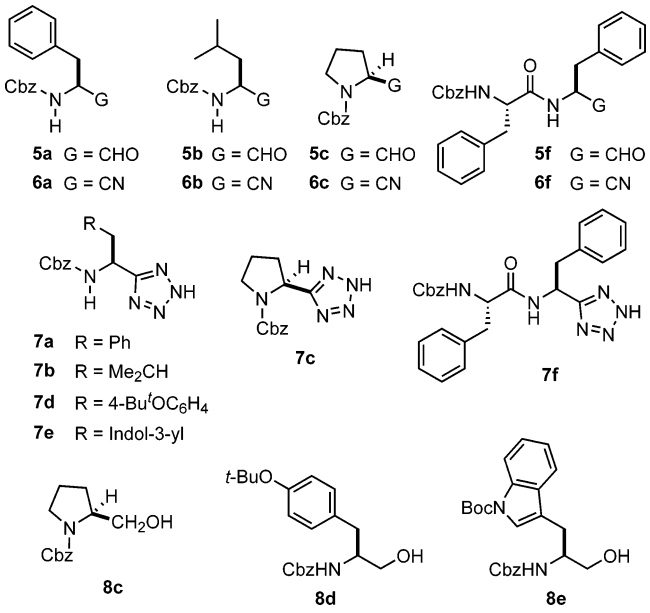


TABLE 1. Direct Conversion of Aldehydes to Triazines and Tetrazoles via Cycloadditions of Intermediate Nitriles with Dicyandiamide and Sodium Azide by Microwave-Assisted Methods

		products (yield, %)[a]	
aldehyde	R =	triazine[b]	tetrazole[c]
1a	C_6H_5	**3a** (71)	**4a** (79)
1b	4-$MeOC_6H_4$	**3b** (69)	**4b** (77)
1c	4-$O_2NC_6H_4$	**3c** (76)	**4c** (76)
1d	2-furyl	**3d** (77)	**4d** (70)
1e	2-thienyl	**3e** (83)	**4e** (83)

[a] Overall yield of two steps. [b] The aldehyde was stirred with I_2 in ammonia water for 1 h, followed by addition of dicyandiamide, and the mixture was exposed to microwave irradiation at 80 °C for 15−30 min. [c] The aldehyde was stirred with I_2 in ammonia water for 1 h, followed by addition of NaN_3 and $ZnBr_2$, and the mixture was exposed to microwave irradiation at 80 °C for 10 min.

The microwave-assisted cycloadditions of nitriles with NaN_3 and cyanoarylboronate esters with trimethylsilyl azide have been carried out at high temperature (150−220 °C) in DMF or DME solutions.[7,12] As the drastic reaction conditions and the organic solvents are not preferable, the microwave-assisted reaction in aqueous media is more appealing.[1] In particular, the high heat capacity of water is able to mitigate the explosion hazards on using sodium azide. In this study, a one-pot procedure for the direct conversion of aldehydes to tetrazoles was carried out by the microwave-assisted method. Thus, aldehydes **1a**−**e** were subjected to oxidation with I_2 in ammonia water and in situ cycloadditions with $NaN_3/ZnBr_2$ by microwave irradiation at 80 °C for 10 min to give the 5-aryl-1,2,3,4-tetrazoles **4a**−**e** in 70−83% overall yields (Table 1). In comparison with the conventional heating method using prolonged reflux (17−48 h) at a high temperature (>100 °C),[5,13] the current microwave-accelerated reaction in aqueous media is safer and more efficient.



We also prepared the *N*-Cbz-α-aminonitriles **6a**−**c** and dipeptidyl nitrile **6f** by a similar approach,[5] i.e., treatment of appropriate aldehydes **5a**−**c** with I_2 in ammonia water at room temperature.[16] Furthermore, the *N*-Cbz-α-aminonitriles **6a**−**c** generated in situ were treated with NaN_3 and $ZnBr_2$ under microwave irradiation for 30 min to furnish the *N*-Cbz-α-aminotetrazoles **7a**−**c** in high yields (84−88%).[14] The microwave-assisted direct conversion of dipeptidyl aldehyde **5f** to dipeptidyl tetrazole **7f** (78% yield) was similarly carried out. The ^1H NMR analysis (600 MHz) indicated that no apparent existence of the diastereomers of **7f** (see Supporting Information).

The scope of this method was further broadened by combination with the direct oxidative conversion of primary alcohols to nitriles in iodine−ammonia water.[15] Thus, the microwave-promoted reactions of benzyl alcohol (**8a**), *N*-Cbz-prolinol (**8c**), and the tyrosine-derived primary alcohol (**8d**) with iodine (4 equiv) in ammonia water gave the corresponding nitriles, which underwent cycloadditions with sodium azide in one pot to

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furnish the desired tetrazole products **4a**, **7c**, and **7d** in 80%, 77%, and 82% yields, respectively. The direct conversion of the tryptophan-derived primary alcohol **8e** was similarly performed, albeit by using a larger quantity of NaN_3 (18 equiv) and $ZnBr_2$ (9 equiv) for a longer period (45 min), to obtain a 70% yield of the tryptophan tetrazole **7e** with concomitant removal of the Boc group. The cycloaddition of the tryptophan nitrile generated from **8e** was more sluggish presumably as a result of its low solubility in the reaction conditions. The α-aminotetrazoles **7a**−**e** prepared as such showed only minimal racemerization (3.5−6%) during the microwave-assisted one-pot tandem reactions according to the HPLC analyses on a chiral column (see Supporting Information).

We have demonstrated an expedient microwave-assisted method for the direct transformation of primary alcohols and aldehydes into triazines and tetrazoles in aqueous media. The alcohols and aldehydes reacted with iodine in ammonia water to provide the corresponding nitrile intermediates (e.g., **2a**−**e**, **6a**−**c**, and **6f**), which readily underwent [2 + 3] cycloadditions with dicyandiamide and sodium azide on exposure to microwave irradiation to give the corresponding 4-aryl-2,6-diamino-1,3,5-triazines (**3a**−**e**), 5-aryl-1,2,3,4-tetrazoles (**4a**−**e**), *N*-Cbz-α-aminotetrazoles (**7a**−**c**), and dipeptidyl tetrazole (**7f**) in a one-pot operation. This method circumvents the problem in prior preparation of nitrile compounds from halides and toxic cyanides. The one-pot tandem reactions were conducted in aqueous media, and the products (triazines and tetrazoles) were obtained simply by extraction or filtration. In comparison with the previously reported heating methods, microwave irradiation has an advantage in the acceleration of reactions. No caustic KOH was required in the microwave-accelerated synthesis of triazines.

The optically active α-aminotetrazoles, e.g., **7c** derivative of L-proline, have been employed as versatile chiral catalysts in organic reactions.[16] Because the tetrazole products have a striking structural resemblance to their triazole analogues, our method for an easy access to optically active α-aminotetrazoles in aqueous media may have a growing impact on drug discovery similar to that demonstrated by the click chemistry of alkynes with azides.[17]

Experimental Section

CAUTION: Iodine may react with ammonia water under certain conditions to give the explosive powder nitrogen triiodide monoamine ($NI_3{\cdot}NH_3$),[18] and the reaction of sodium azide may release a minute amount of hazardous hydrazoic acid (HN_3). Although we did not encounter any incidents in this study, one should avoid using excess reagents or high concentrations of iodine−ammonia water and sodium azide in the following procedures.

General Procedure for Direct Conversion of Aldehydes to Triazines Using Microwave Irradiation. A solution of aromatic aldehyde (**1a**−**e**, 1 mmol) and iodine (1.1 mmol) in ammonia water (9 mL of 28% solution) and THF (1 mL) was placed in a round-bottomed flask equipped with a condenser. The dark solution was stirred for 1 h at room temperature and became colorless at the end of the reaction. After addition of dicyandiamide (1.1 mmol), the mixture was irradiated in a single mode microwave reactor (100 W power) at approximately 80 °C (as indication of the reactor's temperature setting) for 15−30 min. The reaction mixture was cooled; the precipitates were filtered and rinsed with Et_2O to give the desired pure product 6-aryl-2,4-diamino-1,3,5-triazine (**3a**−**e**) in 69−83% yields (Table 1). The physical and spectroscopic properties of **3a**−**e** were in agreement with those data previously reported (see Supporting Information).

General Procedure for Direct Conversion of Aldehydes to Tetrazoles Using Microwave Irradiation. A solution of α-aminoaldehyde (**5a**, 1 mmol) and iodine (1.1 mmol) in ammonia water (8 mL of 28% solution) and THF (2 mL) was stirred at room temperature for 1−2 h. The dark solution became colorless at the end of reaction. NaN_3 (4 mmol) and $ZnBr_2$ (2 mmol) were then added sequentially. The reaction mixture was exposed to microwave irradiation (80 W) at 80 °C for 30 min. The reaction mixture was cooled, aqueous HCl (1 M solution) and EtOAc were added, and the mixture was vigorously stirred until no solid was present. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The desired (*S*)-*N*-Cbz-α-aminotetrazole **7a** was obtained in 88% yield by crystallization from EtOAc/Et_2O solution.

Conversion of aldehydes **1a**−**e**, **5b**, **5c**, and **5f** to the corresponding tetrazoles **4a**−**e**, **7b**, **7c**, and **7f** using microwave irradiation was carried out by the procedure described for **7a**. The physical and spectroscopic properties of tetrazoles **4a**−**e** and **7a**−**c** were in agreement with the previously reported data.[5,14]

General Procedure for Direct Conversion of α-Amino Alcohols to α-Aminotetrazoles Using Microwave Irradiation. A solution of (*S*)-(benzyloxycarbonyl)prolinol **8c** (3 mmol) and iodine (12 mmol) in ammonia water (12 mL of 28% solution) and THF (3 mL) was placed in a round-bottomed flask equipped with a condenser. The mixture was stirred for 5 min at room temperature and exposed to microwave irradiation in a single mode microwave reactor (100 W) at 60 °C (as indication of the reactor's temperature setting) for 15−30 min. The mixture was cooled to room temperature, NaN_3 (12 mmol) and $ZnBr_2$ (6 mmol) were added sequentially, and the mixture was again subjected to microwave irradiation at 80 °C for 30 min. The reaction mixture was cooled, aqueous HCl (1 M solution) and EtOAc were added, and the mixture was vigorously stirred until no solid was present. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2×). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and chromatographed on a silica gel column to give the desired (*S*)-tetrazole product **7c** (77% yield, 93% ee).

Conversion of benzyl alcohol (**8a**) and the tyrosine- and tryptophan-derived primary alcohols **8d** and **8e** using microwave irradiation was carried out by the procedure described for **8c**, giving the tetrazoles **4a** (80% yield), **7d** (82% yield, 92% ee), and **7e** (70% yield, 88% ee), respectively. The physical and spectroscopic properties of **7c** and **7e** are listed in Supporting Information.

HPLC Analysis. The enantiomeric purity of tetrazoles **7a**−**e** was determined by HPLC analysis on a Chiralcel OD-H column (0.46 cm i.d. × 25 cm) at 30 °C. The tetrazole sample (5.0 mg/mL in 2-propanol) was prepared, and 20 μL was loaded for each analysis. The mobile phase of hexane/2-propanol (85:15, v/v) with a flow rate of 0.5 mL/min was applied, and the signals of the sample were

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recorded by a UV detector at 206 nm wavelength. The ratio of enantiomers was calculated from the areas of each enantiomer signals.

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Supporting Information Available: General experimental section, characterization of compounds, ^{1}H and ^{13}C NMR spectra of new compounds, and HPLC analyses of tetrazoles **7a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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