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An efficient one-pot synthesis of pyrrolines and tetrahydropyridines from their chloro-precursors via in situ aza-Wittig reaction

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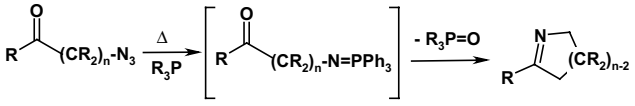
Abstract—A simple and efficient method for synthesizing pyrrolines and tetrahydropyridines via an intramolecular aza-Wittig reaction has been achieved by microwave irradiation of the corresponding chloro-alkane derivatives in the presence of tertiary phosphite and sodium azide. The in situ formation of the alkyl azides makes this a facile and safe method for aza-Wittig reactions.

Pyrrolines and tetrahydropyridine derivatives are crucial intermediates for synthesizing a large variety of functionalized aza-heterocycles that have significant biological and pharmacological activities.[1] Aza-heterocyclo derivatives are also valuable flavor compounds. For example, heterocycles **1** and **2** are natural ingredients of cooked rice and bread crust (Scheme 1).[2] Compound **2** has been isolated from the leaves of *Panadanus amaryllifolius* Roxb, which are used in Asia in the cooking of everyday rice to provide a resemblance of the scent of more luxurious fragrant Basmati rice. Compound **1** has been identified as the major bread flavor component that yields a strong cracker flavor in freshly baked bread. Compound **2** has also been identified as one of the volatile fractions in the urine of tigers, which they use for territorial and sexual statements.[3]

Scheme 1.

Common approaches to synthesize simple aza-heterocycles such as 2-phenylpyrrolines are (a) adding organometallic reagents to *N*-vinyl lactams,[4] lactim ethers,[5] *N*-(trimethyl silyl) lactams[6] and ω-halo nitriles,[7] (b) radical cyclization of sulphenyl imines,[8] (c) acid-catalyzed rearrangement of tertiary azides,[9] (d) palladium-catalyzed oxidation of unsaturated amines[10] and (e) aza-Wittig reactions of azido alkylketones.[11] Of these methods the aza-Wittig reaction is the least complicated, only requiring the addition of tertiary phosphine to an organic azide. The resulting iminophosphorane can then react with a carbonyl group to form an imine (see Scheme 2).[12]

The introduction of combinatorial and robotized parallel synthesis has led to a need for fast reactions and efficient purification procedures.[13] Thus, microwave irradiation has become widespread since it requires shorter reaction times, and generally gives high yields



Scheme 2.

Keyword: Aza-Wittig reaction.
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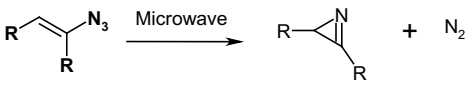
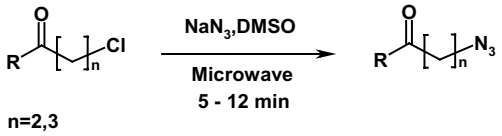


Scheme 3.



Scheme 4.

and enhanced selectivity compared to conventional heating.[14] We have recently demonstrated that vinyl alkyl azides can be activated with microwave irradiation to form 2H-azidirines in high selectivity and yield (see Scheme 3).[15] We have shown also that β- and γ-azido-substituted arylketones are stable enough to be prepared by briefly exposing the corresponding halo arylketones and sodium azide to microwave irradiation in DMSO (see Scheme 4).[16] Hence, we set out to study the microwave-assisted aza-Wittig reaction of alkyl azides, and determine whether it is possible to combine the aza-Wittig reaction and the preparation of the alkyl azide by microwave irradiation of chloroketones in DMSO with sodium azide and tertiary phosphite.

First, we prepared γ-azidobutyrophenones **3** in Scheme 5 as we have previously reported,[16] and investigated their reactivity with triethylphosphite under microwave irradiation. Since azide **3f** has not been prepared previously, we characterized it from its ^{1}H and ^{13}C NMR and IR spectra.[17]

In a typical experiment, γ-azidobutyrophenone **3a** (180 mg, 1 mmol) was dissolved in DMSO (5 mL) in a test tube and triethylphosphite (258 mg, 1.5 mmol) added, and the resulting solution stirred. Since the microwave oven cannot be fitted with a condenser to prevent overheating,[18] we followed the procedure of Chan and co-workers,[19] and ran the reaction in a water bath inside the microwave oven. We placed the test tube in a glass beaker containing water, and irradiated the beaker with microwaves. The reaction was monitored with TLC. After completion, the reaction mixture was poured into water to remove the triethylphosphate formed in the reaction, and then extracted with diethyl ether. The organic layer was dried over $MgSO_4$ and the solvent removed under vacuum to yield an oil that was purified on a short silica column eluted with 95:5 hexane: ethyl acetate to yield 2-phenylpyrroline **4a** in 96% yield.

For comparison, we prepared **3a** by the same procedure but rather than aid the reaction by microwave irradiation, we placed the test tube in boiling water and followed the reaction with TLC. The reaction was not completed until after 3 h of heating, verifying that the microwave irradiation facilitates the reaction more efficiently than conventional heating. Furthermore, De Kimpe et al. have shown that this conversion takes 14 h by stirring the reactant at room temperature.[20]

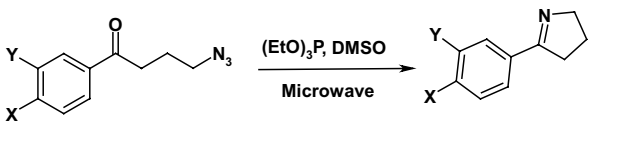
2-Phenylpyrrolines **4a–c** were characterized from their ^{1}H NMR, IR, and MS spectra, which were identical to those in the literature.[20,21] We characterized pyrrolines **4d–f** from their ^{1}H NMR, ^{13}C NMR, IR, and mass spectra.[21]

The isolated yields and reaction times for preparing several 2-phenylpyrrolines are shown in Table 1. In all instances the 2-phenylpyrrolines **4** are formed in good yield after a reaction time of only 8–12 min. Thus there is a noteworthy acceleration in the reaction rate compared to conventional heating.

We simplified further the preparation of 2-phenylpyrrolines **4a–f** by microwave irradiation of the corresponding γ-chlorobutyrophenone, sodium azide and triethylphosphite in DMSO (see Scheme 6).

Table 1. Isolated yields for forming 2-phenylpyrroline **4** from γ-azidobutyrophenone **3**

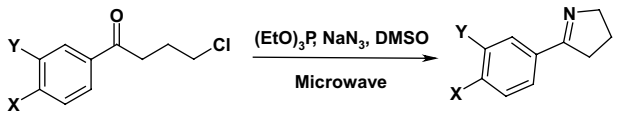
3	Microwave irradiation	
	Reaction time (min)	Isolated yields of **4** (%)
a	8	96
b	10	87
c	10	92
d	8	80
e	12	86
f	12	93



3a: Y = X = H
3b: Y = H, X = OMe
3c: Y = H, X = Br
3d: Y = H, X = OH
3e: Y = H, X = C(CH3)3
3f: Y = X = CH3

4a: Y = X = H
4b: Y = H, X = OMe
4c: Y = H, X = Br
4d: Y = H, X = OH
4e: Y = H, X = C(CH3)3
4f: Y = X = CH3

Scheme 5.



5a: Y = X = H
5b: Y = H, X = OMe
5c: Y = H, X = Br
5d: Y = H, X = OH
5e: Y = H, X = C(CH3)3
5f: Y = X = CH3

4a: Y = X = H
4b: Y = H, X = OMe
4c: Y = H, X = Br
4d: Y = H, X = OH
4e: Y = H, X = C(CH3)3
4f: Y = X = CH3

Scheme 6.

In a standard experiment, γ-chlorobutyrophenone **5a** (182 mg, 1.0 mmol), sodium azide (100 mg, 1.5 mmol) and triethylphosphite (250 mg, 1.5 mmol) were dissolved in DMSO (5 mL) and the resulting solution stirred. The reaction was carried out in a water bath inside the microwave oven for 25 min. The reaction progress was followed with TLC and when all the starting material had reacted, the reaction mixture was poured into water and extracted with diethyl ether. The organic layer was dried over $MgSO_4$ and the solvent removed under vacuum to yield an oil, which was purified on a short silica column eluted with 5% ethyl acetate in hexane to give 2-phenylpyrroline **4a** (130 mg, 0.93 mmol) in 95% yield.

The isolated yields and the reaction times for preparing phenylpyrroline derivatives **4** from the microwave irradiation of γ-chlorobutyrophenone are listed in Table 2. In all cases yields are similar or better than for microwave irradiation of the azidobutyrophenone **3** (see Table 1). Hence, 2-phenylpyrrolines can be prepared directly just as easily from the corresponding γ-chlorobutyrophenone, triethyphosphite and sodium azide, rather than first preparing the analogous γ-azidobutyrophenones and then reacting the azido compounds with triethylphosphite. The in situ formation of the alkyl azides makes this a facile and safe method for aza-Wittig reactions.

We were curious whether we could use this simple approach to make azo-heterocyclic compounds from aliphatic ketones, so we set out to prepare flavor compound **1**. We followed the method of De Kimpe et al. and prepared **1** from **6** as shown in Scheme 7,[23] but rather than using conventional heating, we used microwave irradiation to accelerate the formation of **10** and **11** (see Table 3). Thus we made compounds **10** and **11** in better yield and much shorter reaction times by using microwave irradiation. We then modified the procedure for forming **1** by doing in situ aza-Wittig reaction to prepare **11** from **9** in one step. We obtained **11** in 98% yield after 18 min of microwave irradiation.

Compounds **7**–**11** and **2** were characterized by their IR and ^1H NMR spectroscopy and the IR and ^1H NMR spectra fits with the literature.[22,24–29]

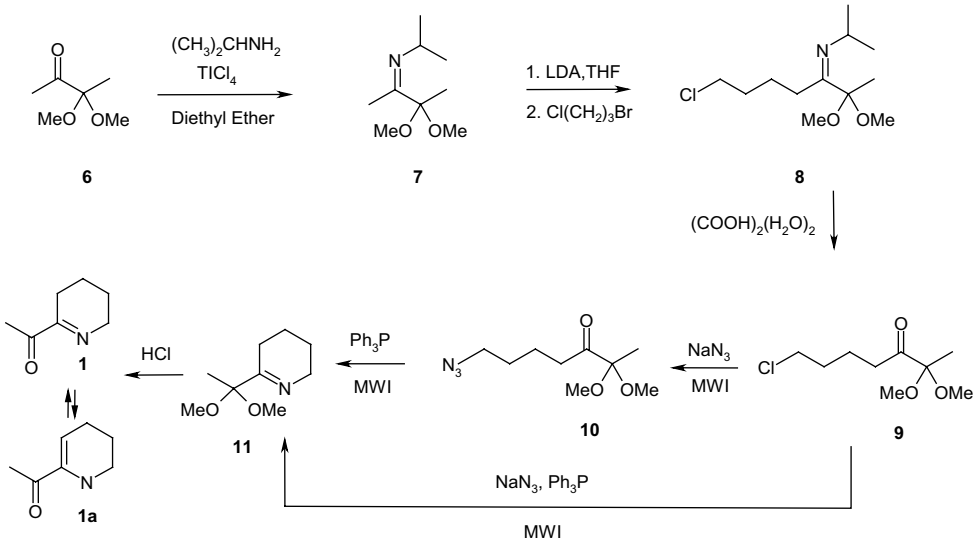
In conclusion, we have shown that substituted pyrrolines and tetrahydropyridines can be synthesized in a simple one-pot approach from the corresponding chloro-alkanes, tertiary phosphite and sodium azide by flash heating with microwave irradiation. Thus microwave assisted in situ aza-Wittig reactions are an efficient and safe method to form pyrroline and tetrahydropyridines derivatives in high purities, yields and short reaction times.

Table 2. Isolated yields for forming 2-phenylpyrroline **4** from γ-chlorobutyrophenone **5**

Chloride **5**	Microwave irradiation	
	Reaction time (min)	Isolated yields of **4** (%)
a	20	95
b	20	94
c	28	88
d	28	90
e	25	90
f	25	96

Table 3. Isolated yields for forming **10** and **11** as shown in Scheme 7

	Conventional heating[22]		Microwave irradiation	
	Yield (%)	Reaction time (h)	Yield (%)	Reaction time (min)
10	80	12–16	98	12
11	73	23–24	95	15



Scheme 7.

Acknowledgments

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17. Azide **3f**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.99 (m, 2H), 2.31 (s, 6H), 3.01 (t, 7 Hz, 2H), 3.37 (t, 7 Hz, 2H), 7.19 (t, 8 Hz, 2H); 7.67 (t, 7.6 Hz, 2H), 7.73 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.78, 20.0, 23.4, 35.0, 50.9, 125.7, 129.1, 129.8, 134.6, 136.9, 142.7, 198.8 ppm. IR (Neat): 1677, 2097 cm^{-1}.
18. We used a conventional microwave oven, 2450 MHz, 1100 W.
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21. The ^{1}H NMR and IR of phenylpyrrolines **4a**–**f** are as follows **4a**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.03 (m, 2H), 2.91 (m, 2H), 4.07 (m, 2H), 7.38 (m, 3H), 7.81 (m, 2H) ppm. IR (KBr): 1622 cm^{-1}; MS (70 eV, EI) 145 (M^+). Compound **4b**: Crystalline solid mp: 76 °C (lit.[18d] 77–78 °C). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.00 (quintet 7 Hz, 2H), 2.88 (t, 7 Hz, 2H), 3.82 (s, 3H), 4.02 (t, 7 Hz, 2H), 6.89 (d, 8 Hz 2H), 7.76 (d, 8 Hz, 2H) ppm. IR (KBr): 1614 cm^{-1}. MS (70 eV, EI) m/e 175 (M^+). Compound **4c**: Crystalline solid, mp: 83–84°C (lit.[18b] 87–88 °C), ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.05 (m, 2H), 2.92 (m, 2H), 4.05 (m, 2H), 7.55 (d, 7.5 Hz, 2H), 7.72 (d, 7.5 Hz 2H) ppm. IR (KBr) 1622 cm^{-1}. MS (70 eV, EI) e/m 225 (M^+). Compound **4d**: Crystalline solid mp: 230–232 °C (lit.[17c] 234 °C). ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.08 (m, 2H), 3.01 (m, 2H), 3.96 (m, 2H), 6.81 (d, 8 Hz, 2H), 7.65 (broad s, 1H), 7.69 (d, 8 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.1, 35.9, 60.8, 116.6, 130.0, 131.1, 162.6,m 176.5 ppm. IR (KBr): 3453, 2943, 2861, 1587, 1524, 1451 cm^{-1}. MS (70 eV, EI) e/m 160 (M^+). Compound **4e**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.33 (s, 9H), 2.01 (m, 2H), 2.93 (m, 2H), 4.05 (m, 2H), 7.44 (d, 7.5 Hz, 2H), 7.79 (d, 7.5 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6, 31.2, 34.8, 34.9, 61.4, 125.3, 127.4, 131.8, 153.6, 173.1 ppm. IR (KBr): 1615 cm^{-1}. MS (70 eV, EI) e/m 200 (M^+-1). Compound **4f**: Crystalline solid m.p. 64–66°C, ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.99 (m, 2H), 2.15 (s, 6H), 2.93 (m, 2H), 4.00 (t, 7 Hz, 2H), 7.13 (d, 8 Hz, 2H), 7.49 (d, 8 Hz, 2H), 7.66 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.7, 19.7, 22.6, 34.8, 61.3, 125.2, 128.6, 129.6, 132.3, 136.6, 139.1, 173.3 ppm. IR (KBr): 1614 cm^{-1}; MS (70 eV, EI) 173 (M^+).
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24. Preparation of **7**. A solution of 3,3-dimethoxy-2-butanone (1.32 g, 10 mmol) and isopropyl amine (2.36 g, 40 mmol) in dry diethyl ether (50 mL) in an icebath was stirred vigorously under an N_2 atmosphere. To this solution was added dropwise solution of titanium(iv)chloride (1.14 g, 60 mmol) in pentane (5 mL). The reaction mixture was stirred for 30 min at room temperature and poured into aqueous 0.5 N sodium hydroxide (50 mL) and extracted three times with diethyl ether (30 mL). The combined organic layers were dried with magnesium sulfate, filtered and evaporated in vacuo to yield imine **7** (1.65 g, 9.5 mmol) in 95% yields. IR (neat): 2850, 1670 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): 1.16 (d, 6 Hz, 6H), 1.88 (s, 3H), 1.41 (s, 3H), 3.26 (s, 6H), 3.75 (septet, 6 Hz, 1H) ppm.
25. Preparation of **8**. A solution of lithium diisopropylamide (12 mmol) was prepared by addition of butyl lithium (7.2 mL 1.65 M) in hexane to a solution of diisopropylamine (1.31 g, 13 mmol) in dry tetrahydrofuran (20 mL) at 0°C under argon and magnetic stirring. To this solution, was added drop-wise a solution of *N*-(3,3-dimethoxy-2-

butylidene)isopropylamine **7** (1.73 g, 10 mol) in dry tetrahydrofuran (2 mL). This mixture was stirred for 3 h at 0°C and 1-bromo-3-chloropropane (1.83 g, 12 mmol) was added drop-wise with a syringe. The resulting solution was stirred for 20 h during which the mixture warmed to ambient temperature. The reaction mixture was poured into 0.05 N aqueous sodium hydroxide (100 mL) and extracted three times with diethyl ether (50 mL). The combined organic extracts were dried with magnesium sulfate, filtered and evaporated under vacuum to yield **8** (2.45 g, 9.8 mmol) in 98% yield. IR (neat): 1660 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 1.16 (d, 6 Hz, 6H), 1.40 (s, 3H), 3.20 (s, 6H), 1.5–1.7 (m, 2H), 1.8–2.0 (m, 2H), 2.2–2.5 (m, 2H), 3.57 (t, 6.5 Hz, 2H), 3.70 (septet, 6 Hz, 1H) ppm.

26. Preparation of **9**: Oxalic acid dihydrate (970 mg, 7.2 mmol) dissolved in water (20 mL) was added to a solution of iminoacetal **8** (1.19 g, 4.8 mmol) in dichloromethane (25 mL). The resulting mixture was refluxed for 1 h and extracted three times with dichloromethane. The extract was dried with magnesium sulfate and evaporated under vacuum to yield **9** as an oil (0.820 g, 3.9 mmol, 82% yield). IR (neat): 2835, 1730 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): 1.26 (s, 3H), 1.5–1.9 (m, 4H), 2.57 (t, 6 Hz, 2H), 3.18 (s, 6H), 3.52 (t, 6.5 Hz, 2H) ppm.
27. Preparation of **10**: A solution of **9** (206 mg, 0.99 mmol) and sodium azide (100 mg, 1.5 mmol) was dissolved in DMSO (5 mL). The solution was stirred and the test tube placed in a glass beaker containing water, and irradiated with microwaves. The reaction was monitored by TLC until all the starting material had reacted (12 min). At the end water (20 mL) was added. The reaction mixture was extracted with diethyl ether (50 mL), dried over magnesium sulfate and evaporated under vacuum to give **10** (209 mg, 0.97 mmol, 98% yield) as a clear oil. IR (neat): 2100, 1733 cm^{-1}. ^1H NMR ($CDCl_3$): 1.36 (s, 3H), 1.5–1.8 (m, 4H), 2.65 (t, 2H), 3.24 (s, 6H), 3.3 (m, 2H) ppm.
28. Preparation of **11**. A solution of **10** (645 mg, 3.0 mol) and triphenyl phosphine (786 mg, 3.0 mmol) in DMSO (5 mL) was placed in a test tube and stirred. The test tube was placed in a glass beaker containing water and irradiated with microwaves. The reaction was monitored by tlc until all the starting material had reacted (15 min). At the end of the reaction the triphenylphosphine oxide was filtered off and washed with cold diethyl ether (20 mL). The diethyl ether solutions was evaporated under vacuum to yield **11** (487 mg, 2.85 mmol, 95% yield). Alternatively, sodium azide (296 mg, 4.6 mmol) and triphenyl phosphine (1.21 g, 4.6 mmol) was added to **9** (636 mg, 3.04 mmol) in DMSO and microwaved for 18 min. Diethyl ether (20 mL) was added to the remaining oil and the resulting triphenylphosphine oxide precipitated filter. The remaining diethyl ether solution was evaporated under vacuum to yield **11** (510 mg, 2.98 mmol, 98% yield). IR (neat): 2830, 1623 cm^{-1}. ^1H NMR ($CDCl_3$): 1.42 (s, 3H), 1.4–1.8 (m, 4H), 2.0–2.2 (m, 2H), 3.25 (s, 6H), 3.6–3.9 (m, 2H) ppm.
29. Preparation of **1**. A solution of **11** (380 mg, 2.2 mol) in dichloromethane (10 mL) and 2 N aqueous HCl acid (11 mL, 2.2 mol) was stirred for 24 h. The reaction mixture was made alkaline with 4 N sodium hydroxide. The aqueous phase was extracted twice with dichloromethane (20 mL). The combined organic extracts were dried over magnesium sulfate, filtered and evaporated under vacuum to yield the imine **1** and enamine **1a** in 4:1 ratio (207 mg, 1.7 mmol, 75% yield). Compound **1a**: IR (neat): 1630, 1670 cm^{-1}. ^1H NMR ($CDCl_3$): 2.2 (m, 4H), 2.38 (s, 3H) 5.64 (t, 4 Hz, 2H) ppm. Compound **1**: IR (neat): 1700, 1660 cm^{-1}. ^1H NMR ($CDCl_3$): 1.4–2.0 (m, 4H), 2.3 (m, 2H), 2.37 (s, 3H) 3.5–4.0 (m, 2H) ppm.