Performing Inert Microwave Chemistry

Introduction

Microwave heating is employed in numerous synthetic transformations, including nanomaterial assembly, polymerization reactions, and small molecule synthesis.[1–3] Nearly any conventionally heated transformation can be adapted for microwave irradiation, including those employing sensitive synthons and transition-metal catalysts.[4] Benefits of microwave heating include decreased waste generation, increased product purity, and shortened reaction times.

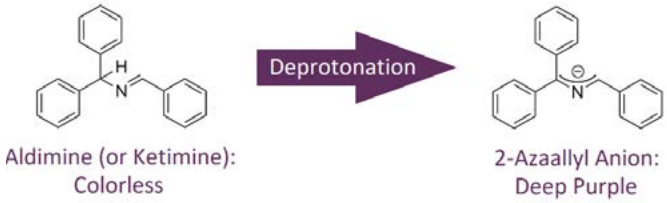

Figure 1: Generation of 2-azaallyl anions from benzhydryl-substituted aldimines (or benzophenone-substituted ketimines)

The elevated reaction rates observed with microwave irradiation enables quick reaction optimization and rapid compound library screening. Productivity is further improved when partnered with autosampler accessories, such as CEM's Discover® 2.0 with Autosampler 12 or 48, which allows multiple experiments to be prepared simultaneously and then queued to run sequentially. For experiments utilizing sensitive reagents, however, successful autosampler implementation relies on the reaction vessel's ability to maintain an inert atmosphere while in queue and post-reaction.

To demonstrate the Discover 2.0 10 and 35 mL vessel's ability to maintain an inert atmosphere, a study employing 2-azaallyl anions was performed. 2-Azaallyl anions, which are generated through deprotonation of benzhydryl-substituted aldimines (and benzophenone-substituted ketimines) (**Figure 1**), are air-sensitive synthons receiving much attention for their utility in amine assembly.[5–8] Upon formation, 2-azaallyl anions are vibrantly colored (often purple) and when quenched, turn colorless and transparent (**Figure 2**). This dramatic color change allows for ready observation of vessel atmospheric conditions.

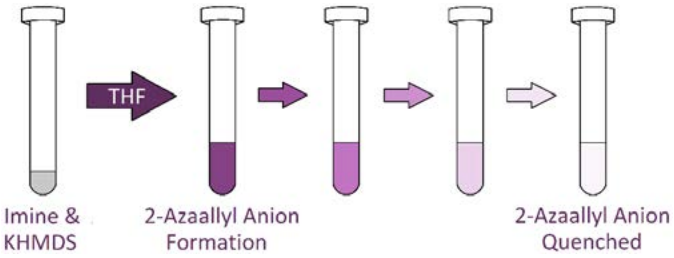

Figure 2: 2-Azaallyl anion solutions are vibrantly colored (often purple) upon formation, turning colorless and transparent when quenched.

Materials and Methods

Reagents

Potassium bis(trimethylsilyl)amide (KHMDS) and anhydrous tetrahydrofuran (THF) were obtained from Sigma Aldrich (St. Louis, MO). α-Phenyl-N-(phenylmethylene)benzenemethan-amine (aldimine) was prepared according to an established literature procedure[5] utilizing benzhydrylamine, benzaldehyde, sodium sulfate, dichloromethane, and hexanes, which were obtained from Sigma Aldrich (St. Louis, MO).

Procedure[5]

Open to Atmosphere

An oven-dried (180 °C) 10 mL vessel, equipped with stir bar, was charged with α-phenyl-N-(phenylmethylene) benzenemethanamine (imine, 27.1 mg, 0.100 mmol, 1.00 equiv.) and potassium bis(trimethylsilyl)amide (KHMDS, 21.9 mg, 0.110 mmol, 1.10 equiv.). Then, anhydrous tetrahydrofuran (THF, 2.0 mL) was added to the vessel and the solution was allowed to stir at room temperature until the deep purple solution turned colorless. (Experiments employing the 35 mL vessels were performed identically, but reaction scale was doubled.)

Punctured Cap

An oven-dried (180 °C) 10 mL vessel, equipped with stir bar, was charged with α-phenyl-N-(phenylmethylene) benzenemethanamine (imine, 27.1 mg, 0.100 mmol, 1.00 equiv.) and potassium bis(trimethylsilyl)amide (KHMDS, 21.9 mg, 0.110 mmol, 1.10 equiv.). Then, the vial was sealed with a Teflon-lined silicon cap and purged with N_2. The cap was quickly replaced with a new, unpunctured Teflon-lined silicon cap and anhydrous tetrahydrofuran (THF, 2.0 mL) was added to the vessel via syringe-addition (20 G). The solution was allowed to stir at room temperature until the deep purple solution turned colorless. (Experiments employing the 35 mL vessels were performed identically, but reaction scale was doubled.)

Unpunctured Cap

An oven-dried (180 °C) 10 mL vessel, equipped with stir bar, was charged with α-phenyl-N-(phenylmethylene) benzenemethanamine (imine, 27.1 mg, 0.100 mmol, 1.00 equiv.) and potassium bis(trimethylsilyl)amide (KHMDS, 21.9 mg, 0.110 mmol, 1.10 equiv.). Then, the vial was sealed with a Teflon-lined silicon cap and purged with N_2. While purging with N_2, anhydrous tetrahydrofuran (THF, 2.0 mL) was added to the vessel and the cap was quickly replaced with a new, unpunctured Teflon-lined silicon cap. The solution was allowed to stir at room temperature until the deep purple solution turned colorless. (Experiments employing the 35 mL vessels were performed identically, but reaction scale was doubled.)

Punctured Cap with Microwave Heating

An oven-dried (180 °C) 10 mL vessel, equipped with stir bar, was charged with α-phenyl-N-(phenylmethylene) benzenemethanamine (imine, 27.1 mg, 0.100 mmol, 1.00 equiv.) and potassium bis(trimethylsilyl)amide (KHMDS, 21.9 mg, 0.110 mmol, 1.10 equiv.). Then, the vial was sealed with a Teflon-lined silicon cap and purged with N_2. The cap was quickly replaced with a new, unpunctured Teflon-lined silicon cap and anhydrous tetrahydrofuran (THF, 2.0 mL) was added to the vessel via syringe-addition (20 G). The vessel was then placed in the Discover 2.0 microwave cavity, where the solution was heated to 100 °C. After 20 min of heating, the solution was allowed to cool to room temperature and stir until the deep purple solution turned colorless. (Experiments employing the 35 mL vessels were performed identically, but reaction scale was doubled.)

Unpunctured Cap with Microwave Heating

An oven-dried (180 °C) 10 mL vessel, equipped with stir bar, was charged with α-phenyl-N-(phenylmethylene) benzenemethanamine (imine, 27.1 mg, 0.100 mmol, 1.00 equiv.) and potassium bis(trimethylsilyl)amide (KHMDS, 21.9 mg, 0.110 mmol, 1.10 equiv.). Then, the vial was sealed with a Teflon-lined silicon cap and purged with N_2. While purging with N_2, anhydrous tetrahydrofuran (THF, 2.0 mL) was added to the vessel and the cap was quickly replaced with a new, unpunctured Teflon-lined silicon cap. The vessel was then placed in the Discover 2.0 microwave cavity, where the solution was heated to 100 °C. After 20 min of heating, the solution was allowed to cool to room temperature and stir until the deep purple solution turned colorless. (Experiments employing the 35 mL vessels were performed identically, but reaction scale was doubled.)

Results

The 2-azaallyl anion solution was quenched within 4-6 min of formation when allowed to stir open to atmosphere. As expected, when the 2-azaallyl anion solution was allowed to stir under an inert (anhydrous and anaerobic) atmosphere, the longevity of the 2-azaallyl anion greatly improved (**Table 1**). Though employing a punctured cap, at room temperature the

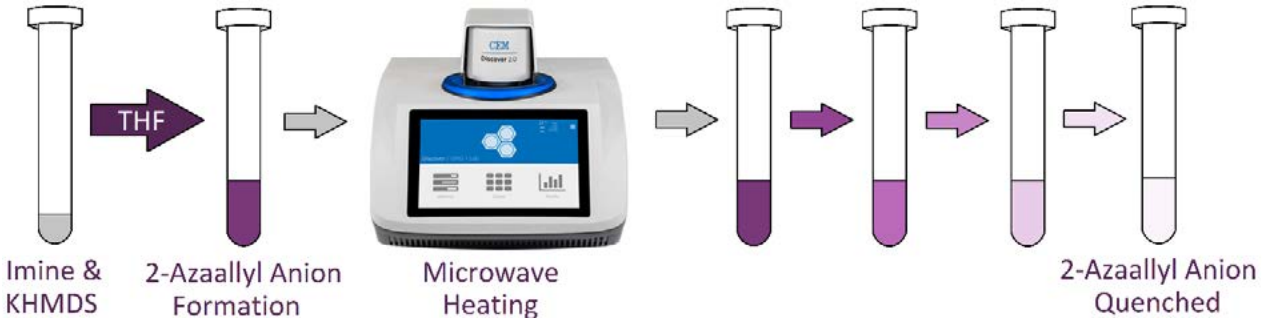

Table 1: 2-Azaallyl anion longevity under various atmospheric and temperature conditions.

Experiment	Microwave Heating Period	Anion Quenched: 10 mL vessel	Anion Quenched: 35 mL vessel
Open to Atmosphere	N/A	6 min	4 min
Punctured Cap	N/A	4 h	1 h
Unpunctured Cap	N/A	6+ h	6+ h
Punctured Cap with Microwave Heating	20 min, 100 °C	6+ h	1.5 h
Unpunctured Cap with Microwave Heating	20 min, 100 °C	6+ h	6+ h

2-azaallyl anion persisted for 1 h in the 35 mL vessel and for 4 h in the 10 mL vessel. After 20 min of heating at 100 °C, both vessels employing punctured caps were able to sustain the 2-azaallyl anion solution for even longer periods: 1.5 h for 35 mL vessel and over 6 h for the 10 mL vessel. Particular success was observed when employing unpunctured caps; regardless of heating procedure and vessel size, the 2-azaallyl anion was maintained for over 6 h.

Conclusion

The Discover 2.0 10 and 35 mL vessels are capable of maintaining an inert atmosphere for over 6 h. Though vessels employing punctured caps can experience a decrease in effectiveness when allowed to sit and/or stir at room temperature, this is combatted after microwave irradiation. However, vessels employing unpunctured caps are able to sustain the longevity of sensitive synthons and reagents, regardless of heating procedure. This capability facilitates employment of sensitive reaction conditions with autosampler technologies, thereby improving workflow efficiency and productivity.

References

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United States (Headquarters)
800-726-3331
704-821-7015
info@cem.com

France
33 (01) 69 35 57 80
info.fr@cem.com

Germany, Austria, Switzerland
(49) 2842-9644-0
info@cem.de

Ireland
+353 (0) 1 885 1752
info.ireland@cem.com

Italy
(39) 35-896224
info.srl@cem.com

Japan
+81-3-5793-8542
info@cemjapan.co.jp

United Kingdom
(44) 1280-822873
info.uk@cem.com

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