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Broadening the scope of 1,2,4-triazine synthesis by the application of microwave technology

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Abstract—By the application of microwave technology, a general protocol has been developed for the rapid synthesis of diverse 3,5,6-trisubstituted 1,2,4-triazines in excellent yield and purity, including many previously unknown 3-heterocyclic-1,2,4-triazines.

Substituted triazines represent an important class of nitrogen-containing heterocycles. The 1,2,4-triazine core is a versatile synthetic platform to access a wide-range of condensed heterocyclic ring systems via intramolecular Diels–Alder reactions with a vast array of dienophiles.[1] In addition, the triazine ring system is a key component of commercial dyes, herbicides, insecticides and more recently, pharmaceutical compositions.[2] As our efforts are directed at an iterative analog library approach to support nascent medicinal chemistry programs, this latter application for the triazine scaffold attracted our attention.

While developing structure activity relationships (SAR) for a small heterocyclic lead compound, the need arose for a general protocol to synthesize 3-heterocyclic-1,2,4-triazines, preferably in a manner amenable to analog library synthesis (Fig. 1). Examination of the literature provided numerous methods for the synthetic preparation of triazines.[3] However, the examples highlighted by these protocols typically focus on only simple aliphatic, phenyl and ester substituents at R_1–R_3.[1–4] This was

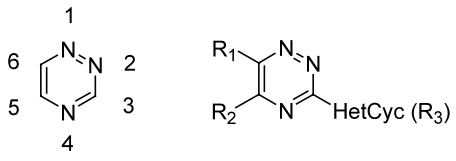
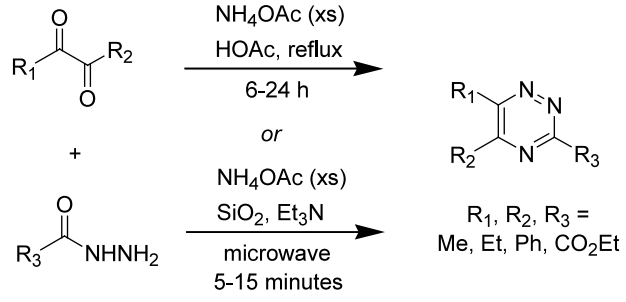
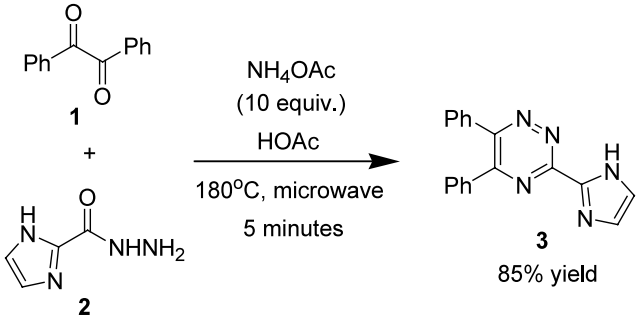


Figure 1. Generic and target 3-heterocyclic-1,2,4-triazine.



Scheme 1.



Scheme 2.

especially true for the synthesis of 1,2,4-triazines via the condensation of 1,2-diketones with acyl hydrazides and ammonium acetate under traditional thermal and 'dry media' microwave-assisted reaction conditions (Scheme 1).[4] Due to our in-house reagent library of diverse acyl hydrazides, our efforts centered on exploring this synthetic route.

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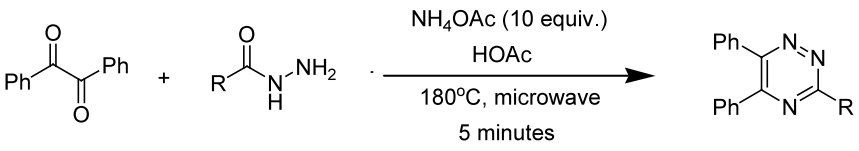
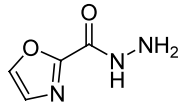
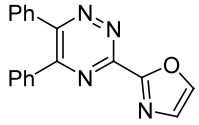
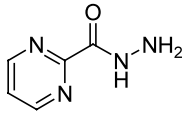
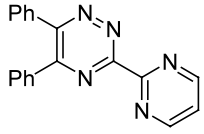
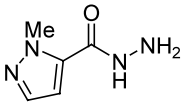
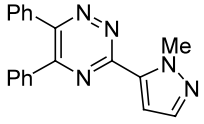
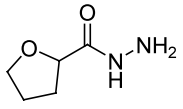
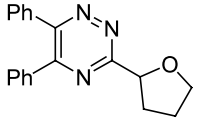
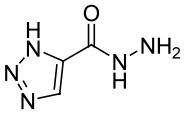
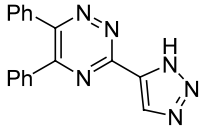
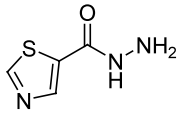
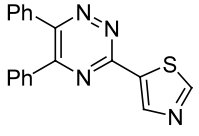
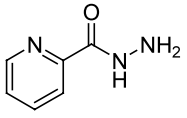
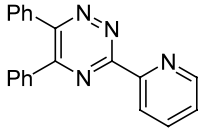
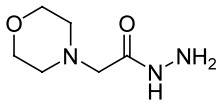
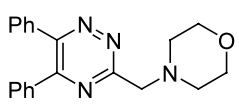
The traditional thermal conditions involve heating a 1,2-diketone and an acyl hydrazide, in a 1:1 ratio, with excess ammonium acetate in refluxing acetic acid for 6–24 h.

In our hands, these conditions with either a heterocyclic acyl hydrazide or heterocylic-containing 1,2-diketone afforded low yields (<30%), required extended heating to consume starting materials (10–24 h) and resulted in numerous side products. Applying these same reaction conditions with non-heterocyclic starting materials delivered the desired triazines in under 8 h and in >65% isolated yields, in accord with literature precedent.[1,4a]

Recently, 'dry media' microwave-assisted protocols have emerged wherein an inorganic support, such as

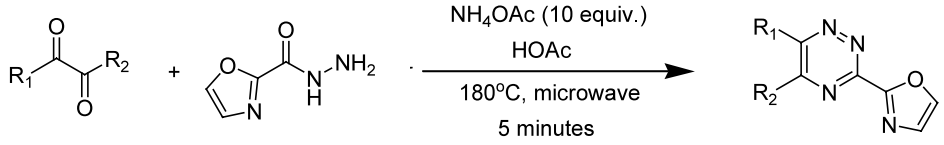
Table 1. Representative 3-substituted-1,2,4-triazines

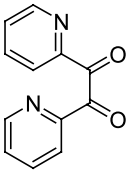
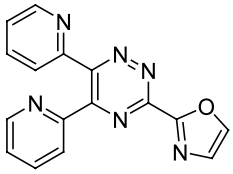
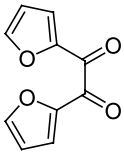
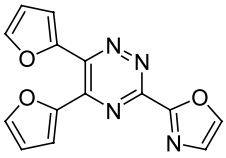
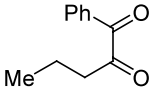
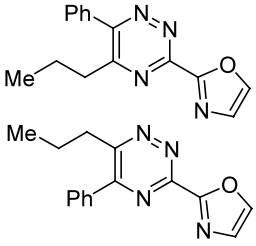
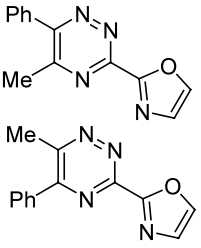


entry	$RCONHNH_2$	Product	yield (%)[a]
1			84
2			83
3			80
4			79
5			89
6			92
7			90
8			81

a: yields for analytically pure compounds fully characterized by LCMS, NMR and HRMS.

Table 2. 1,2-Diketone diversity in 1,2,4-triazine synthesis



entry	R_1COCOR_2	Product	yield (%)[a]
1			92
2			90
3			64 (75)[b]
4			69 (80)[b]

a: yields for analytically pure compounds fully characterized by LCMS, NMR and HRMS; b: yields when reaction extended to 10 minutes.

silica gel, is employed as the energy transfer medium in lieu of solvent.[5] This approach has been applied to the preparation of 1,2,4-triazines to successfully deliver products in good yields using a conventional microwave oven.[4b] Unfortunately, attempts to reproduce this work utilizing Personal Chemistry's Smithsynthesizer™ afforded poor yields with non-heterocyclic reactants and no desired product when heterocyclic reactants were employed.[6]

However, developing a microwave-assisted protocol was still of paramount interest. Abbreviated reaction times held promise for less product loss from decomposition due to the prolonged heating required for a traditional thermal reaction with heterocyclic reactants. Indeed, microwave protocols have been developed to rapidly access a number of heterocylic frameworks with abbreviated reactions times and yields far exceeding conventional thermal methods.[7] In addition, the Smithsynthesizer™ is ideal for library synthesis as the entire library can be run unattended under carefully controlled and reproducible reaction conditions.[8]

Conventional thermal conditions were quickly adapted and optimized on the Smithsynthesizer™ (Scheme 2) to deliver the previously unknown 3-imidazoly-1,2,4-triazine **3** in 85% isolated yield.[9] The optimized conditions involved reacting benzil **1** and an imidazoyl acyl hydrazide **2**, in a 1:1 ratio, with 10 equiv. of ammonium acetate in 1 mL of acetic acid for 5 min at 180°C, 60°C above the boiling point of HOAc. During the course of the reaction, the pressure never exceeded 5 psi. Upon rapid cooling of the reaction vessel to 40°C (a standard feature of the Smithsynthesizer™), a yellow precipitate formed which proved to be **3**. With this result in hand, a 48-membered library was then synthesized employing

a diverse set of acyl hydrazides using **1** as the 1,2-diketone component. The desired product was obtained in every instance, with crude LCMS purity in excess of 75% and isolated yields in excess of 79%. For ~60% of this library, the desired product precipitated out of solution upon rapid cooling, and clean material could be obtained by filtration and washing. The remaining 40% of the library was purified by mass-triggered preparative LCMS on a custom Agilent 1100 instrument.[10] Representative library members are depicted in Table 1 and include such 3-position heterocycles as oxazole (entry 1), pyrimidine (entry 2), pyrrole (entry 3), triazole (entry 5), thiazole (entry 6) and pyridine (entry 7). This new protocol also allowed for the synthesis of saturated heterocyclic congeners (entry 4) as well as other aminoalkyl derivatives (entry 8) demonstrating the generality of this methodology for analog library synthesis.[11] The majority of the triazine analogs from this library have not been previously described in the primary or patent literature and represent novel heterobicyclic structures.[12]

This methodology is not only general with respect to the acyl hydrazide component, but also appears to be general for the 1,2-diketone component as well. Representative examples from another library aimed at this diversity element are illustrated in Table 2. Again, excellent crude LCMS purities (>70%) and isolated yields were attained under standard reaction conditions for heterocyclic (entries 1 and 2), and 1-alkyl-2-phenyl-3,4-diketones (entries 3 and 4).[13] As entries 3 and 4 involved unsymmetrical 1,2-diketones, a 1:1 ratio of regioisomers was obtained; moreover, extending the reaction time from 5 to 10 min increased the yields by ~15% for these entries.

In summary, a microwave-assisted protocol for the general synthesis of functionalized 1,2,4-triazines has been developed on a Smithsynthesizer™. In addition to providing high yielding access to a number of previously unknown 3-heterocyclic-1,2,4-triazines, overall reaction times have been reduced 60–300-fold over conventional thermal conditions. Additional applications of microwave technology for analog library synthesis are in progress and will be reported in due course.

Acknowledgements

We would like to thank Dr. Charles W. Ross III for obtaining HRMS data (accurate mass measurements).

References

1. For an excellent review, see: (a) Boger, D. L. *Chem Rev*. **1986**, *86*, 781; (b) Benson, S. C.; Li, J.-H.; Snyder, J. K. *J. Org. Chem*. **1992**, *57*, 5285.
2. (a) Hurst, D. T. *Prog. Heterocyclic Chem*. **1995**, *7*, 244; (b) Groger, H.; Sans, J.; Gunther, T. *Chim. Oggi* **2000**, *18*, 12; (c) Bondinell, W. E. et. al. WO 0,276,984, 2002; (d) Bettati, M. et. al. WO 0,238,568, 2002.
3. (a) Robinson, L.; Vanderwala, P. H.; Laakso, P. V. *Tetrahedron* **1957**, *1*, 103; (b) Metze, R. *Chem Ber*. **1955**, *88*, 772; (c) Metze, R. *Chem Ber*. **1954**, *87*, 1540; (d) Saraswathi, T. V.; Srinivasan, V. R. *Tetrahedron Lett*. **1977**, *33*, 1043; For excellent reviews, see: (e) Neunhoeffer, H. *Chemistry of 1,2,3-Triazines and 1,2,4-Triazines, Tetrazines and Pentazines*; Wiley-Interscience: New York, 1978; pp. 194–200; (f) Neunhoffer, H. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R.; Rees, C. W.; Boulton, A. J.; McKilop, A., Eds.; Pergamon: Oxford, 1984; Vol. 3, pp. 385–456.
4. (a) Taylor, E. C.; French, L. G. *J. Org. Chem*. **1989**, *54*, 1245 and references cited therein; (b) Rostamizadeh, S.; Sadeghi, K. *Synth. Commun*. **2002**, *32*, 1899; (c) Mazaahir, K.; Pooja, S.; Bhushan, K.; Pretti, M. *Synth. Commun*. **2001**, *31*, 1639.
5. Kidwai, M. *Pure Appl. Chem*. **2001**, *73*, 147.
6. Due to vague experimental procedures in Ref. 4b, repeating the published work proved difficult. However, attempts to optimize reaction variables in the Smithsynthesizer™, in place of a conventional microwave oven, afforded very poor results with 'dry media'.
7. For a review with accounts of heterocycles synthesized by microwave heating, see: Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 925.
8. For information on Personal Chemistry's microwave technology for organic synthesis, see: http:\\www.personalchemistry.com.
9. *Experimental for* ***3***: To a 5 mL Smithsynthesizer™ reaction vial (Part # 351521) with a stir bar was placed benzil, **1**, (42 mg, 0.2 mol) the imidazoly acyl hydrazide, **2**, (26 mg, 0.2 mmol), ammonium acetate (154 mg, 2.0 mmol) and 1 mL of glacial HOAc. The reaction vessel was heated in the Smithsynthesizer™ reactor cavity for 5 min at 180°C. After 5 min, the vessel was rapidly cooled to 40°C by the unit. Upon removal from the reactor cavity, a bright yellow precipitate was collected by filtration from the reaction vessel. The solid was washed with water and dried in a vacuum oven overnight at 50°C to afford 51 mg (85%) of **3** as a bright yellow solid. Analytical LCMS indicated a single peak (2.190 min, CH_3CN/H_2O/0.1%TFA, 4 min gradient) >98% pure by UV (214 nm) and 100% pure by ELSD. ^1H NMR (300 MHz, DMSO-d_6): δ 13.3 (bs, 1H), 7.83 (d, $J=3$ Hz, 2H), 7.76 (d, $J=9$ Hz, 2H), 7.54 (m, 2H), 7.48 (m, 6H); HRMS calcd for $C_{18}H_{13}N_5$(M+H), 300.1244; found 300.1248 (M+H).
10. Leister, W. H.; Strauss, K. A.; Wisnoski, D. D.; Zhao, Z.; Lindsley, C. W. *J. Comb. Chem*., submitted.
11. Representative analytical data for library members in Table 1: (entry 3): Analytical LCMS indicated a single peak (3.403 min, CH_3CN/H_2O/0.1%TFA, 4 min gradient) >98% pure by UV (214 nm) and 100% pure by ELSD. ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (m, 1H), 7.62 (m, 2H), 7.60 (m, 2H), 7.39 (m, 7H), 4.47 (s, 3H); HRMS calcd for $C_{19}H_{15}N_5$(M+H), 314.1400; found 314.1403 (M+H); (entry 4): Analytical LCMS indicated a single peak (3.230 min, CH_3CN/H_2O/0.1%TFA, 4 min gradient) >98% pure by UV (214 nm) and 100% pure by ELSD. ^1H NMR (300 MHz, $CDCl_3$): δ 7.56 (m, 4H), 7.36 (m, 6H), 5.44 (dd, $J=1.5$, 5.7 Hz, 1H), 4.27 (m, 1H), 4.1 (m, 1H), 2.51 (m, 1H), 2.39 (m, 1H), 2.26 (m, 1H), 2.11 (m, 1H); HRMS calcd for $C_{19}H_{17}N_3O$ (M+H), 304.1445; found 304.1445

(M+H); (entry 6): Analytical LCMS indicated a single peak (3.393 min, CH_3CN/H_2O/0.1%TFA, 4 min gradient) >98% pure by UV (214 nm) and 100% pure by ELSD. ^1H NMR (300 MHz, $CDCl_3$): δ 8.99 (s, 1H), 8.94 (s, 1H), 7.60 (m, 4H), 7.41 (m, 6H); HRMS calcd for $C_{18}H_{12}N_4S$ (M+H), 317.0857; found 317.0856 (M+H).

12. Searches of CAS, SciFinder and Bielstein indicated that these compounds are new chemical entities, unknown in the primary and/or patent literature.
13. Note, as an unsymmetrical 1,2-diketone was employed in entries 3 and 4, a 1:1 mixture of regioisomers was obtained. Representative analytical data for library members in Table 2: (entry 2): Analytical LCMS indicated a single peak (2.519 min, CH_3CN/H_2O/0.1%TFA, 4 min gradient) >98% pure by UV (214 nm) and 100% pure by ELSD. ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.72 (m, 1H), 7.67 (m, 1H), 7.51 (s, 1H), 7.25 (m, 1H), 7.10 (d, $J=3.8$ Hz, 1H), 6.69 (m, 1H), 6.61 (m, 1H); HRMS calcd for $C_{14}H_8N_4O_3$ (M+H), 281.0669; found 281.0670 (M+H); (entry 4): Analytical LCMS indicated a single peak (2.909 min, CH_3CN/H_2O/0.1%TFA, 4 min gradient) >98% pure by UV (214 nm) and 100% pure by ELSD. By NMR, a 1:1 ratio of regioisomers: Isomer **1**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.66 (m, 2H), 7.57 (m, 3H), 7.52 (s, 1H), 2.97 (t, $J=7.8$ Hz, 2H), 1.84 (m, 2H), 0.93 (t, $J=8$ Hz, 3H); Isomer **2**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.74 (m, 2H), 7.57 (m, 3H), 7.49 (s, 1H), 3.19 (t, $J=7.8$ Hz, 2H), 1.84 (m, 2H), 0.93 (t, $J=8$ Hz, 3H); HRMS calcd for $C_{15}H_{14}N_4O$ (M+H), 267.1241; found 267.1242 (M+H).