Pergamon

Tetrahedron Letters 40 (1999) 7665–7669

TETRAHEDRON LETTERS

Microwave-accelerated three-component condensation reaction on clay: solvent-free synthesis of imidazo[1,2-*a*] annulated pyridines, pyrazines and pyrimidines

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Received 16 July 1999; accepted 13 August 1999

Abstract

A rapid one-pot synthesis of imidazo[1,2-*a*] annulated pyridines, pyrazines and pyrimidines is described that occurs in the presence of recyclable montmorillonite K 10 clay under solvent-free conditions using microwave irradiation.

Combinatorial chemistry has gained importance as a tool for the synthesis of a wide variety of useful compounds including pharmaceuticals.[1] In this context, the multiple component condensation (MCC) approach is specially appealing due to the fact that products are formed in a single step and the diversity can be achieved simply by varying the reacting components. The advantageous attributes of combinatorial synthesis over traditional synthetic methodology are to generate a large number of desired compounds with an array of functional groups appended with minimal expense of time and effort thus promoting the atom economy concept in one-pot operations.[1c,d] The initial work in this domain centered around the well-developed technologies for the solid phase synthesis of oligonucleotides[2] and peptides.[3] However, a recent surge of activity focuses on the generation of small-molecule libraries targeted for bioactive compounds, an endeavor that requires development of efficient synthetic methodologies with special emphasis on ease of reaction manipulation.

The imidazo[1,2-*a*] annulated nitrogen heterocycles bearing pyridine, pyrazine and pyrimidine moities constitute a class of biologically active compounds that are potent antiinflamatory agents,[4] antibacterial agents,[5] inhibitors of gastric acids secretion,[6] and calcium channel blockers.[7] The conventional two-component synthesis of imidazo[1,2-*a*] annulated pyridines, pyrazines and pyrimidines requires lachrymatory α-haloketones and the corresponding 2-aminopyridines, pyrazines or pyrimidines, respectively, which restricts the generation of a diverse library of these molecules.[8] Among the existing one-pot

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0040-4039/99/$ - see front matter
PII: S0040-4039(99)01585-3

methods available, one involves the condensation of 2-aminopyrazine, formaldehyde and sodium cyanide thus limiting the desired diversification in the molecules[9] while the other pH-dependent protocol requires longer time (overnight) for completion of the reaction wherein the isonitrile component is partially consumed.[10] Consequently, there is need to develop a facile method that can be adapted for the parallel synthesis of these compounds.

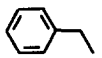
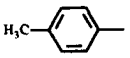
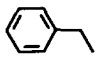
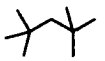
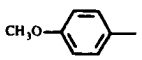
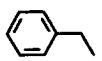
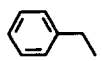
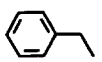
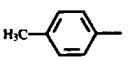
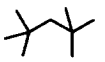
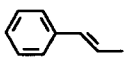
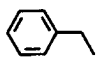
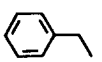
There has been considerable interest in the development of synthetic protocols that utilize a variety of mesoporous inorganic solids[11a] including clay[11b] due to their inexpensive and recyclable nature.[11] In view of our interest in the clay-catalyzed reactions, especially those that enable the expeditious construction of heterocyclic molecules[12] under solvent-free condition using microwave (MW) irradiation,[13] we now wish to report a facile and rapid protocol that is amenable to the generation of a library of imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines and imidazo[1,2-*a*]pyrimidines.

Our solventless one-pot method simply involves irradiating a mixture of aldehydes and corresponding 2-aminopyridine, pyrazine or pyrimidine in the presence of a small amount of clay with microwaves to generate iminium ion. Subsequently, isocyanide is added and the reactants are further exposed to microwaves at a reduced power level (50%) for an appropriate time (see Table 1) to afford the corresponding imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines and imidazo[1,2-*a*]pyrimidines **4**. We find that 50 mg of montmorillonite K 10 clay/mmol is optimum for the smooth conversion. The protocol is general for all the three components, e.g. aldehydes (aliphatic, aromatic and vinylic), isocyanides (aliphatic, aromatic and cyclic) and amines (2-aminopyridine, 2-aminopyrazine and 2-aminopyrimidine). Thus, a library of imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines and imidazo[1,2-*a*]pyrimidines can be readily obtained by simply varying the three components. The reaction is completed in all cases within 3.0–3.5 min with the exception of 2-aminopyrimidines that provides only modest yields of products with incomplete consumption of the starting material. The exact control experiments in a traditional oil bath are not feasible in view of the volatile nature of the reactants, especially isocyanides. The exposure to microwaves at reduced power level with intermittent heating and cooling periods in the second step allows the reaction to proceed in good yields. However, the reaction upon stirring in acetic acid overnight resulted in some unreacted starting material.[10] Importantly, the clay used in these reactions can be recycled without any effect on the product yield or purity. We have successfully used the recovered clay twice to prepare **4c**, that produced pure products in 84 and 82% yields in the first and second cycles, respectively.

The formation of these heterocycles can be rationalized by initial formation of iminium ion by the condensation of aldehyde and an amine, which is followed by nucleophilic attack of isocyanide. In a departure from the classical 4-component Ugi reaction, internal nucleophilic attack of nitrogen atom of the corresponding heterocycles leads to bicyclic adduct which upon aromatization and 1,3 shift of hydrogen atom results in the formation of desired product, **4a–n**.

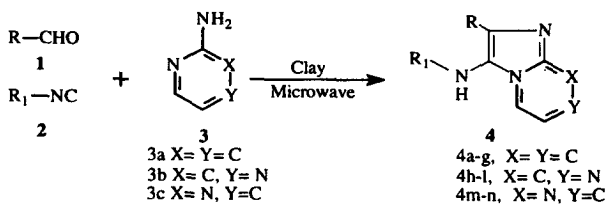
General procedure: The synthesis of **4a** is representative of the general protocol followed. A mixture of benzaldehyde (106 mg, 1 mmol) and 2-aminopyridine (94 mg, 1 mmol) was irradiated in an unmodified household microwave oven for 1 min (at full power of 900 W) in the presence of montmorillonite K 10 clay (50 mg). After addition of benzyl isocyanide (117 mg, 1 mmol), the reaction mixture was further irradiated successively (2 min) at 50% power level for a duration of 1 min followed by a cooling period of 1 min. The resulting product was dissolved in dichloromethane (2×5 mL) and the clay was filtered off. The solvent was removed under reduced pressure and the crude product was purified either by crystallization or by passing it through a small bed of silica gel using EtOAc:hexane (1:4, v/v) as eluent to afford **4a**: mp 112–113°C (from methanol); δ_H (300 MHz, $CDCl_3$) 4.14 (s, 2H, CH_2-NH), 6.72 (dd, 1H, *J*=1.1, 6.9, H-6), 7.10 (dd, 1H, *J*=1.1, 7.7, H-7), 7.21–7.49 (m, 9H, H-Ar), 7.53 (d, 1H, *J*=8.8, H-8), 7.96–7.98 (m, 3H, H-Ar, H-5); δ_C (75 MHz, $CDCl_3$) 52.47, 111.85, 117.40, 122.46, 124.26, 125.75, 127.11, 127.56, 127.72, 128.24, 128.75, 134.08, 139.04, 141.49.

Table 1
Solvent-free synthesis of imidazo[1,2-*a*] annulated pyridines, pyrazines and pyrimidines using microwave irradiation

Product [a]	X, Y	R	R_1	Time (min)	Yield (%)[b]
4a	X = Y = C			3.0	86
4b	X = Y = C			3.0	88
4c	X = Y = C			3.0	86
4d	X = Y = C			3.5	85
4e	X = Y = C			3.5	82
4f	X = Y = C		t-Bu	3.0	84
4g	X = Y = C	$(CH_3)_2CH$		3.0	85
4h	X = C, Y = N			3.0	81
4i	X = C, Y = N			3.0	82
4j	X = C, Y = N			3.0	81
4k	X = C, Y = N			3.0	83
4l	X = C, Y = N			3.5	64
4m	X= N, Y = C			3.5	58
4n	X= N, Y = C			3.5	56

[a]Compounds were analyzed for C, H, and N and the results are in agreement with the theoretical values.

[b]Yields refer to pure isolated products.



3a X= Y= C
3b X= C, Y= N
3c X= N, Y=C

4a-g, X= Y= C
4h-l, X= C, Y= N
4m-n, X= N, Y=C

4b: mp 90–91°C; δ_H (300 MHz, $CDCl_3$) 2.38 (s, 3H, CH_3), 4.15 (s, 2H, CH_2-NH), 6.69 (dd, 1H, *J*=1.1, 6.8, H-6), 7.10 (dd, 1H, *J*=1.1, 7.7, H-7), 7.20-7.44 (m, 7H, H-Ar), 7.51 (d, 1H, *J*=8.8, H-8), 7.86 (d, 2H, *J*=8.2, H-2′, H-6′), 7.93 (d, 1H, *J*=6.9, H-5); δ_C (75 MHz, $CDCl_3$) 21.38, 52.43, 111.75, 117.27, 122.41, 124.12, 125.44, 126.97, 127.69, 128.26, 128.75, 129.48, 131.17, 137.33, 139.13.

4c: mp 174–175°C; δ_H (300 MHz, $CDCl_3$) 1.13–1.24 (m, 6H, cyclohexyl), 1.55–1.80 (m, 4H, cyclohexyl), 2.85–2.94 (m, 1H, cyclohexyl), 6.75 (dd, 1H, *J*=5.7, 6.6, H-6), 7.09 (dd, 1H, *J*=6.6, 7.7, H-7), 7.23–7.34 (m, 1H, H-Ar), 7.40–7.45 (m, 2H, H-Ar), 7.50–7.53 (m, 1H, H-Ar), 8.01–8.04 (m, 3H, H-Ar); δ_C (75 MHz, $CDCl_3$) 24.89, 25.79, 34.23, 56.98, 111.60, 117.41, 122.80, 123.92, 125.04, 127.13, 127.32, 128.58, 134.56, 136.57, 139.45, 141.63.

4d: mp 87–88°C; δ_H (300 MHz, $CDCl_3$) 0.91 (s, 6H, NH-C(CH_3)$_2$), 1.00 (s, 9H, C(CH_3)$_3$), 1.54 (s, 2H, CH_2), 6.75 (dd, 1H, *J*=5.7, 7.7, H-6), 7.09 (dd, 1H, *J*=6.6, 7.9, H-7), 7.25–7.32 (m, 1H, H-Ar), 7.38–7.43 (m, 2H, H-Ar), 7.52 (d, 1H, *J*=9.0, H-8), 7.80–7.83 (m, 2H, H-Ar), 8.21 (d, 1H, *J*=6.9, H-5); δ_C (75 MHz, $CDCl_3$) 28.97, 31.77, 31.91, 57.07, 60.75, 111.35, 117.35, 123.45, 123.68, 124.03, 127.46, 128.34, 128.49, 135.54, 139.92, 142.08.

4e: mp 105–106°C; δ_H (300 MHz, $CDCl_3$) 3.83 (s, 3H, OCH_3), 4.16 (s, 2H, CH_2), 6.69 (dd, 1H, *J*=1.1, 6.9, H-6), 6.96 (d, 2H, *J*=9.1, H-3′, H-5′), 7.14 (dd, 1H, *J*=1.1, 6.6, H-7), 7.31–7.33 (m, 5H, H-Ar), 7.55 (dd, 1H, *J*=1.1, 9.1, H-8), 7.89–7.92 (m, 3H, H-5, H-2′, H-6′); δ_C (75 MHz, $CDCl_3$) 52.46, 55.37, 111.64, 114.17, 117.26, 122.32, 123.93, 124.90, 126.86, 127.71, 128.26, 128.35, 128.76, 139.16, 141.49, 159.17.

4f: mp 74–75°C (from hexane); δ_H (300 MHz, $CDCl_3$) 0.90 (t, 3H, *J*=7.3, CH_3), 1.39–1.42 (m, 2H, CH_2), 1.53–1.57 (m, 2H, CH_2), 3.01–3.04 (m, 2H, CH_2-NH), 6.79 (dd, 1H, *J*=1.1, 6.9, H-6), 7.12 (dd, 1H, *J*=1.3, 6.6, H-7), 7.28–7.34 (m, 1H, H-Ar), 7.41–7.46 (m, 2H, H-Ar), 7.55 (dd, 1H, *J*=1,1, 8.1, H-8), 7.95–7.98 (m, 2H, H-Ar), 8.05 (dd, 1H, *J*=1.1, 6.9, H-5); δ_C (75 MHz, $CDCl_3$) 13.99, 20.29, 32.89, 48.17, 111.95, 117.31, 122.53, 124.28, 126.50, 127.07, 127.51, 128.73, 133.98, 135.12, 141.24.

4g: mp 63–64°C; δ_H (300 MHz, $CDCl_3$) 1.29 (d, 6H, CH(CH_3)$_2$), 3.01 (septet, 1H, CH(CH_3)$_2$), 4.11 (d, 2H, *J*=6.1, CH_2-NH), 6.69 (dd, 1H, *J*=6.6, 6.9, H-6), 7.05 (dd, 1H, *J*=7.7, 8.0, H-7), 7.25–7.33 (m, 5H, H-Ar), 7.48 (d, 1H, *J*=9.0, H-8), 7.95 (d, 1H, *J*=6.9, H-5); δ_C (75 MHz, $CDCl_3$) 22.80, 26.49, 53.39, 111.26, 117.18, 122.17, 123.09, 123.94, 127.67, 128.34, 128.72, 139.48, 141.46, 144.59.

4h: mp 153–154°C; δ_H (300 MHz, $CDCl_3$) 4.17 (d, 2H, *J*=6.1, CH_2-NH), 7.24–7.41 (m, 8H, H-Ar), 7.70–7.90 (m, 2H, H-Ar), 7.92 (d, 2H, *J*=3.4, H-5, H-6), 8.90 (s, 1H, H-8); δ_C (75 MHz, $CDCl_3$) 52.23, 115.35, 127.33, 127.91, 128.16, 128.29, 128.86, 133.36, 136.69, 138.62, 143.33.

4i: mp 141–142°C; δ_H (300 MHz, $CDCl_3$) 1.11–1.23 (m, 6H, cyclohexyl), 1.57–1.80 (m, 4H, cyclohexyl), 2.92–3.04 (m, 1H, cyclohexyl), 7.35–7.47 (m, 3H, H-Ar), 7.82–7.99 (m, 4H, H-Ar), 8.95 (s, 1H, H-8); δ_C (75 MHz, $CDCl_3$) 24.84, 25.49, 25.63, 34.34, 56.95, 115.68, 126.61, 127.36, 128.20, 128.82, 128.98, 133.60, 136.80, 139.00, 143.36.

4j: mp 145–146°C (from hexane); δ_H (300 MHz, $CDCl_3$) 1.16–1.22 (m, 6H, cyclohexyl), 1.68–1.82 (m, 4H, cyclohexyl), 2.39 (s, 3H, CH_3), 2.93–3.04 (m, 1H, cyclohexyl), 7.26 (d, 2H, *J*=9.0, H-3′, H-5′), 7.83–7.90 (m, 3H, H-5, H-2′, H-6′), 8.02 (d, 1H, *J*=1.6, 4.7, H-6), 8.96 (s, 1H, H-8); δ_C (75 MHz, $CDCl_3$) 21.41, 24.85, 25.64, 34.35, 56.91, 115.65, 126.49, 127.24, 128.80, 129.57, 130.49, 136.55, 138.24, 139.17, 142.83.

4k: mp 111–112°C (from hexane); δ_H (300 MHz, $CDCl_3$) 0.95 (s, 6H, C(CH_3)$_2$), 1.01 (s, 9H, C(CH_3)$_3$), 1.54 (s, 2H, CH_2), 7.34–7.45 (m, 3H, H-Ar), 7.80–7.84 (m, 3H, H-6, H-2′, H-6′), 8.14 (d, 1H, *J*=9.0, H-5), 8.97 (d, 1H, *J*=1.1, H-8); δ_C (75 MHz, $CDCl_3$) 29.09, 31.87, 57.00, 61.30, 116.54, 125.04, 128.26, 128.57, 128.95, 134.52, 137.36, 143.46.

4l: mp 149–150°C (from EtOAc–hexane); δ_H (300 MHz, $CDCl_3$) 4.23 (d, 2H, CH_2-NH), 6.88 (d, 1H, *J*=15.9, CH=CH-C_6H_5), 7.28–7.39 (m, 8H, H-Ar), 7.43–7.48 (m, 2H, H-Ar), 7.56 (d, 1H, *J*=15.9,

CH=CH-C_6H_5), 7.74–7.76 (m, 2H, H-Ar), 8.91 (s, 1H, H-8); δ_C (75 MHz, $CDCl_3$) 53.16, 115.09, 117.24, 126.78, 128.11, 128.30, 128.74, 128.97, 131.70, 136.95, 137.28, 137.99, 138.87, 143.06.

4m: mp 162–163°C (from hexane); δ_H (300 MHz, $CDCl_3$) 1.14–1.20 (m, 6H, cyclohexyl), 1.66–1.78 (m, 4H, cyclohexyl), 2.93–2.96 (m, 1H, cyclohexyl), 6.78 (dd, 1H, *J*=4.3, 5.2, H-6), 7.25–7.43 (m, 3H, H-Ar), 8.06–8.09 (m, 2H, H-Ar), 8.38–8.43 (m, 2H, H-5, H-7); δ_C (75 MHz, $CDCl_3$) 24.81, 25.72, 34.21, 57.13, 108.00, 123.37, 127.40, 127.83, 128.62, 130.40, 133.95, 138.23, 144.69, 149.14.

4n: mp 164–165°C (from methanol); δ_H (300 MHz, $CDCl_3$) 4.16 (d, 2H, CH_2-NH), 6.64 (dd, 1H, *J*=6.9, 9.6, H-3), 7.25–7.42 (m, 8H, H-Ar), 8.03–8.07 (m, 2H, H-Ar), 8.11 (dd, 1H, *J*=2.2, 6.9, H-2), 8.38 (dd, 1H, *J*=2.0, 4.2, H-4); δ_C (75 MHz, $CDCl_3$) 52.63, 107.95, 124.05, 127.36, 127.81, 127.99, 128.33, 128.80, 130.10, 133.70, 137.09, 138.91, 144.60, 149.24.

In conclusion, we have demonstrated that the condensation of aldehydes, amines and isocyanides provides a rapid and solventless method for the synthesis of multisubstituted imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines and imidazo[1,2-*a*]pyrimidines using microwave irradiation, a process that is adaptable for the parallel assembly of a library of compounds. Additionally, the use of inexpensive clay and its recyclability renders this an economical and eco-friendly procedure.

References

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