Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 6623–6627
Tetrahedron Letters

Microwave-assisted solvent-free synthesis of a quinoline-3,4-dicarboximide library on inorganic solid supports

Annalisa Mortoni,[a,*] Marisa Martinelli,[a,*] Umberto Piarulli,[b] Nickolas Regalia[a,b] and Stefania Gagliardi[a]

[a]*NiKem Research, Via Zambeletti 25, 20021 Baranzate di Bollate, Milan, Italy*
[b]*Dipartimento di Scienze Chimiche e Ambientali, Università degli Studi dell'Insubria, Via Valleggio 11, 22100 Como, Italy*

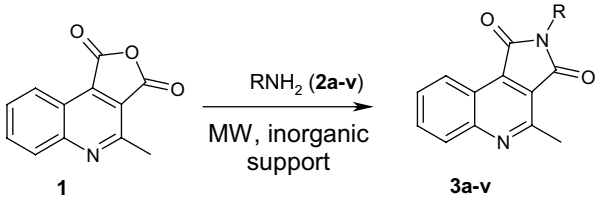
Received 12 May 2004; revised 5 July 2004; accepted 6 July 2004
Available online 23 July 2004

Abstract—Inorganic solid supports are useful media for the rapid and efficient synthesis of a library of quinoline-3,4-dicarboximides. In particular, wet clay K10 was shown to be the best medium for the condensation reaction between 2-methylquinoline-3,4-dicarboxylic anhydride and several primary amines. Microwave irradiation is essential for a rapid and complete conversion.

The increasing need to rapidly provide highly pure small molecules as potential modulators of therapeutic targets is driving the development of novel technologies that can produce compounds at a very high rate. Microwave-assisted organic chemistry is a relatively new technology that has been shown to significantly improve productivity in the generation of combinatorial libraries and complex target molecules.[1] In recent years, microwave irradiation has been demonstrated not only to dramatically accelerate many organic reactions, but also to improve yields and selectivity. The impact of microwave-assisted organic synthesis on medicinal chemistry[2] is just beginning to be realised, but is clearly evident in the rapid increase in the number of lectures and published articles focusing on the use of this technology to drive the discovery and optimisation of new leads.

The coupling of MW irradiation with the use of inorganic supported reagents, under solvent-free conditions,[3] provides a chemical process having special advantages such as enhanced reaction rates, higher yields, ease of manipulation, the opportunity to work with open vessels and finally the possibility to upscale the reaction to multi-gram amounts. Work-up procedures are considerably simplified, as in many cases, the pure product can be obtained directly from the crude reaction mixture by simple extraction, distillation or sublimation. In addition solvent-free organic reactions make synthesis simpler, save energy, and prevent solvent wastes, hazards and toxicity.

In this letter, we report the results of a preliminary investigation of a microwave-assisted imide formation[4] by the reaction of 2-methylquinoline-3,4-dicarboxylic anhydride **1**[5] and several primary amines **2** to afford the corresponding imides **3** (Scheme 1). Many derivatives of 4-quinolinecarboxylic acid have been described as promising therapeutic agents for the treatment of various human diseases.[6] In a recent paper, 2-methyl-6-sulfamoylquinoline-3,4-dicarboxylic anhydride was converted, in low to moderate yields, into the corresponding imide library by refluxing the reagents in toluene.[7] Substantial improvements in imide formation have been described using microwave irradiation both in solution[8] and in solvent-free conditions.[9] The valuable



Scheme 1.

Keywords: Microwave irradiation; Solvent-free synthesis; Solid media; Quinoline; Imide.
* Corresponding authors. Tel.: +39-02356947342; fax: +39-023-56947606 (A.M.); e-mail: annalisa.mortoni@nikemresearch. com

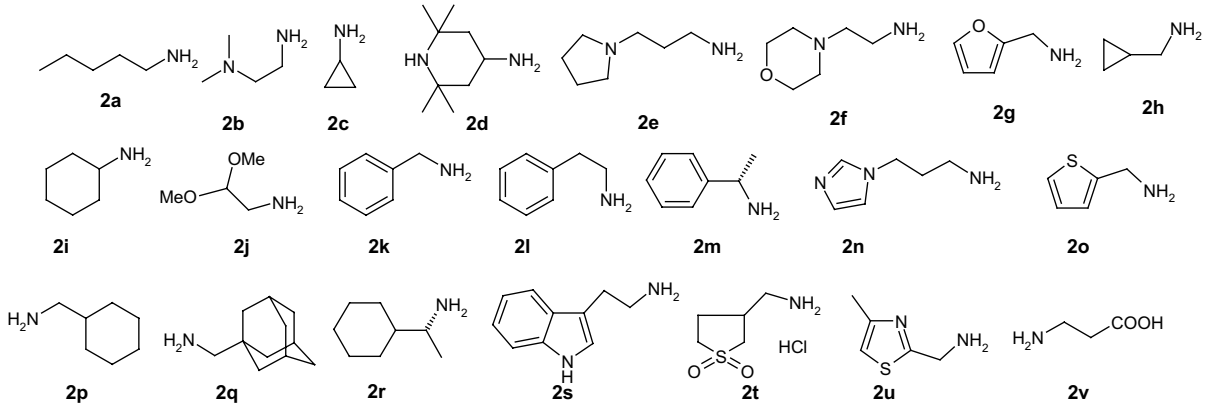
0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.07.026

features of our report include (i) shorter reaction times and higher yields, (ii) simpler work-up procedures and (iii) a solvent-free approach to green chemistry.

Our first aim was to develop an improved procedure for the preparation of a set of imides starting from the corresponding dicarboxylic anhydride. As a starting point, we studied the microwave-assisted condensation between the quinoline anhydride (**1**) and pentylamine (**2a**) in toluene (Table 1, entry 2). The solution was heated to 150 °C for 30 min in a sealed vessel. Compound **3a** was isolated in high yield and purity, after evaporation of toluene and basic washing. We further investigated the same reaction using solvent-free conditions in the presence of silica gel as inorganic solid support.

Although the use of inorganic solid supports in combination with microwave irradiation is well documented,[3,10] no examples of imide formation on solid support without the addition of a strong Lewis acid have been reported so far. Best yields were obtained when a mixture of anhydride **1** and silica gel were ground in a mortar until a homogeneous powder was formed. One equivalent of primary amines **2a–v** was then added and the residue irradiated in the microwave oven at 150 °C for 15 min. The reaction mixture was finally transferred on the top of a cartridge filled with silica gel and the final

Table 1. Condensation of 2-methylquinoline-3,4-dicarboxylic anhydride with primary amines



Entry	Amine	Conditions (temperature/time)	Method[a]	Product (%)
1	**2a**	150 °C/15 min	A	**3a** (95,[b] 80[c])
2	**2a**	150 °C/ 30 min	B	**3a** (90,[b] 78[c])
3	**2b**	150 °C/15 min	A	**3b** (>95,[b] 75[c])
4	**2c**	150 °C/15 min	A	**3c** (>95,[b] 65[c])
5	**2d**	150 °C/15 min	A	**3d** (90[b])
6	**2d**	150 °C/120 min	B	**3d** (90[b])
7	**2e**	150 °C/15 min	A	**3e** (>95[b])
8	**2f**	150 °C/15 min	A	**3f** (>95[b])
9	**2g**	150 °C/15 min	A	**3g** (>95[b])
10	**2h**	150 °C/15 min	A	**3h** (>95,[b] 65[c])
11	**2i**	150 °C/15 min	A	**3i** (95[b])
12	**2i**	150 °C/90 min	B	**3i** (90[b])
13	**2j**	150 °C/15 min	A	**3j** (>95[b])
14	**2k**	150 °C/30 min	A	**3k** (>95[b])
15	**2l**	150 °C/30 min	A	**3l** (>95,[b] 70[c])
16	**2m**	150 °C/30 min	A	**3m** (75[b], 60[c])
17	**2n**	150 °C/30 min	A	**3n** (>95[b])
18	**2o**	150 °C/30 min	A	**3o** (>95[b])
19	**2p**	150 °C/75 min	A	**3p** (>95[b], 70[c])
20	**2q**	150 °C/120 min	A	**3q** (—)
21	**2r**	150 °C/120 min	A	**3r** (—)
22	**2s**	150 °C/20 min	A	**3s** (60[b])
23	**2s**	180 °C/15 min	B	**3s** (40[b])
24	**2t**	180 °C/120 min	B	**3t** (80[b])
25	**2u**	150 °C/ 15 min	A	**3u** (90,[b] 72[c])
26	**2u**	180 °C/120 min	B	**3u** (85[b])
27	**2v**	150 °C/15 min	A	**3v** (75,[b] 60[c])

[a] Method A: anhydride (0.5 mmol), amine (1 equiv), SiO_2 (250 mg); method B: anhydride (0.5 mmol), amine (1 equiv), toluene (4 mL).
[b] Conversion of **1** in **3a–v** determined by LC-MS analysis of the crude reaction mixtures.
[c] Isolated yield after crystallisation (purity >98%).

product was separated from the more polar by-products by elution with a mixture of DCM/MeOH.[11]

These conditions were applied for the preparation of a library of *N*-substituted 4-methyl-pyrrolo[3,4-c]quinoline-1,3-diones. The procedure proved to be optimal for a wide variety of primary amines and the results in Table 1 show that conversions for almost all the 22 imides **3** are very high. Moreover, even without any additional purification, the HPLC purities were typically 80–95%, which is usually sufficient for primary biological screening.

The reaction times varied from 15 min to 2 h, with only adamantan-1-yl-methylamine (**2q**) and cyclohexyl-ethylamine (**2r**) showing no formation of the desired products even when the heating was prolonged for 2 h.

While the conversion yields obtained by applying methods A or B were comparable, the reaction times were shorter when a solid support was used (Table 1, entries 1, 5, 11, 22 and 25 vs 2, 6, 12, 23 and 26). Furthermore, the work-up of these solvent-free reactions was simpler and could be easily transferred to an automated approach.

We further investigated the condensation reaction on silica gel with solid amines having melting points both lower (entry 22, tryptamine, mp: 119 °C) or higher (entry 27, β-alanine, mp: 202 °C) than the reaction temperature. It has been reported[9a] that solvent-free microwave reactions between phthalic anhydride and amines need at least one liquid phase. Therefore, reactions between two solids may not take place and require the use of a high boiling solvent. In our case, when the solid amine **2v** was reacted with quinoline anhydride **1** (mp 200 °C), the desired imide **3v** was obtained in good yield and purity (Table 1, entry 27). This unexpected result can probably be ascribed to an effective higher temperature inside the reaction vessels.

In order to further optimise the reaction conditions and the purity of the resulting imides, we investigated the use of inorganic supports other than silica. For this reason three amines (**2i**, **2l**, **2p**), selected on the basis of their different reaction times (15, 30 and 75 min, respectively, method A, Table 1) and one (**2r**) that did not afford any product after heating for 2 h, were selected to investigate other reaction media. Among the possible inorganic supports, Al_2O_3 (neutral, acidic and basic) and montmorillonite K10 were considered. For all the experiments in Table 2, the temperature and the reaction time were fixed at 150 °C and 15 min. Among the various inorganic media tested, the best results were obtained with clay K10, which afforded complete conversions, also with amines showing low reactivity on silica (Table 2, entries 3 and 4). Moreover, we found that the use of commercial montmorillonite led to complete conversions, which were not obtained when vacuum-dried montmorillonite[12] was used (Table 2). This effect could be due to the presence of an unquantified amount of water that strongly interacts with the microwaves and increases the medium capability to absorb the microwave energy.

In order to evaluate the synergy between the inorganic solid support and microwave irradiation, parallel experiments both with microwave-assisted and conventional heating were carried out (Table 3).

Conversions obtained by microwave heating were higher than those gained warming the reactions in an oil bath. Different hypotheses have been proposed to account for the observed rate enhancement under microwave irradiation.[3a,13] It is noteworthy that mineral oxides are often very poor conductors of heat. Using conventional oil bath, heating is difficult and nonhomogeneous with large temperature gradient and overheating on the vessel walls. By contrast they behave as very efficient microwave absorbents and this led to a very rapid and homogeneous heating. Improvement in temperature homogeneity and heating rates imply faster reactions when compared with those obtained in classical conditions.

In conclusion, we have demonstrated the utility of inorganic solid supports as reaction media for imide formation. In particular 'wet' montmorillonite[14] K10 seems to be the favoured solid support for this kind of reaction. The protocol is convenient and environmentally

Table 2. Imide formation with a reaction time of 15 min using different inorganic solid supports

Entry	Amine	Neat	SiO_2	Al_2O_3 neutral	Al_2O_3 acidic	Al_2O_3 basic	Clay K10	Dried clay K10
1	**2i**	**3i** (55%)	**3i** (95%)	**3i** (85%)	**3i** (65%)	**3i** (73%)	**3i** (90%)	**3i** (80%)
2	**2l**	**3l** (80%)	**3l** (20%)	**3l** (77%)	**3l** (30%)	**3l** (40%)	**3l** (100%)	**3l** (60%)
3	**2p**	**3p** (5%)	**3p** (5%)	**3p** (90%)	**3p** (90%)	**3p** (95%)	**3p** (100%)	**3p** (95%)
4	**2r**	**3r** (—)	**3r** (—)	**3r** (60%)	**3r** (73%)	**3r** (50%)	**3r** (100%)	**3r** (58%)

Conversions determined by LC-MS.

Table 3. Comparison between microwave-assisted and conventional heating

Ex.	Amine	Solid support	Product[a] (%) MW	Product[a] (%) convent. heat.
1	**2i**	SiO_2	**3i** (95)	**3i** (25)
2	**2l**	Clay K10	**3l** (100)	**3l** (50)
3	**2p**	Al_2O_3	**3p** (90)	**3p** (—)
4	**2r**	Clay K10	**3r** (100)	**3r** (—)

[a] Conversions determined by LC-MS after 15 min at 150 °C.

friendly. We have also shown that microwave irradiation is essential for rapid and high yielding reactions.

Acknowledgements

We wish to thank Dr. Alberto Cerri for analytical support.

References and notes

1. (a) Ley, S. V.; Baxendale, I. R. *Nature Rev.* **2002**, *1*, 573–585; (b) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, R. *J. Comb. Chem.* **2002**, *4*, 95–105; (c) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283; (d) Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624–630; (e) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002; (f) Braxendale, I. R.; Lee, A.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1850–1857; (g) Leadbeater, N. E.; Marco, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1407–1409; (h) Baxendale, I. R.; Davidson, T. D.; Ley, S. V.; Perni, R. H. *Heterocycle* **2003**, *60*, 2707–2715.
2. Dzierba, C. D.; Combs, A. P. *Annu. Rep. Med. Chem.* **2002**, *37*, 247–256.
3. (a) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathè, D. *Synthesis* **1998**, 1213–1234; (b) Sartori, G.; Ballini, R.; Bigi, F.; Bosica, G.; Maggi, R.; Righi, P. *Chem. Rev.* **2004**, *104*, 199–250; (c) Kidwai, M. *Pure Appl. Chem.* **2001**, *73*, 147–151; (d) Varma, R. S. *Pure Appl. Chem.* **2001**, *73*, 193–198; (e) Usyatinsky, A. Y., Y. L.; Khmelnitsky, Y. L. *Tetrahedron Lett.* **2000**, *41*, 5031–5034.
4. In this work we used a CEM discover microwave apparatus, equipped with an internal probe that monitors reaction temperature and pressure, and maintains the desired temperature by computer control.
5. Campaigne, E.; Hutchinson, J. H. *J. Heterocycl. Chem.* **1970**, *7*, 655–659.
6. (a) Blaney, F. E.; Raveglia, L. F.; Artico, M.; Cavagnera, S.; Dartois, C.; Farina, C.; Grugni, M.; Gagliardi, S.; Lutmann, M. A.; Martinelli, M.; Nadler, G. M. M. G.; Parini, C.; Petrillo, P.; Sarau, H. M.; Scheiderel, M. A.; Hay, D. W. P.; Giardina, G. A. M. *J. Med. Chem.* **2001**, *44*, 1675–1689; (b) Ganjian, I.; Khorshidi, M.; Lalezari, I. *J. Heterocycl. Chem.* **1991**, *28*, 1173–1175(c) Koga, H; Ishizawa, T. JP173067, 1994.
7. Ivachtchenko, A. V.; Kobak, V. V.; Il'yin, A. P.; Trifilenkov, A. S.; Busel, A. A. *J. Comb. Chem.* **2003**, *5*, 645–652.
8. (a) Blanco, M. M.; Levin, G. J.; Schapira, C. B.; Perillo, I. A. *Heterocycles* **2002**, *57*, 1881–1887; (b) Peng, Y.; Song, G.; Qian, X. *Synt. Comm.* **2001**, *31*, 1927–1931; (c) Bose, A. K.; Manhas, M. S.; Ghosh, M.; Raju, V. S.; Tabei, K.; Urbanczyk-Lipkowska, Z. *Heterocycles* **1990**, *30*, 741–744.
9. (a) Vidal, T.; Petit, A.; Loupy, A.; Gedye, R. N. *Tetrahedron* **2000**, *56*, 5473–5478; (b) Borah, N. H.; Boruah, R. C.; Sandhu, J. S. *J. Chem. Res. (S)* **1998**, 272–273; (c) Chandrasekhar, S.; Takhi, M.; Uma, G. *Tetrahdron Lett.* **1997**, *38*, 8089–8092; (d) Seijas, J. A.; Vázquez-Tato, M. P.; Montserrat Martínez, M.; Núñez-Correidoira, G. *J. Chem. Res. (S)* **1999**, 420–421; (e) Barchín, B. M.; Cuadro, A. M.; Alvarez-Builla, J. *Synlett* **2002**, *2*, 343–345; (f) Chandrasekhar, S.; Padmaja, M. B.; Raza, A. *Synlett* **1999**, *10*, 1597–1599.
10. (a) Varma, R. S.; Kumar, D.; Liesen, P. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4093–4096; (b) Olsson, R.; Hansen, H. C.; Andersson, C. *Tetrahedron Lett.* **2000**, *41*, 7947–7950; (c) Loghmani-Khouzani, H.; Sadeghi, M. M.; Safari, J.; Minaeifar, A. *Tetrahedron Lett.* **2001**, *42*, 4363–4364.
11. Typical experimental procedure for preparation of imides on inorganic solid support: the quinolineanhydride (**1**) (100 mg, 0.47 mmol) was mechanically dispersed on inorganic solid support (250 mg) in a 10 mL microwave vial. Then amine was added (0.47 mmol). The vial was sealed with a crimped cap and was placed in a CEM Discover microwave apparatus. The initial power supplied was 150 W; once the temperature reached 150 °C, the instrument adjusted the power to maintain constant temperature. Heating time at 150 °C was 15 min. After completion of the reaction, a mixture 1/1 of DCM/methanol was added to the reaction mixture, inorganic solid support was filtered and the final product recovered after solvent evaporation. Compound **3a**: Solid, mp: 77–78 °C, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.67 (d, J = 8.2 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.94 (td, J = 8.2 and 1.3 Hz, 1H), 7.79 (td, J = 8.2 and 0.6 Hz, 1H), 3.60 (t, J = 6.9 Hz, 2H), 2.90 (s, 3H), 1.63–1.54 (m, 2H), 1.38–1.22 (m, 4H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 168.1, 167.9, 154.1, 150.5, 135.6, 132.4, 128.9, 128.8, 124.0, 122.0, 119.8 37.4, 28.8, 28.3, 21.5 (2C), 13.6. MS: *m*/*z*: 283 M+. Elemental analysis: calcd for $C_{17}H_{18}O_2N_2$ (282.345): C, 72.32; H, 6.43; N, 9.92; found: C, 72.12; H, 6.23; N, 9.98. Compound **3b**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.64 (d, J = 8.2 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.95 (dd, J = 8.2 and 7.3 Hz, 1H), 7.79 (dd, J = 8.2 and 7.2 Hz, 1H), 3.71 (t, J = 6.3 Hz, 2H), 2.91 (s, 3H), 2.54 (t, J = 6.3 Hz, 2H), 2.21 (s, 6H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 168.0, 167.8, 154.1, 150.5, 135.5, 132.5, 128.9, 128.8, 124.0, 121.9, 119.8, 56.3, 44.9 (2C), 35.5, 21.5. MS: *m*/*z*: 284 M+. Compound **3c**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.67 (d, J = 8.2 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.94 (td, J = 8.2 and 1.6 Hz, 1H), 7.79 (td, J = 8.2 and 1.3 Hz, 1H), 2.90 (s, 3H), 2.69 (m, 1H), 0.99–0.91 (m, 4H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 168.5, 168.4, 154.1, 150.4, 135.2, 132.4, 128.9, 128.8, 124.0, 121.7, 119.8, 21.5, 20.4, 4.7 (2C). MS: *m*/*z*: 253 M+. Compound **3d**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.69 (d, J = 8.2 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 7.96 (td, J = 8.2 and 1.6 Hz, 1H), 7.83 (td, J = 8.2 and 1.3 Hz, 1H), 4.61 (tt, J = 13.2 and 3.2 Hz, 1H), 2.98 (s, 3H), 2.44 (dd,J = 13.2 and 13.2 Hz, 2H), 1.90 (dd, J = 13.2 and 3.2 Hz, 2H), 1.50 (s, 6H), 1.45 (s, 6H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 167.9, 167.8, 154.1, 150.5, 135.4, 132.6, 129.0, 128.9, 123.9, 121.8, 119.9, 41.7 (2C), 37.3, 29.9 (2C), 23.9 (4C), 21.5. MS: *m*/*z*: 352 M+. Compound **3e**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.68 (d, J = 8.2 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.97 (t, J = 8.2, Hz, 1H), 7.82 (t, J = 8.2, Hz, 1H), 3.71 (t, J = 6.6 Hz, 2H), 3.25–3.05 (m, 6H), 2.93 (s, 3H), 2.05 (m, 2H), 1.93–180 (m, 2H), 1.72–154 (m, 2H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 168.2, 168.0, 154.1, 150.5, 135.8, 132.6, 129.0, 128.9, 124.1, 122.2, 119.9, 52.8 (2C), 51.5, 34.9, 24.6, 22.6 (2C), 21.5. MS: *m*/*z*: 324 M+. Compound **3f**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.68 (d, J = 8.2 Hz, 1H), 8.11 (d, J = 8.2 Hz, 1H), 7.96 (td, J = 8.2 and 1.6 Hz, 1H), 7.81 (td, J = 8.2 and 1.3 Hz, 1H), 3.74 (t, J = 6.6 Hz, 2H), 3.51 (dd, J = 4.7 and 4.7 Hz, 4H), 2.92 (s, 3H), 2.57 (t, J = 6.6 Hz, 2H), 2.44 (dd, J = 4.7 and 4.7 Hz, 4H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 168.0, 167.8, 154.1, 150.5, 135.6, 132.6, 129.0, 128.9, 124.0, 122.0, 119.9, 66.1 (2C), 55.4, 53.0 (2C), 34.7, 21.5. MS: *m*/*z*: 326 M+. Compound **3g**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.65 (d, J = 8.2 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.97 (td, J = 8.2 and 1.25 Hz, 1H), 7.57 (td, J = 8.1

and 1.25 Hz, 1H), 7.59 (s br, 1H), 6.47–6.39 (m, 2H), 4.80 (s, 2H), 2.95 (s, 3H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 167.3, 167.2, 154.3, 150.5, 149.1, 142.6, 135.5, 132.6, 129.0, 128.9, 124.0, 122.0, 119.9, 110.5, 108.2, 34.1, 21.6. MS: *m/z*: 293 M+. Compound **3h**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.69 (d, J = 8.2 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.96 (td, J = 8.2 and 1.6 Hz, 1H), 7.82 (td, J = 8.2 and 1.3 Hz, 1H), 3.51 (d, J = 7.2 Hz, 2H), 2.93 (s, 3H), 1.21–1.05 (m, 1H), 0.55–0.33 (m, 4H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 168.5, 168.4, 154.2, 150.5, 135.3, 132.5, 128.9, 128.8, 124.1, 122.0, 119.9, 41.9, 21.6, 10.0, 3.6 (2C). MS: *m/z*: 267 M+. Compound **3i**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.66 (d, J = 8.2 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.94 (td, J = 8.2 and 1.6 Hz, 1H), 7.79 (td, J = 8.2 and 1.3 Hz, 1H), 4.02 (tt, J = 12.0 and 3.8 Hz, 1H), 2.90 (s, 3H), 2.19–2.00 (m, 2H), 1.89–1.61 (m, 5H), 1.44–1.10 (m, 3H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 168.0, 167.8, 154.1, 150.4, 135.3, 132.4, 128.9, 128.8, 124.0, 121.8, 119.8, 50.2, 29.3 (2C), 25.4 (2C), 24.8, 21.5. MS: *m/z*: 295 M+. Elemental analysis: calcd for $C_{18}H_{18}O_2N_2$ (294.356): C, 73.45; H, 6.16; N, 9.52; found: C, 73.36; H, 6.12; N, 9.58. Compound **3j**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.64 (d, J = 8.2 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.96 (td, J = 8.2 and 1.3 Hz, 1H), 7.80 (td, J = 8.2 and 0.9 Hz, 1H), 4.69 (t, J = 5.7 Hz, 1H), 3.71 (d, J = 5.7 Hz, 2H), 3.32 (s, 6H), 2.91 (s, 3H) ^{13}C NMR (DMSO-d_6, proton decoupled): δ 167.7, 167.5, 154.2, 150.5, 135.3, 132.6, 129.0, 128.9, 124.0, 121.8, 119.7, 100.1, 53.2, 38.6 (2C), 21.5. MS: *m/z*: 301 M+. Compound **3k**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): 8.76 (d, J = 8.2 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.96 (td, J = 8.2 and 1.6 Hz, 1H), 7.81 (td, J = 8.2 and 1.3 Hz, 1H), 7.40–7.23 (m, 5H), 4.82 (s, 2H), 2.92 (s, 3H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 167.9, 167.8, 154.3, 150.5, 136.3, 135.5, 132.6, 128.9, 128.8, 128.4 (2C), 127.4 (2C), 127.3, 124.1, 122.1, 119.9, 40.9, 21.6. MS: *m/z*: 303 M+. Compound **3l**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.64 (d, J = 8.2 Hz, 1H), 8.10 (d, J = 8.2, 1H), 7.96 (td, J = 8.2 and 1.3 Hz, 1H), 7.80 (td, J = 8.2 and 1.3 Hz, 1 H), 7.31–7.16 (m, 5H), 3.85 (m, 2H), 2.96 (m, 2H), 2.91 (s, 3H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 167.9, 167.6, 154.1, 150.5, 138.1, 135.5, 132.6, 129.0, 128.8, 128.5 (2C), 128.4 (2C), 126.3, 124.0, 121.9, 119.8, 33.6 (2C), 21.5. MS: *m/z*: 317 M+. Elemental analysis: calcd for $C_{20}H_{16}O_2N_2$ (316.363): C, 75.93; H, 5.10; N, 8.85; found: C, 75.78; H, 5.95; N, 8.90. Compound **3m**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.67 (d, J = 8.2 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.95 (t br, J = 8.2 Hz, 1H), 7.79 (t br, J = 8.2 Hz, 1H), 7.46 (d br, J = 7.6 Hz, 2H), 7.35 (m, 2H), 7.27 (m, 1H), 5.50 (q, J = 7.55, 1H), 2.91 (s, 3H), 1.87 (d, J = 7.55 Hz, 3H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 167.9, 167.8, 154.2, 150.5, 140.3, 135.3, 132.5, 128.9, 128.8, 128.3 (2C), 127.2, 126.6 (2C), 124.0, 121.8, 119.9, 48.8, 21.5, 17.4. MS: *m/z*: 317 M+ $[\alpha]_D$ + 41.5, (c 1.0 $CHCl_3$). Compound **3n**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.60 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.93 (t, J = 8.2 Hz, 1H), 7.77 (t, J = 8.2 Hz, 1H), 7.63 (s br, 1H), 7.19 (s br, 1H), 6.86 (s br, 1H), 4.06 (t, J = 6.9 Hz, 2H), 3.59 (t, J = 6.9 Hz, 2H), 2.87 (s, 3H), 2.09 (m, 2H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 168.1, 167.9, 154.0, 150.4, 137.2, 135.6, 132.4, 128.8, 128.7, 128.2, 124.0, 122.0, 119.8, 119.1, 43.5, 34.9, 29.4, 21.5. MS: *m/z*: 321 M+. Compound **3o**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.64 (d, J = 8.2 Hz, 1H), 8.07 (d, J = 8.2 Hz, 1H), 7.93 (td, J = 8.2 and 1.6 Hz, 1H), 7.78 (td, J = 8.2 and 1.3 Hz, 1H), 7.45 (dd, J = 5.0 and 1.3 Hz, 1H), 7.15 (m, 1H), 6.98 (dd, J = 5.0 and 3.5 Hz, 1H), 4.97 (s, 2H), 2.90 (s, 3H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 167.4, 167.2, 154.3, 150.5, 138.1, 125.5, 132.6, 129.0, 128.9, 127.1, 126.8, 126.1, 124.0, 121.9, 119.8, 35.6, 21.6. MS: *m/z*: 309 M+. Compound **3p**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.80 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.85 (td, J = 8.2 and 1.6 Hz, 1H), 7.79 (td, J = 8.2 and 0.9 Hz, 1H), 3.45 (d, J = 6.6 Hz, 2H), 2.91 (s, 3H), 1.79–1.51 (m, 6H), 1.26–1.08 (m, 3H), 1.06–0.89 (m, 2H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 168.3, 168.1, 154.1, 150.5, 135.5, 132.4, 128.9, 128.8, 124.1, 122.0, 119.9, 43.5, 36.4, 30.1 (2C), 25.7, 25.1 (2C), 21.5. MS: *m/z*: 309 M+. Elemental analysis: calcd for $C_{19}H_{20}O_2N_2$ (308.383): C, 74.00; H, 6.54; N, 9.08; found: C, 73.88; H, 6.13; N, 10.03. Compound **3r**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.69 (d, J = 8.5 Hz, 1H); 8.10 (d, J = 8.5 Hz, 1H); 7.95 (td, J = 8.5 and 1.3 Hz, 1H); 7.80 (td, J = 8.5 and 1.3 Hz, 1H); 3.95 (m, 1H); 2.92 (s, 3H); 2.03–1.82 (m, 2H); 1.73 (m, 1H); 1.59 (m, 2H); 1.44 (d, J = 6.9 Hz, 3H); 1.32–0.76 (m, 6H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 168.3, 168.1, 154.2, 150.0, 135.1, 132.4, 128.9, 128.8, 124.1, 121.7, 119.9, 51.7, 29.8 (2C), 28.5 (2C), 25.6, 25.3, 21.5, 15.8. MS: *m/z*: 323 M+. Elemental analysis: calcd for $C_{20}H_{22}O_2N_2$ (322.411): C, 75.51; H, 6.88; N, 8.69; found: C, 75.16; H, 6.73; N, 8.73. $[\alpha]_D$ = + 12.5, (c=1,0 MeOH). Compound **3s**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.82 (s br, 1H), 8.68 (d, J = 8.2 Hz, 1H), 8.11 (d, J = 8.2 Hz, 1H), 7.96 (td, J = 8.2 and 1.3 Hz, 1H), 7.81 (td, J = 8.2 and 0.9 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.23 (d, J=2.5 Hz, 1H), 7.06 (td, J = 7.9 and 0.9 Hz, 1H), 6.98 (td, J = 7.9 and 1.3 Hz, 1H), 3.88 (m, 2H), 3.07 (m, 2H), 2.92 (s, 3H). δ ^{13}C NMR (DMSO-d_6, proton decoupled): δ 168.0, 167.8, 154.1, 150.5, 136.2, 135.7, 132.5, 128.9, 128.8, 126.9, 124.1, 122.9, 122.1, 120.9, 119.9, 118.3, 117.8, 111.4, 110.5, 38.3, 23.8, 21.5. MS: *m/z*: 356 M+. Compound **3t**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.69 (d, J = 8.2 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.97 (td, J = 8.2 and 1.3 Hz, 1H), 7.82 (td, J = 8.2 and 1.3 Hz, 1H), 3.76 (d, J = 6.9 Hz, 2H), 3.46–2.98 (m, 4H), 2.93 (s, 3H), 2.84–2.68, (m, 1H), 2.29 (m, 1H), 2.00–1.83 (m, 1H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 168.2, 167.9, 154.1, 150.4, 135.8, 132.5, 128.9, 128.8, 124.1, 122.2, 119.9, 53.9, 51.1, 38.6, 35.4, 25.8, 21.5. MS: *m/z*: 345 M+. Compound **3u**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.67 (d, J = 8.2 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 7.98 (td, J = 8.2 and 1.6 Hz, 1H), 7.83 (td, J = 8.2 and 1.2 Hz, 1H), 7.23 (q, J = 0.9 Hz, 1H), 5.74 (s, 2H), 2.94 (s, 3H), 2.31 (d, J = 0.9 Hz, 3H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 167.3, 167.2, 163.4, 154.4, 151.7, 150.6, 135.5, 132.8, 129.2, 128.9, 124.1, 121.9, 119.8, 115.0, 38.6, 21.6, 16.5. MS: *m/z*: 324 M+. Compound **3v**: Solid, ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.66 (d, J = 8.2 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.96 (dd, J = 8.2 and 6.6 Hz, 1H), 7.80 (dd, J = 8.2 and 6.6 Hz, 1H), 3.84 (t, J = 7.2 Hz, 2H), 2.91 (s, 3H), 2.66 (t, J = 7.2 Hz, 2H). ^{13}C NMR (DMSO-d_6, proton decoupled): δ 171.9, 167.8, 167.6, 154.1, 150.5, 135.6, 132.5, 129.0, 128.8, 124.0, 122.0, 119.8, 33.5, 32.2, 21.5. MS: *m/z*: 285 M+. Elemental analysis: calcd for $C_{15}H_{12}N_2O_4$ (284.274): C, 63.38; H, 4.25; N, 9.85; found: C, 62.89; H, 4.36; N, 9.98.

12. Commercial montmorillonite K10 was dried under vacuum at 100 °C till constant weight was observed.
13. (a) Loupy, A.; Perreux, L. *Tetrahedron* **2001**, *57*, 9199–9223; (b) Kuhnert, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1863–1866; (c) Garbacia, S.; Desai, B.; Lavastre, O.; Kappe, O. *J. Org. Chem.* **2003**, *68*, 9136–9139; (d) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888–892.
14. Commercial montmorillonite can be used directly as 'wet montmorillonite K10'.