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N-Methoxy-*N*-methyl-3-bromopropionamide: a new three carbon homologating agent for the synthesis of unsymmetrical 1,4-diketones

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This work is dedicated to Professor M. S. Wadia

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Abstract—A synthetic route based on a three carbon homologation of an α-aminonitrile was developed for the synthesis of unsymmetrical 1,4-diketones. The key steps were the alkylation of various aryl and heteroaryl α-aminonitriles with *N*-methoxy-*N*-methyl-3-bromopropionamide followed by the addition of a Grignard reagent to the alkylated product and then subsequent hydrolysis.

1. Introduction

1,4-Diketones are useful intermediates for the preparation of five membered carbocyclic and heterocyclic compounds.[1] The most versatile process to 1,4-diketones in the literature involves conjugate acylation[2] of the enones, for which various acyl anions have been developed.[3] Another attractive route to 1,4-diketones involves acylation of homoenolates[4] with acid halides. Symmetrical 1,4-diketones can be prepared by homocoupling of carbonylmethyl radicals,[5] metal enolates[6] and α-halocarbonyls.[7] In contrast coupling of carbonylmethyl anions and cations for unsymmetrical 1,4-diketones has remained a challenge until recently.[8] In another approach, Echavarren[9] made an elegant use of the stannane, (*E*)-1,2-bis (tri-*n*-butylstannyl)ethene, as ethane 1,2-dianion equivalent, for the synthesis of unsymmetrical 1,4-diketones by reaction with acid chlorides under palladium catalysed conditions. Similarly, acetylene dimagnesium bromide or dilithium acetylide have been used[10] as ethane 1,2-dianions during preparation of alkynediols, which subsequently served as a potential precursor for facile palladium catalysed isomerisation to 1,4-diketones.[11]

In this paper, we outline an alternative approach to unsymmetrical 1,4-diketones using the disconnection shown in Fig. 1. It was clear and obvious that the success of the proposed route would exclusively rely on the availability of a stable synthetic equivalent for the three carbon synthon **Y**. It appeared that the corresponding Weinreb amide[12] of 3-bromopropionic acid would be the simplest equivalent possible. For acyl anion, we were attracted by the less frequently used α-aminonitriles **1**[13] due to the simplicity and convenience involved in their preparation on a multigram scale. It also prevented the use of obnoxious smelling propane and ethane dithiols in large quantities for the more commonly used alkyl and aryl dithianes[14] as acyl anion equivalents.

2. Results and discussion

Scheme 1 summarizes our initial results. Amide **3a** was obtained in good yield (78%) by the reaction of the carbanion from the aminonitrile **1a** (R^1=Ph) and **2**[15] in DMF at room temperature. Although a weak cyano stretching frequency at 2258 $cm^{-1}$was observed in the IR spectrum of **3a**, a firm evidence for the presence of cyano functionality in **3a** came from a peak at 116.6 ppm in its ^{13}C NMR spectrum. Since it is an established fact that no overaddition of the organometallic reagent (RLi or RMgX) occurs to Weinreb amides, in a model reaction **3a** was treated with 3 equiv. of butylmagnesium bromide in THF at −78°C and no reaction occurred at this temperature. However, a clean reaction ensued at 0°C in 1 h as indicated by TLC. The ^1H NMR spectrum of the isolated product on work up was clearly indicative of a clean reaction at the amide carbonyl

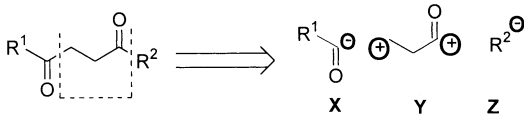

Figure 1.

Keywords: 1,4-diketone; Weinreb amide; homologating agent; Grignard reagent; α-aminonitrile.

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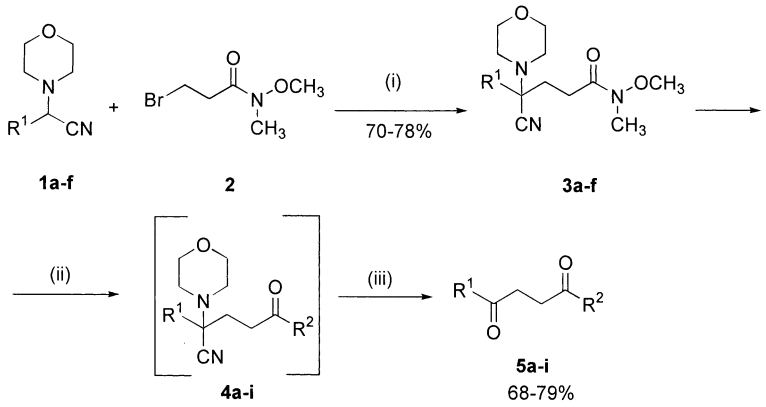

Scheme 1. *Reagents*: (i) NaH, DMF, rt, 6 h; (ii) R^2MgBr, THF, 0°C, 1 h; (iii) $CuSO_4$, aq. MeOH, reflux, 3 h.

by the absence of singlets at δ 3.49 ($-OCH_3$) and 3.07 ($N-CH_3$). Direct hydrolysis of the product **4a** by the use of $CuSO_4 \cdot 5H_2O$ in aqueous methanol at reflux conditions,[16] finally afforded the unsymmetrical 1,4-diketone **5a**, in an isolated yield of 76% after purification.

Various other aryl and heteroaryl aminonitriles (**1b–f**) were prepared according to Dyke's procedure[17] and conveniently alkylated with **2** affording **3b–f** in good yields (Table 1). Compounds **3b–f** were purified by chromatography over silica gel and thoroughly dried before their reaction with various alkyl and aryl Grignard reagents. In all cases clean reaction occurred in 1–1.5 h at 0°C affording the intermediates **4b–i**. These intermediates **4b–i** were then directly hydrolysed to furnish the corresponding unsymmetrical 1,4-diketones **5a–i** in good isolated yields (Table 2). The sequence, first the reaction of acyl anion with **2** followed by the reaction with Grignard reagent is crucial and vital for the success of the route as reversal in the order of the reactions fails to afford the desired products. In an independent reaction, when substrate **2** was first reacted with 3 equiv. of butylmagnesium bromide in THF at 0°C, it afforded in good yields, *N*-methyl heptanamide as the sole product. Substrate **2** probably underwent a facile E2 elimination forming in situ *N*-methoxy-*N*-methyl acrylamide, which underwent Michael reaction followed by deformylation[18] or vice versa with the additional 2 equiv. of butylmagnesium bromide affording the heptanamide after aqueous work up.

Table 1. Alkylation of α-aminonitriles **1a–f** with **2**

Entry	α-Aminonitrile	R^1	Product	Yield (%)[a]
1	**1a**	C_6H_5	**3a**	78
2	**1b**	3-ClC_6H_4	**3b**	75
3	**1c**	4-$CH_3C_6H_4$	**3c**	71
4	**1d**	4-$CH_3OC_6H_4$	**3d**	75
5	**1e**	2-Furyl	**3e**	72[b]
6	**1f**	2-Thienyl	**3f**	70[b]

[a] Isolated yield.
[b] 1 h at 0°C, then 5 h at rt.

Table 2. Various *unsymmetrical* 1,4-diketones **5a–i** were prepared

Product	R^1	R^2	Yield (%)[a]
5a	C_6H_5	C_4H_9	76
5b	C_6H_5	1-Naphthyl	72
5c	3-ClC_6H_4	$(CH_3)_2CH$	69
5d	3-ClC_6H_4	4-$CH_3C_6H_4$	70
5e	3-ClC_6H_4	C_4H_9	79
5f	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	75
5g	4-$CH_3OC_6H_4$	1-Naphthyl	73
5h	2-Furyl	C_4H_9	72
5i	2-Thienyl	C_6H_5	68

[a] Isolated yield based on **3**.

3. Conclusion

To conclude, a strategy based on a new disconnection, and making use of **2** as a new valuable three carbon homologating agent has been realized. Although a convenient use of α-aminonitriles as acyl anion equivalents have been made here, the ready availability of more commonly used dithianes as acyl anion equivalents makes the approach even more versatile and flexible.

4. Experimental

4.1. General

All the solvents and reagents were distilled before use. Dry solvents were prepared as per standard procedures. Reactions requiring inert atmosphere were carried out under dry nitrogen atmosphere. Melting points were determined in capillary using a Toshniwal melting point apparatus and are uncorrected. NMR spectra were recorded on Bruker (300 MHz ^1H, 75 MHz ^{13}C) or Jeol (400 MHz ^1H, 100 MHz ^{13}C) NMR spectrometers using TMS as an internal standard. IR spectra were recorded on Shimadzu IR 470 instrument. Elemental analyses were performed on a Heraeus CHN analyzer. The TLC for monitoring the course of the reaction were performed on the silica gel (Merck, TLC grade) coated on a glass plate (7×2.5 cm) followed by staining in iodine vapours. For column chromatography, silica gel (100–200 mesh) was used, unless otherwise indicated.

4.2. Preparation of starting materials

α-Aminonitriles **1a–f** were prepared according to the

general procedure described in the literature.[17] *N*-Methoxy-*N*-methyl-3-bromopropionamide **2** was prepared according to the procedure described in the literature.[15] All Grignard reagents were prepared according to the classical procedure.

4.3. General procedure for the alkylation of α-aminonitriles (1a–f) with 2

Sodium hydride (0.36 g, 15 mmol, 60% suspension in paraffin oil) was washed with dry hexane and suspended in dry DMF (10 mL) under a nitrogen atmosphere. A solution of an α-aminonitrile (10 mmol) in dry DMF (10 mL) was added at room temperature (0°C in case of **3e** and **3f**). The resulting red coloured suspension was stirred for 0.5 h and *N*-methoxy-*N*-methyl-3-bromopropionamide **2** (2 g, 10 mmol) in dry DMF (10 mL) was added. After stirring for 6 h, the excess of NaH was destroyed with saturated NH_4Cl solution. The organic portion was extracted with EtOAc (3×50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was column chromatographed on neutral alumina with hexane/EtoAc (9:1) as an eluent to afford **3a–f**.

4.3.1. 4-Cyano-4-morpholino-4-phenyl-*N*-methoxy-*N*-methylbutyramide (3a). Yield 78%; colourless solid; mp 42–44°C; R_f=0.35 (hexane/EtOAc, 8:2); IR ($CHCl_3$): ν 2976, 2258, 1683, 1436, 1376 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 1.95 (t, 2H, $-CCH_2CH_2-$, J=6.3 Hz), 2.21–2.42 (m, 6H, $-CH_2CH_2CO-$, $-N(CH_2)_2-$), 3.07 (s, 3H, $-NCH_3$), 3.49 (s, 3H, $-OCH_3$), 3.70 (m, 4H, $-O(CH_2)_2$), 7.35–7.43 (m, 3H, Ar–*H*), 7.55–7.57 (m, 2H, Ar–*H*) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 26.9 (t), 30.9 (t), 33.4 (q), 48.2 (t), 60.7, (q), 66.4, (t), 69.9, (s), 116.6, (s), 126.4 (d) 128.1 (d), 128.5 (d), 136.5 (s), 172.0 (s) ppm; Anal. calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.28; H, 7.42; N, 13.35.

4.3.2. 4-(3-Chlorophenyl)-4-cyano-4-morpholino-*N*-methoxy-*N*-methylbutyramide (3b). Yield 75%; colourless solid; mp 45–48°C; R_f=0.48 (hexane/EtOAc, 8:2); IR ($CHCl_3$): ν 2986, 2255, 1688, 1436, 1375 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 1.85 (t, 2H, $-CCH_2CH_2-$, J=6.5 Hz), 2.25–2.51 (m, 6H, $-CH_2CH_2CO-$, $-N(CH_2)_2-$), 3.10 (s, 3H, $-NCH_3$), 3.58 (s, 3H, $-OCH_3$), 3.70 (m, 4H, $-O(CH_2)_2$), 7.55–7.61 (m, 4H, Ar–*H*) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 25.7 (t), 31.8 (t), 33.5 (q), 49.5 (t), 61.1 (q), 66.8 (t), 69.9 (s), 117.6 (s), 125.1 (d), 126.7 (d), 128.1 (d), 129.5 (d), 134.9 (s), 136.4 (s), 171.4 (s) ppm; Anal. calcd for $C_{17}H_{22}ClN_3O_3$: C, 58.03; H, 6.30; N, 11.94. Found: C, 57.98; H, 6.38; N, 12.05.

4.3.3. 4-Cyano-4-(4-methylphenyl)-4-morpholino-*N*-methoxy-*N*-methylbutyramide (3c). Yield 71%; colourless solid; mp 35–38°C; R_f=0.38 (hexane/EtOAc, 8:2); IR ($CHCl_3$): ν 2955, 2254, 1683, 1435, 1375 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 1.85 (t, 2H, $-CCH_2CH_2-$, J=6.3 Hz), 2.21 (s, 3H, Ar–CH_3), 2.28–2.50 (m, 6H, $-CH_2CH_2CO-$, $-N(CH_2)_2-$), 3.10 (s, 3H, $-NCH_3$), 3.61 (s, 3H, $-OCH_3$), 3.70 (m, 4H, $-O(CH_2)_2$), 7.33–7.41 (m, 4H, Ar–*H*) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 21.3 (q), 26.1 (t), 32.3 (t), 33.6 (q), 49.8 (t), 62.5 (q), 65.7 (t), 66.8 (s), 116.6 (s), 126.5 (d), 128.4 (d), 129.2 (s), 137.8 (s), 173.2 ppm; Anal. calcd for $C_{18}H_{25}N_3O_3$: C, 65.23; H, 7.60; N, 12.68. Found: C, 65.18; H, 7.48; N, 12.55.

4.3.4. 4-Cyano-4-(4-methoxyphenyl)-4-morpholino-*N*-methoxy-*N*-methylbutyramide (3d). Yield 75%; colourless syrup; R_f=0.30 (hexane/EtOAc, 8:2); IR ($CHCl_3$): ν 2891, 2255, 1689, 1444, 1378 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 1.98 (t, 2H, $-CCH_2CH_2-$, J=6.5 Hz), 2.25–2.48 (m, 6H, $-CH_2CH_2CO-$, $-N(CH_2)_2-$), 3.10 (s, 3H, $-NCH_3$), 3.58 (s, 3H, $-OCH_3$), 3.70 (s, 3H, Ar–OCH_3), 3.75 (m, 4H, $-O(CH_2)_2$), 7.55–7.61 (m, 4H, Ar–*H*) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 26.1 (t), 31.2 (t), 32.2 (q), 49.4 (t), 59.7 (q), 65.8 (t), 66.4 (q), 68.9 (s), 116.8 (s), 118.9 (d), 125.5 (d), 129.5 (s), 159.9 (s), 172.5 9(s) ppm; Anal. calcd for $C_{18}H_{25}N_3O_4$: C, 62.23; H, 7.25; N, 12.10. Found: C, 62.19; H, 7.18; N, 12.35.

4.3.5. 4-Cyano-4-(2-furyl)-4-morpholino-*N*-methoxy-*N*-methylbutyramide (3e). Yield 72%; colourless syrup; R_f=0.32 (hexane/EtOAc, 8:2); IR ($CHCl_3$): ν 2864, 2240, 1680, 1462, 1388 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 2.11 (t, 2H, $-CCH_2CH_2-$, J=6.5 Hz), 2.49–2.67 (m, 6H, $-CH_2CH_2CO-$, $-N(CH_2)_2-$), 3.11 (s, 3H, $-NCH_3$), 3.56 (s, 3H, $-OCH_3$), 3.65 (m, 4H, $-O(CH_2)_2$), 6.32 (d, 1H, Ar–*H*, J=3.6 Hz), 6.50 (m, 1H, Ar–*H*) 7.40 (d, 1H, Ar–*H*, J=1.8 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 27.2 (t), 30.7 (t), 32.6 (q), 48.5 (t), 61.1 (q), 65.0 (t), 66.6 (s), 110.3 (s), 111.0 (d), 116.1 (d), 143.5 (d), 148.1 (s), 173.0 (s) ppm; Anal. calcd for $C_{15}H_{21}N_3O_4$: C, 58.62; H, 6.89; N, 13.67. Found: C, 58.89; H, 6.78; N, 13.75.

4.3.6. 4-Cyano-4-morpholino-4-(2-thienyl)-*N*-methoxy-*N*-methylbutyramide (3f). Yield 70%; colourless syrup; R_f=0.29 (hexane/EtOAc, 8:2); IR ($CHCl_3$): ν 2872, 2245, 1689, 1472, 1389 cm^{-1};^1H NMR ($CDCl_3$, 300 MHz): δ_H 1.99 (t, 2H, $-CCH_2CH_2-$, J=6.5 Hz), 2.38–2.52 (m, 6H, $-CH_2CH_2CO-$, $-N(CH_2)_2-$), 3.07 (s, 3H, $-NCH_3$), 3.61 (s, 3H, $-OCH_3$), 3.68 (m, 4H, $-O(CH_2)_2$), 7.11 (d, 1H, Ar–*H*, J=3.8 Hz), 7.15 (m, 1H, Ar–*H*), 7.30 (d, 1H, Ar–*H*, J=4.1 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 26.1 (t), 31.7 (t), 32.8 (q), 49.1 (t), 61.5 (q), 65.6 (t), 66.8 (s), 116.27 (s), 123.1 (d), 124.4 (d), 126.8 (d), 138.0 (s), 173.1 (s) ppm; Anal. calcd for $C_{15}H_{21}N_3O_3S$: C, 55.71; H, 6.54; N, 12.99. Found: C, 55.86; H, 6.58; N, 12.81.

4.4. General procedure for the addition of Grignard reagents to 3a–f

To a solution of **3** (2.5 mmol) in THF (20 mL), the appropriate Grignard reagent (7.5 mmol) was added under a nitrogen atmosphere at 0°C. The mixture was stirred for a 1.5 h period. The hydrolysis was achieved by the cautious addition of saturated NH_4Cl solution. After returning to room temperature, the two phases were separated and the aqueous phase was extracted with EtOAc (3×20 mL). The organic phases were combined, washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product **4a–i**, which was directly hydrolysed without further purification following a literature procedure.[16]

4.5. General procedure for the hydrolysis of 4a–i

To the crude product obtained from the above reaction, a

solution of $CuSO_4 \cdot 5H_2O$ (0.6 g, 2.5 mmol) and 3:1 aqueous CH_3OH (15 mL) was added and heated at reflux. After stirring for 3 h, the reaction mixture was cooled to room temperature and the organic portion was extracted with EtOAc (3×20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product which on purification by column chromatography (10% EtOAc in hexane) afforded the pure 1,4-diketones **5a**–**i**.

1,4-diketones **5a**,[9] **5b**,[4b] **5g**,[4b] and **5i**[11f] are known compounds and their physical and spectroscopic data (IR, ^{1}H NMR) agreed with the reported values. Other products were characterized as follows.

4.5.1. 1-(3-Chlorophenyl)-5-methylhexane-1, 4-dione (5c). Yield 69%; colourless syrup; R_f=0.41 (hexane/EtOAc, 9:1); IR ($CHCl_3$): ν 2976, 1715, 1689, 1459, 1420, 1340 cm^{-1};^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 1.14 (d, 6H, –CH(CH_3)$_2$, J=7.4 Hz), 2.69 (m, 1H, –CH(CH_3)$_2$), 2.89 (t, 2H, –CH_2CH$_2$–, J=6.4 Hz), 3.20 (t, 2H, –CH$_2$CH_2–, J=6.4 Hz), 7.34–7.51 (m, 2H, Ar–H), 7.84–7.92 (m, 2H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 18.2 (q), 32.3 (d), 33.8 (t), 40.8 (t), 126.0 (d), 128.1 (d), 129.7 (d), 132.7 (d), 134.8 (s), 138.2 (s), 197.4 (s), 212.9 (s) ppm; Anal. calcd for $C_{13}H_{15}ClO_2$: C, 65.41; H, 6.33. Found: C, 65.50; H, 6.38.

4.5.2. 1-(3-Chlorophenyl)-4-(4-methylphenyl)-1,4-butanedione (5d). Yield 70%; colourless solid; mp 108–110°C; R_f=0.32 (hexane/EtOAc, 9:1); IR ($CHCl_3$): ν 2912, 1689, 1606, 1504, 1414, 1337, 1315 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 2.39 (s, 3H, Ar–CH_3), 3.39 (m, 4H, –CH_2CH_2–), 7.23–7.53 (m, 4H, Ar–H), 7.89–7.98 (m, 4H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 21.6 (q), 32.4 (t), 32.6 (t), 126.1 (d), 128.1(d), 128.2 (d), 129.2 (d), 129.8 (d), 132.9 (d), 134.1 (s), 134.9 (s), 138.7 (s), 143.9 (s), 197.5 (s), 197.9 (s) ppm; Anal. calcd for $C_{17}H_{15}ClO_2$: C, 71.20; H, 5.27. Found: C, 70.99; H, 5.19.

4.5.3. 1-(3-Chlorophenyl)-1,4-octanedione (5e). Yield 79%; colourless solid; mp 38–40°C; R_f=0.35 (hexane/EtOAc, 9:1); IR ($CHCl_3$): ν 2960, 1718, 1686, 1459, 1414, 1344 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 0.82 (t, 3H, CH_3CH$_2$–, J=7.3 Hz) 1.25 (m, 2H, CH$_3$CH_2CH$_2$–) 1.50 (m, 2H, –CH$_2$CH_2CH$_2$–) 2.42 (t, 2H, CH$_2$CH_2CO–, J=7.3 Hz)), 2.76 (t, 2H, –COCH_2CH$_2$–, J=6.3 Hz), 3.13 (t, 2H, –CH$_2$CH_2CO–, J=6.3 Hz), 7.27–7.40 (m, 2H, Ar–H), 7.73–7.83 (m, 2H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 13.6 (q), 22.1 (t), 25.7 (t), 32.2 (t), 35.8 (t), 42.3 (t), 125.9 (d), 127.9 (d), 129.9 (d) 132.7 (d), 134.6 (s), 138.0 (s), 197.1 (s), 209.1 (s) ppm; Anal. calcd for $C_{14}H_{17}ClO_2$: C, 66.53; H, 6.78. Found: C, 66.71; H, 6.91.

4.5.4. 1-(4-Methoxyphenyl)-4-(4-methylphenyl)-1,4-butanedione (5f). Yield 75%; colourless syrup; R_f=0.42 (hexane/EtOAc, 9:1); IR ($CHCl_3$): ν 2919, 1685, 1551, 1424, 1345 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 2.28 (s, 3H, Ar–CH_3), 3.42 (s, 4H, –CH_2CH_2–), 3.83 (s, 3H, Ar–OCH_3), 6.92 (d, 2H, J=8.2 Hz, Ar–H), 7.49–7.98 (m, 6H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 22.8 (q), 32.6 (t), 32.8 (t), 66.8 (q), 113.6 (d), 128.2 (d), 129.1 (d), 129.8 (d), 130.2 (s), 134.16 (s), 138.3 (s), 158.8 (s), 197.6 (s), 198.7 (s) ppm; Anal. calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.49; H, 6.52.

4.5.5. 1-(2-Furyl)-1,4-octanedione (5h). Yield 72%; colourless solid; mp 45–48°C; R_f=0.29 (hexane/EtOAc, 9:1); IR ($CHCl_3$): ν 2960, 1718, 1683, 1571, 1468, 1254 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 0.84 (t, 3H, CH_3CH$_2$–, J=7.2 Hz) 1.25 (m, 2H, CH$_3$CH_2CH$_2$–) 1.50 (m, 2H, –CH$_2$CH_2CH$_2$–) 2.43 (t, 2H, CH$_2$CH_2CO–, J=7.2 Hz)), 2.77 (t, 2H, –COCH_2CH$_2$–, J=6.3 Hz), 3.06 (t, 2H, –CH$_2$CH_2CO–, J=6.3 Hz), 6.47 (dd, 1H, Ar–H, J=3.0, 1.4 Hz), 7.14 (d, 1H, Ar–H, J=3.0 Hz), 7.52 (d, 1H, Ar–H, J=1.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 13.7 (q), 22.1 (t), 22.5 (t), 29.2 (t), 35.6 (t), 42.4 (t), 116.5 (d), 116.9 (d), 146.2 (d), 152.3 (s), 187.7 (s), 209.3 (s) ppm; Anal. calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.11; H, 7.84.

4.5.6. Addition of butylmagnesium bromide to 2. To a solution of **2** (2.5 mmol) in THF (15 mL), butylmagnesium bromide (7.5 mmol) was added under a nitrogen atmosphere at 0°C. The mixture was stirred for a 1.5 h period. The hydrolysis was achieved by the cautious addition of saturated NH_4Cl solution. After returning to room temperature, the two phases were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The organic phases were combined, washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product which on purification by column chromatography (20% EtOAc in hexane) afforded *N*-methylheptanamide as a colourless syrup.

Yield 0.25 g, (71%); R_f=0.35 (hexane/EtOAc, 7:3); IR ($CHCl_3$): ν 2955, 1660, 1342, 1177, 1121 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 0.80 (t, 3H, CH_3CH$_2$–, J=7.3 Hz), 1.20 (m, 6H, CH$_3$(CH_2)$_3$CH$_2$CH$_2$CO–), 1.55 (m, 2H, –CH$_2$CH_2CH$_2$CO–) 2.15 (t, 2H, –CH$_2$CH_2CO– J=7.3 Hz) 2.75 (d, 3H, –NHCH_3, J=5 Hz), 6.40 (br s, –NHCH$_3$) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 13.8 (q), 22.3 (t), 25.6 (t), 26.0 (t), 28.8 (t), 31.4 (t), 36.4 (q), 174.2 (s) ppm; Anal. calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.18; H, 11.88; N, 9.77.

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