Monatsh Chem (2009) 140:205–207
DOI 10.1007/s00706-008-0064-8

ORIGINAL PAPER

A synthesis of diethyl alkylsulfanylmethylmalonates catalyzed by KOH in an ionic liquid

Issa Yavari · Rahimeh Hajinasiri · S. Zahra Sayyed-Alangi

Received: 24 August 2008 / Accepted: 6 September 2008 / Published online: 15 October 2008

Abstract 1-Ethyl-3-methylimidazolium bromide was used as a green recyclable alternative to volatile organic solvents for KOH catalyzed three-component synthesis of diethyl alkylsulfanylmethylmalonates from aldehydes, diethyl malonate, and alkylthiols.

Keywords Alkylmalonate · Alkylthiol · Ionic liquid

Introduction

Ionic liquids (ILs) have gained tremendous attention in the last 15 years [1–3]. They are, among other uses, solvents and are frequently fitted with attributes like "modern," "green," "designable," "non-volatile," "non-coordinating," etc., although it is increasingly recognized that none of these labels should be used lightly. Nonetheless, many chemical reactions have been attempted and successfully performed in IL media, and oftentimes these systems show interesting and peculiar features. However, considerable work in IL chemistry is still based on trial-and-error rather than fundamental understanding and rational design. To rationalize the differences between ILs and molecular solvents, it is important to understand their properties [1–6].

The Michael reaction has been studied for more than one century. The conjugate addition of amines to carbon–carbon double bonds is a useful protocol in synthetic organic chemistry [7, 8], and it is used extensively in the synthesis of pharmaceutical intermediates, peptide analogues, antibiotics, and other biologically active molecules and drugs [9–11]. In the past few years, a number of alternative procedures have been developed for the conjugate addition of amines to α,β-unsaturated nitriles and carbonyl compounds. In particular, various Lewis-acid-catalyzed reactions have been reported [12–16]. Recently, there were also some reports of this reaction conducted in $Cu(acac)_2$/ionic liquid [17–19], water [20, 21], β-cyclodextrin in water [22], cerium ammonium nitrate [23], $HClO_4$–SiO_2 [24], and indium(III) chloride[25]. As part of our current studies, on the development of in situ thia-Michael addition, we wish to report a one-pot synthesis of sulfanylmethylmalonates catalyzed by KOH.

Results and discussion

Thus, three-component reaction of aldehyde **1**, diethyl malonate **2**, and alkyl thiols **3** catalyzed by KOH proceeds smoothly in ionic liquid to produce diethyl alkylsulfanylmethylmalonates **4** in good yields (Scheme 1).

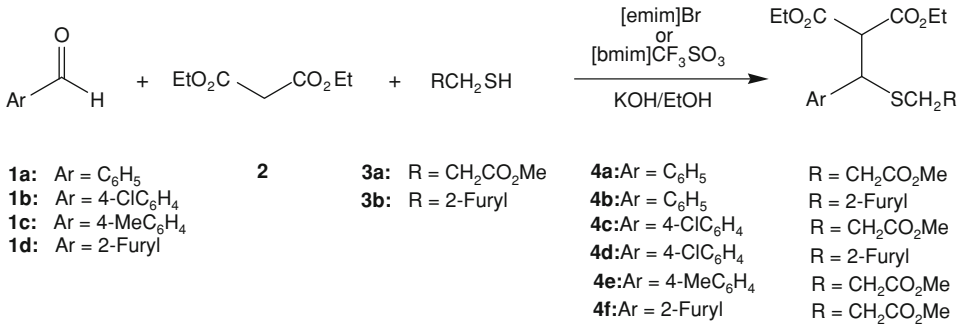
The products were characterized based on their IR, ^{1}H NMR, and ^{13}C NMR. The mass spectra of compounds **4a–f** displayed molecular ion peaks at appropriate *m/z* values. The ^{1}H NMR spectra of **4a–f** exhibited characteristic doublets for the vicinal CH protons. The proton-decoupled ^{13}C NMR spectra of **4a–f** showed resonances in agreement with the proposed structures.

The following mechanism may be invoked for the formation of compounds **4**. Conceivably, the starting point of reaction is formation of the Knoevenagel condensation adduct **6** between diethyl malonate and aldehyde **1**, which

I. Yavari · R. Hajinasiri · S. Z. Sayyed-Alangi
Chemistry Department, Science and Research Campus, Islamic Azad University, Ponak, Tehran, Iran

I. Yavari (✉) · S. Z. Sayyed-Alangi
Chemistry Department, Tarbiat Modares University, PO Box 14115-175, Tehran, Iran
e-mail: yavarisa@modares.ac.ir

Scheme 1



undergoes Michael addition by alkylthiol **3** to produce **4** (Scheme 2).

In conclusion, we report a novel transformation involving diethyl malonate and aldehydes in the presence of alkyl thiols in ionic liquid, which affords diethyl alkylsulfanylmethylmalonates in good yields. The advantage of the present procedure is that the reaction is performed in green and environmentally benign media by simple mixing of the starting materials.

Experimental

Compounds **1–3** and the ionic liquids were obtained from Fluka and were used without further purification. M.p.: Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra: Bruker DRX-300 AVANCE instrument; in $CDCl_3$ at 300 and 75 MHz; δ in ppm, J in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer. The results agreed favorably with the calculated values.

*General procedure for the preparation of compounds **4***

To a stirred solution of 0.03 g KOH in 1 cm^3 of EtOH and 2 cm^3 of [emim]Br was added 0.34 g (2 mmol) of **2** and 2 mmol of aldehyde **1**. After 5 min, 2 mmol of alkylthiol **3** was added. After completion of the reaction (0.5–2 h), as indicated by TLC (EtOAc/*n*-hexane, 2:1), the products were extracted with Et_2O (2 × 10 cm^3). The solvent was evaporated under reduced pressure to leave the crude product, which was purified by column chromatography on silica gel and eluted with a mixture of *n*-hexane:EtOAc (3:1) to afford pure title compounds.

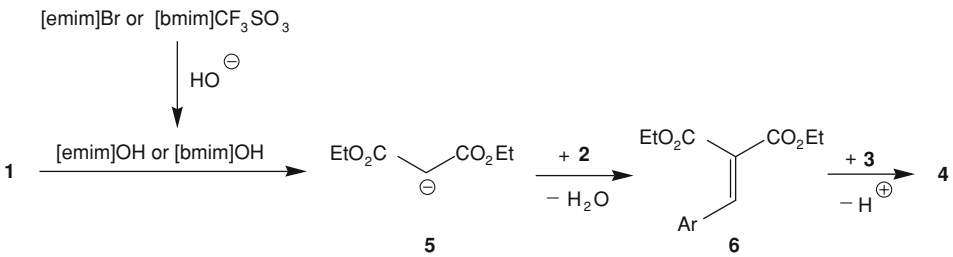
Diethyl 2-{[(3-methoxy-3-oxopropyl)sulfanyl](phenyl) methyl}malonate (**4a**, $C_{18}H_{24}O_6S$)

Yellow oil; yield: 0.56 g (80%). IR (KBr): $\bar{\nu}$ = 1740 (C=O), 2980 (CH) cm^{-1}. EI-MS: *m/z* = 354 (2, M$^+$), 309 (5), 295 (35), 235 (80), 195 (85), 119 (90), 91 (45), 87 (100), 59 (35), 45 (35); ^{1}H NMR: δ = 0.95 (t, ^3J = 7.1, Me), 1.28 (t, ^3J = 7.1, Me), 2.46–2.70 (m, 2CH$_2$), 3.6 (s, OMe), 3.90 (q, ^3J = 7.1, OCH$_2$), 3.92 (d, ^3J = 11.6, CH), 4.23 (q, ^3J = 7.1, OCH$_2$),4.47 (d, ^3J = 11.6, CH), 7.24–7.47 (m, 5 CH) ppm; ^{13}C NMR: δ = 13.5 (Me), 13.9 (Me), 26.4 (CH$_2$), 34.3 (CH$_2$), 48.9 (CH), 51.3 (OMe), 58.4 (CH), 61.4 (OCH$_2$), 61.8 (OCH$_2$), 127.9 (CH), 128.7 (2CH), 128.8 (2CH), 140.3 (C), 166.4 (C=O), 167.0 (C=O), 171.9 (C=O) ppm.

Diethyl 2-{[(2-furylmethyl)sulfanyl](phenyl)methyl} malonate (**4b**, $C_{19}H_{22}O_5S$)

Yellow oil; yield: 0.60 g (83%). IR (KBr): $\bar{\nu}$ = 1755 (C=O), 2982 (CH) cm^{-1}. EI-MS: *m/z* = 362 (2, M$^+$), 317 (5), 250 (85), 202 (90), 113 (95), 91 (35), 81 (100), 45 (35); ^{1}H NMR: δ = 0.95 (t, ^3J = 7.1, Me), 1.28 (t, ^3J = 7.0, Me), 3.58 (AB q, $\Delta\nu_{AB}$ = 51 Hz, J_{AB} = 14.7, SCH$_2$), 3.90 (q, ^3J = 7.1, OCH$_2$), 3.95 (d, ^3J = 11.5, CH), 4.18 (q, ^3J = 7.0, OCH$_2$), 4.50 (d, ^3J = 11.5, CH), 6.21–6.23 (m, 1 CH), 6.35–6.37 (m, 1 CH), 7.27–7.47 (m, 6 CH) ppm; ^{13}C NMR: δ = 13.5 (Me), 13.8 (Me), 27.8 (CH$_2$), 48.43 (CH), 58.3 (CH), 61.4 (OCH$_2$), 61.7 (OCH$_2$), 108.0

Scheme 2



(CH), 110.8 (CH), 127.9 (CH), 128.6 (2CH), 128.9 (2CH), 139.8 (C), 142.7 (CH), 151.7 (C), 166.4 (C=O), 166.9 (C=O) ppm.

Diethyl 2-{(4-chlorophenyl)[3-methoxy-3-oxopropyl) sulfanyl]methyl}malonate (**4c**, $C_{18}H_{23}ClO_6S$)
Yellow oil; yield: 0.60 g (75%). IR (KBr): $\bar{\nu} = 1752$ (C=O), 2980 (CH) cm^{-1}. EI-MS: *m/z* = 402 (2, M^+), 357 (5), 343 (25), 283 (80), 243 (85), 119 (95), 87 (100), 91 (50), 59 (45), 45 (35); ^1H NMR: $\delta = 0.99$ (t, $^3J = 7.1$, Me), 1.28 (t, $^3J = 7.0$, Me), 2.56–2.66 (m, $2CH_2$), 3.58 (s, OMe), 3.91 (q, $^3J = 7.1$, OCH_2), 3.95 (d, $^3J = 11.5$, CH), 4.23 (q, $^3J = 7.0$, OCH_2), 4.48 (d, $^3J = 11.5$, CH), 7.21 (d, $^3J = 7.0$, 2CH), 7.48 (d, $^3J = 7.0$, 2CH) ppm; ^{13}C NMR: $\delta = 13.6$ (Me), 13.9 (Me), 26.5 (CH_2), 34.22 (CH_2), 48.1 (CH), 51.3 (OMe), 58.2 (CH), 61.6 (OCH_2), 61.9(OCH_2), 128.7 (2CH), 130.6 (2CH), 133.1 (C), 139.5 (C), 166.3 (C=O), 166.9 (C=O), 171.9 (C=O) ppm.

Diethyl 2-{(4-chlorophenyl)[2-furylmethyl)sulfanyl] methyl}malonate (**4d**, $C_{19}H_{21}ClO_5S$)
Yellow oil; yield: 0.60 g (75%). IR (KBr): $\bar{\nu} = 1756$ (C=O), 2985 (CH) cm^{-1}. EI-MS: *m/z* = 397 (2, M^+), 362 (5), 352 (5), 284 (80), 238 (85), 113 (95), 81 (100), 91 (45), 45 (35); ^1H NMR: $\delta = 1.01$ (t, $^3J = 7.1$, Me), 1.29 (t, $^3J = 7.0$, Me), 3.58 (AB q, $\Delta\nu_{AB} = 41.5$ Hz, $J_{AB} = 14.8$, SCH_2), 3.83 (d, $^3J = 11.4$, CH), 3.94 (q, $^3J = 7.1$, OCH_2), 4.25 (q, $^3J = 7.0$, OCH_2), 4.45 (d, $^3J = 11.4$, CH), 6.13–6.15 (m, CH), 6.23–6.31 (m, CH), 7.21 (d, $^3J = 7.0$, 2CH), 7.27 (d, $^3J = 7.0$, 2CH), 7.33 (m, CH) ppm; ^{13}C NMR: $\delta = 14.1$ (Me), 14.4 (Me), 28.5 (CH_2), 47.8 (CH), 58.5 (CH), 62.1 (OCH_2), 61.4 (OCH_2), 108.4(CH), 110.8 (CH), 128.9 (2CH), 130.2 (2CH), 133.8 (C), 138.0 (C), 142.6 (CH), 151.1 (C), 166.7 (C=O), 167.1 (C=O) ppm.

Diethyl 2-{[(3-methoxy-3-oxopropyl)sulfanyl] (4-methylphenyl)methyl}malonate (**4e**, $C_{19}H_{26}O_6S$)
Yellow oil; yield: 0.65 g (85%). IR (KBr): $\bar{\nu} = 1745$ (C=O), 2984 (CH) cm^{-1}. EI-MS: *m/z* = 382 (2, M^+), 367 (5), 337 (5), 323 (30), 263 (80), 223 (85), 119 (85), 87 (100), 91 (80), 59 (35), 45 (35), 15 (65); ^1H NMR: $\delta = 0.99$ (t, $^3J = 7.1$, Me), 1.32 (t, $^3J = 7.0$, Me), 2.32 (s, Me), 2.42–2.67 (m, $2CH_2$), 3.65 (s, OMe), 3.84 (d, $^3J = 11.5$, CH), 3.93 (q, $^3J = 7.1$, OCH_2), 4.27 (q, $^3J = 7.0$, OCH_2), 4.44 (d, $^3J = 11.5$, CH), 7.11 (d, $^3J = 8.0$, 2CH), 7.23 (d, $^3J = 8.0$, 2CH) ppm; ^{13}C NMR: $\delta = 14.1$ (Me), 14.5 (Me), 21.5 (Me), 26.7 (CH_2), 34.6 (CH_2), 48.8 (CH), 52.11 (OMe), 58.8 (CH), 62.0 (OCH_2), 62.3 (OCH_2), 128.5 (2CH), 129.6 (2CH), 136.4 (C), 137.9 (C), 166.8 (C=O), 167.5 (C=O), 172.5 (C=O) ppm.

Diethyl 2-{2-furyl[(2-methoxy-2-oxopropyl)sulfanyl] methyl}malonate (**4f**, $C_{16}H_{22}O_7S$)
Yellow oil; yield: 0.61 g (85%). IR (KBr): $\bar{\nu} = 1756$ (C=O), 2982 (CH) cm^{-1}. EI-MS: *m/z* = 358 (2, M^+), 313 (5), 239 (75), 199 (75), 119 (80), 87 (100), 81 (95), 59 (65), 45 (75), 29 (100), 15 (70); ^1H NMR: $\delta = 1.10$ (t, $^3J = 7.0$, Me), 1.28 (t, $^3J = 7.0$, Me), 2.44–2.74 (m, 2 CH_2), 3.58 (s, OMe), 4.00 (d, $^3J = 11.5$, CH), 4.04 (q, $^3J = 7.0$, OCH_2), 4.21 (q, $^3J = 7.0$, OCH_2), 4.56 (d, $^3J = 11.5$, CH), 6.35–6.39 (m, 2 CH), 7.21 (d, $^3J = 7.0$, 2CH), 7.49 (d, $^3J = 10.9$, CH) ppm; ^{13}C NMR: $\delta = 13.7$ (Me), 13.8 (Me), 26.2 (CH_2), 34.5 (CH_2), 41.8 (CH), 51.3 (OMe), 56.4 (CH), 61.7 (OCH_2), 61.9 (OCH_2), 107.9 (CH), 110.8 (CH), 142.7 (CH), 157.4 (C), 166.4 (C=O), 166.7.1 (C=O), 171.9 (C=O) ppm.

References

1. Welton T (1999) Chem Rev 99:2071
2. Rogers RD, Seddon KR (eds) (2002) In: Ionic liquids: industrial applications to green chemistry. ACS Symposium Series 818, American Chemical Society, Washington, DC
3. Wasserscheid P, Welton T (eds) (2003) Ionic liquids in synthesis. Wiley, Weinheim
4. Chiappe C (2007) Monatsh Chem 138:1035
5. Paczal A, Kotschy A (2007) Monatsh Chem 138:1115
6. Meindersma GW, Sa′nchez LMG, Hansmeier AR, de Haan AB (2007) Monatsh Chem 138:1125
7. Han LB, Tanaka M (1999) J Chem Soc; Chem Commun 395
8. Arredondo VM, Tian S, MacDonald FE, Marks TJ (1999) J Am Chem Soc 121:3633
9. Hayao S, Schut RN (1961) J Med Chem 26:3414
10. Orjales A, Alonso-Cires L, Labeaga L, Corco′stegui R (1995) J Med Chem 8:1273
11. Ahmad YE, Laurent E, Maillet P, Talab A, Teste JF, Dohkan R, Tran G, Ollivier V (1997) J Med Chem 40:952
12. Bartoli G, Bosco M, Marcantoni E, Petrini M, Sambri L, Torregiani E (2001) J Org Chem 66:9052
13. Wabnitz TC, Spencer JB (2002) Tetrahedron Lett 43:3891
14. Srivastava N, Banik BK (2003) J Org Chem 68:2109
15. Varala R, Alam MM, Adapa SR (2003) Synlett:720
16. Azizi N, Saidi MR (2004) Tetrahedron 60:383
17. Kantam CM, Neeraja V, Kavita B, Neelima B, Chaudhuri MK, Hussain S (2005) Adv Synth Catal 347:763
18. Yadav JS, Reddy BVS, Basak AK, Narsaiah AV (2003) Chem Lett 32:988
19. Xu LW, Li JW, Zhou SL, Xia CG (2004) New J Chem 28:183
20. Khatik GL, Kumar R, Chakraborti AK (2006) Org Lett 8:433
21. Ranu BC, Dey SS, Hajra A (2007) Tetrahedron Lett 48:141
22. Chaudhuri MK, Hussain S, Kantam CM 3, Neelima B (2005) Tetrahedron Lett 46:8329
23. Surendra K, Krishnaveni NS, Sridhar R, Rao KR (2006) Tetrahedron Lett 47:2125
24. Khatik GL, Sharma G, Kumar R, Chakraborti AK (2007) Tetrahedron 63:1200
25. Ranu BC, Dey SS, Samanta S (2005) Arkivoc (iii):44