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Green protocol for Willgerodt–Kindler transformation using [bmim]BF_4 ionic medium☆

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Abstract

Aryl alkyl ketones react readily with morpholine in the presence of sulfur in air and moisture stable ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 to produce the corresponding thiomorpholides in high yields. The use of recyclable ionic liquids makes this process quite simple, more convenient and environmentally friendly.

Keywords: ILs; Willgerodt–Kindler reaction; Sulfur; Thiomorpholide

1. Introduction

The volatile nature of many organic solvents those that are widely used in organic synthesis have posed a serious threat to the environment. Consequently, method that successfully minimize their use are the focus of the much attention [1]. In recent times, ionic liquids are being used as alternative reaction media to more volatile organic solvents. They are emerged as a set of green solvents with unique properties such as a wide liquid range, tunable polarity, high thermal stability, solvating ability, negligible vapor pressure and ease of recyclability [2]. Due to their ability to solubilise both inorganic and organic compounds can result in enhanced rates of chemical processes and can provide higher selectivities compared to conventional solvents (Fig. 1).

As a result of their green credential and potential to enhance reaction rates and selectivities, ionic liquids are finding increasing applications in organic synthesis. They are particularly promising as solvents for the immobilization of transition metal-based catalysts, Lewis acids and enzymes [3]. However, there have been no examples on the use of ionic liquids for the conversion of aryl alkyl ketones to thiomorpholides.

2. Experimental

2.1. General methods

Melting points were recorded on a Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer and Bruker Avance (300 MHz) in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. Column chromatography was performed using E. Merck 60–120, mesh silica gel. All solvents were distilled, dried over CaH_2 and stored under nitrogen prior to use. Starting materials and reagents used in the reactions were obtained commercially from Aldrich, Lancaster, Fluka and were used without purification, unless otherwise indicated.

2.2. General procedure

2.2.1. Experimental procedure

A heterogeneous mixture of acetophenone (1 mmol), morpholine (1.2 mmol) and sulfur (1.4 mmol) in [bmim]BF_4 (3 mL) was heated at 110 °C for the appropriate time (see Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water (3 ml × 10 ml). The precipitated solid was collected by filtration and recrystallized in ethanol to afford pure thioamide. In case of liquid, the

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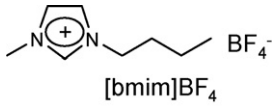


[bmim]BF_4

Fig. 1. Chemical structure of ionic liquid.

products were isolated by simple extraction with diethyl ether. Spectral data of all (**a**-**l**) compounds:

2.2.2. Spectral data for selected products

2.2.2.1. ***3a***. Yellow solid, m.p.: 62–67 °C, IR (KBr): υ_{max}: 3473, 3026, 2968, 2861, 1960, 1711, 1488, 1279, 1109, 958, 707, 622 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.17–7.22 (m, 5H), 4.30–4.35 (t, J = 6.82 Hz, 2H), 4.30 (s, 2H), 3.70–3.78 (t, J = 7.20 Hz, 2H), 3.55–3.52 (t, J = 7.43 Hz, 2H), 3.30–3.40 (t, J = 7.32 Hz, 2H); EIMS: *m/z* (%): 221 (M^+, 36), 188 (10), 135 (36), 117 (10), 91 (100), 86 (57), 65 (24), 51 (36), 49 (38), 43 (37).

2.2.2.2. ***3b***. Colorless liquid, IR (neat): υ_{max}: 2924, 1654, 1484, 1252, 1102, 1000, 752, 572 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.10 (d, J = 6.27 Hz, 2H), 6.90 (d, J = 6.43 Hz, 2H), 4.45 (s, 2H), 4.30 (t, J = 7.20 Hz, 2H), 3.60–3.80 (t, J = 6.24 Hz, 4H), 3.40–3.50 (t, J = 5.20 Hz, 2H), 2.20 (s, 3H); EIMS: *m/z* (%): 235 (M^+, 65), 202 (18), 149 (38), 130 (100), 119 (58), 105 (78), 91 (47), 86 (100), 77 (30), 51 (23), 43 (20).

2.2.2.3. ***3c***. Brown oil IR (neat): υ_{max}: 3461, 2927, 2856, 1608, 1510, 1250, 1113, 1031, 765 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.10–7.30 (d, J = 7.21 Hz, 2H), 6.80 (d, J = 7.32 Hz, 2H), 4.30–4.40 (t, J = 8.30 Hz, 2H), 4.25 (s, 2H), 3.80 (s, 3H), 3.70 (t, J = 6.20 Hz, 2H), 3.63 (t, J = 5.80 Hz, 2H), 3.3–3.34 (t, J = 6.02 Hz, 2H); EIMS: *m/z* (%): 251 (M^+, 20), 167 (22), 137 (25), 121 (43), 112 (20), 105 (30), 86 (80), 77 (45), 57 (100), 43 (65).

2.2.2.4. ***3d***. Yellow solid, m.p.: 105–107 °C, IR (KBr): υ_{max}: 3472, 2922, 1659, 1597, 1505, 1436, 1236, 1169, 1113, 751, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.40 (m, 5H), 7.0 (d, J = 6.25 Hz, 2H), 6.86 (d, J = 6.30 Hz, 2H), 5.03 (s, 2H), 4.28 (s, 2H), 3.88 (t, J = 7.80 Hz, 2H), 3.65–3.70 (t, J = 6.8 Hz, 2H), 3.55–3.63 (t, J = 6.82 Hz, 2H), 3.32 (t, J = 5.0 Hz, 2H); EIMS: *m/z* (%): 327 (M^+, 13), 323 (20), 231 (28), 206 (42), 144 (13), 87 (100), 54 (68).

2.2.2.5. ***3e***. Light yellow solid, m.p.: 94–95 °C, IR (KBr): υ_{max}: 3416, 2922, 2858, 1486, 1432, 1277, 1219, 1111, 1030, 961, 722, 614 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.50 (d, J = 7.49 Hz, 2H), 7.20 (d, J = 6.50 Hz, 2H), 4.35 (t, J = 8.36 Hz, 2H), 4.22 (s, 2H), 3.70–3.80 (t, J = 4.56 Hz, 2H), 3.60 (t, J = 5.2 Hz, 2H), 3.40 (t, J = 5.8 Hz, 2H); EIMS: *m/z* (%): 300 (M^+, 42), 268 (10), 252 (10), 214 (13), 169 (32), 141 (20), 130 (100), 112 (29), 86 (92), 60 (17), 43 (42).

2.2.2.6. ***3f***. Yellow oil, IR (neat): υ_{max}: 3357, 3229, 2922, 2855, 1626, 1589, 1499, 1440, 1319, 1270, 1236, 1171, 1110, 1029, 947, 841, 754, 667 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.75 (d, J = 6.7 Hz, 2H), 6.60 (d, J = 6.9 Hz, 2H), 4.35 (t, J = 7.4 Hz, 2H), 4.20 (s, 2H), 3.94 (t, J = 5.2 Hz, 2H), 3.60 (t, J = 8.7 Hz, 4H); EIMS: *m/z* (%): 266 (M^+, 38), 252 (72), 160 (29), 141 (55), 138 (36), 129 (32), 97 (33), 71 (58), 57 (100), 43 (92).

2.2.2.7. ***3g***. Yellow oil IR (neat): υ_{max}: 3520, 2929, 2855, 2758, 2596, 2280, 2039, 1655, 1590, 1488, 1340, 1272, 1111, 1027, 960, 865, 766 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.90 (s, 1H), 6.75 (s, 2H), 4.30 (t, J = 7.08 Hz, 2H), 4.23 (s, 2H), 3.85 (s, 6H), 3.60–3.70 (m, 4H), 3.40 (t, J = 5.02 Hz, 2H); EIMS: *m/z* (%): 281 (M^+, 20), 270 (22), 130 (18), 117 (60), 91 (58), 84 (100), 57 (43), 57 (43), 47 (45), 35 (30).

2.2.2.8. ***3h***. Yellow solid, m.p.: 92–94 °C, IR (KBr): υ_{max}: 3448, 3054, 2968, 2921, 2855, 1661, 1625, 1492, 1436, 1272, 1112, 1031, 757, 666 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.4–8.05 (m, 7H), 4.5 (s, 1H), 4.36 (t, J = 5.0 Hz, 1H), 4.3 (s, 1H), 3.92 (t, J = 6.25 Hz, 1H), 3.78 (t, J = 5.2 Hz, 2H), 3.7 (t, J = 5.32 Hz, 1H), 3.65 (t, J = 5.7 Hz, 2H), 3.3 (t, J = 6.2 Hz, 1H); EIMS: *m/z* (%): 271 (M^+, 70), 238 (12), 184 (38), 155 (90), 141 (58), 130 (100), 128 (66), 115 (35), 86 (100), 60 (20), 45 (23).

2.2.2.9. ***3i***. Light yellow oil, IR (neat): υ_{max}: 3477, 3120, 3002, 1652, 1499, 1218, 1117, 786, 771 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.40 (d, J = 7.52 Hz, 2H), 7.21–7.30 (d, J = 7.6 Hz, 2H), 6.90 (t, J = 4.20 Hz, 1H), 6.05 (t, J = 4.32 Hz, 1H), 3.80–3.87 (t, J = 6.4 Hz, 4H), 3.10–3.15 (t, J = 6.38 Hz, 4H), 2.00 (t, J = 4.8 Hz, 2H), 1.40 (t, J = 6.7 Hz, 2H); EIMS: *m/z* (%): 283 (M^+, 35), 280 (100), 222 (63), 156 (17), 141 (30), 69 (12), 45 (12).

2.2.2.10. ***3j***. Yellow solid, m.p.: 75–77 °C, IR (KBr): υ_{max}: 3600, 1627, 1487, 1219, 1113, 1030, 954, 864, 769cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 11.3 (brs, 1H, –OH), 7.43–7.6 (m, 1H), 7.0 (d, J = 7.0 Hz, 1H), 6.84 (d, J = 6.8 Hz, 1H), 4.34 (s, 2H), 4.30 (t, J = 6.3 Hz, 1H), 3.85 (t, J = 5.8 Hz, 2H), 3.8 (t, J = 5.2 Hz, 1H), 3.63 (t, J = 6.0 Hz, 4H); EIMS: *m/z* (%): 237 (M^+, 20), 218 (26), 203 (18), 156 (38), 139 (57), 121 (100), 86 (70), 43 (45).

2.2.2.11. ***3k***. Yellow oil, IR (neat): υ_{max}: 3368, 3240, 2820, 1618, 1532, 1400, 1328, 1262, 1208, 1029, 842, 668 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.25–7.80 (m, 24), 4.20 (brs, 2H, $–NH_2$), 4.30–4.33 (t, J = 6.5 Hz, 2H), 4.29 (s, 2H), 3.70–3.76 (t, J = 5.3 Hz, 2H), 3.55–3.52 (t, J = 5.2 Hz, 2H), 3.30–3.40 (t, J = 6.2 Hz, 2H); EIMS: *m/z* (%): 236 (M^+, 26), 201 (29), 149 (42), 132 (37), 119 (32), 103 (52), 86 (100), 51 (92), 43 (43).

2.2.2.12. ***3l***. Yellow solid, m.p.: 85–87 °C, IR (KBr): υ_{max}: 3400, 2950, 2727, 2362, 1499, 1236, 1218, 1117, 776, 732 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.0–7.2 (m, 3H), 4.25–4.30 (t, J = 6.60 Hz, 4H), 3.6–3.7 (t, J = 5.2 Hz, 2H), 3.52–3.58 (t, J = 4.2 Hz, 2H), 3.32 (t, J = 5.24 Hz, 2H); EIMS: *m/z* (%): 227 (M^+, 73), 194 (13), 140 (20), 130 (70), 97 (70), 86 (100), 60 (20), 45 (40).

Table 1
Preparation of thiomorpholides using [bmim]BF4 ionic medium

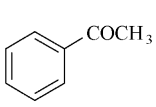
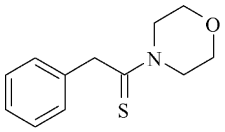
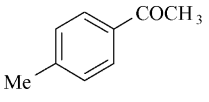
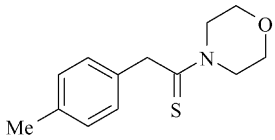
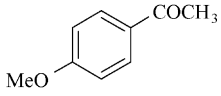
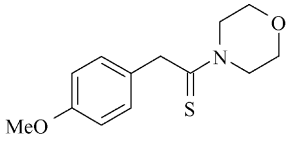
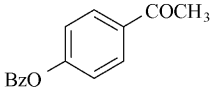
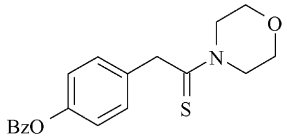
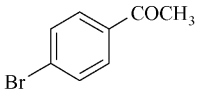
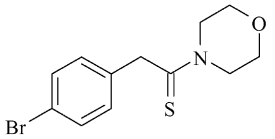
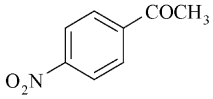
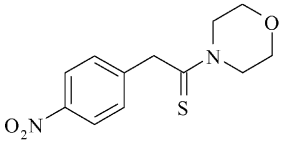
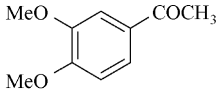
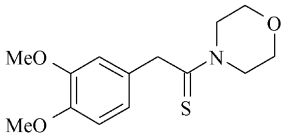
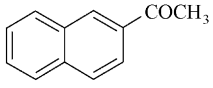
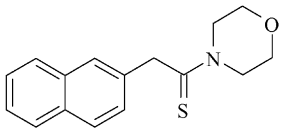
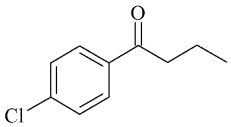
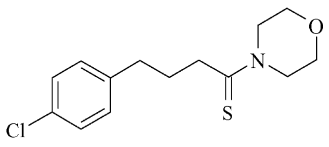
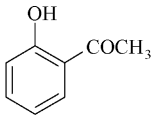
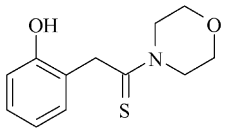
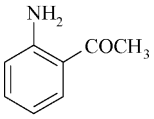
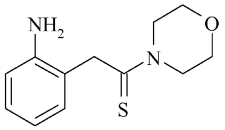
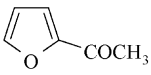
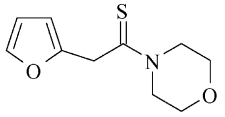
Entry	Aryl alky ketone	Thio morphide[a]	Yield[b] (%)	Time (h)
a			92	3.0
b			85	3.5
c			80	3.5
d			90	4.5
e			80	5.0
f			81	5.5
g			85	6.0
h			70	4.0
i			87	3.0
j			85	3.5

Table 1 (*Continued*)

Entry	Aryl alky ketone	Thio morphide[a]	Yield[b] (%)	Time (h)
k			90	3.0
l			89	3.5

[a] All products were characterised by ^{1}H NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after column chromatography.

3. Results and discussion

In view of the recent surge on the use of ionic liquids in the area of green syntheses [4], we herein report, for the first time, the use of ionic liquids as novel solvents for the preparation of thiomorpholides from aryl alkyl ketones, morpholine and elemental sulfur (Scheme 1).

Accordingly, treatment of acetophenone with morpholine in the presence of sulphur in hydrophilic [bmim]BF_4 ionic liquid at 110 °C for 3 h afforded thiomorpholide in 92% yield. In a similar fashion, various aryl alkyl ketones were efficiently converted into their corresponding thioamides by using this procedure. Both electron rich as well as electron deficient acetophenones reacted well with morpholine in the presence of sulfur to give thioamides in excellent yields. Bulky and sterically hindered substrates such as 2-acetylnaphthalene, 2-aminoacetophenone and 2-hydroxyacetophenone reacted smoothly under similar conditions to produce the corresponding thioamides (entries **h**, **j**, and **k**, Table 1). In all cases, the reactions were carried out at 110 °C using hydrophilic as well as hydrophobic ionic liquids. In case of halogenated acetophenones, no side products were observed arising from nucleophilic displacement of halogen by morpholine under these conditions (entries **e** and **i**, Table 1). Other substrate such as butyrophenone also gave the corresponding thioamide in 87% yield (entry **i**, Table 1). In most of the cases, the products were obtained as solids, therefore, they could be easily separated by filtration with water. The products thus obtained were further purified by crystallization. The rest of the aqueous layer was concentrated in vacuo to recover the ionic liquid. The recoverability of [bmim]BF_4 ionic liquid was facilitated by its hydrophilic nature. Thus, the use of ionic liquids as reaction media for this conversion avoids the use of toxic and more volatile organic solvents. The recovered ionic liquid was reused in five to six subsequent runs with gradual decrease in activity. For instance, treatment of acetophenone with morpholine and sulphur in [bmim]BF_4 afforded thiomorpholide in 92%, 90%, 88%, 88%, and 87% yields over five cycles. This may be due to the loss of reactivity of ionic liquid in water. The products thus obtained could be easily transformed into their respective aryl acetic acid derivatives by using known protocol [5]. Since aryl acetic acids are key intermediates in the synthesis of anti-inflammatory drugs, this method is very useful and attractive strategy for the preparation of thiomorpholides. In the classical Willgerodt–Kindler reaction, morpholine was generally used in large excess as solvent as well as reactant [5]. The use of ionic liquid as a solvent minimizes the quantity of morpholine in the reaction. This is because of the activation of ketones by ionic liquid. The main advantage of this procedure is that high conversions (70–92%) were achieved in short reaction times (3–6 h) by using ionic liquids. Under classical conditions, the yields are generally low and also the reactions require high temperature for long reaction times (8–12 h) [5]. In order to compare the efficiency of ionic liquids, the reactions were also conducted in organic solvents such as benzene and toluene. In these solvents, the products were obtained in low yields (10–20%) after prolonged reaction times 12–24 h) under similar conditions. The scope and generality of this process is illustrated with respect to various aryl alkyl ketones and the results are presented in the Table 1 [6].

Scheme 1.

4. Conclusion

In summary, we describe a novel use of ionic liquids for the three-component condensation of aryl alkyl ketones, morpholine and sulfur to produce thiomorpholides in excellent yields. The notable features of this procedure are high conversions, operational simplicity, enhanced reaction rates, cleaner reaction profiles and ease of isolation of products, which make this process quite simple, more convenient and environmentally benign for the synthesis of thiomorpholides.

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References

[1] (a) K. Tanaka, F. Toda, Chem. Rev. 100 (2000) 1025;
(b) J.H. Clark, Acc. Chem. Res. 35 (2002) 791.
[2] (a) T. Welton, Chem. Rev. 99 (1999) 2071;
(b) P. Wasserchеid, W. Keim, Angew. Chem. Int. Ed. Engl. 39 (2000) 3772.
[3] (a) R. Sheldon, J. Chem. Soc., Chem. Commun. (2001) 2399;
(b) C.M. Gordon, Appl. Catal. A: Gen. 222 (2001) 101.
[4] (a) J.S. Yadav, B.V.S. Reddy, A.K. Basak, A.V. Narsaiah, Tetrahedron Lett. 44 (2003) 1047;
(b) J.S. Yadav, B.V.S. Reddy, G. Baishya, J. Org. Chem. 68 (2003) 7098;
(c) J.S. Yadav, B.V.S. Reddy, J.S.S. Reddy, R. Srinivas Rao, Tetrahedron 59 (2003) 1599;
(d) J.S. Yadav, B.V.S. Reddy, Ch.S. Reddy, K. Rajasekhar, J. Org. Chem. 68 (2003) 2525.
[5] (a) E.V. Brown, Synthesis 37 (1975) 358;
(b) M. Nooshabdi, K. Aghapoor, H.R. Darabi, M.M. Mojtahedi, Tetrahedron Lett. 40 (1999) 7549.
[6] (a) P. Metzner, Synthesis (1992) 1185;
(b) A.F. Spatola, in: B. Weinsein (Ed.), Chemistry and Biochemistry of Aminoacid, Peptides and Proteins, vol. 7, Marcel Dekker, New York, 1983, p. 267 (and references cited therein);
(c) M.C. Murguia, R.A. Rossi, Tetrahedron Lett. 38 (1997) 1355.