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ORIGINAL PAPER

One-pot three-component kinetic controlled and *syn*-diastereoselective Mannich reaction of unfunctionalized ketones in water catalyzed by nano-manganese hydrogen sulfate particles

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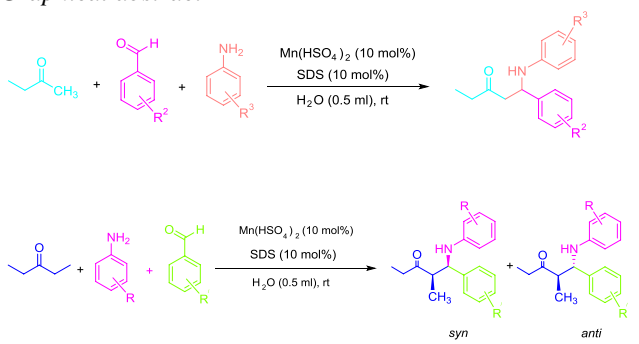
Abstract Direct catalytic three component Mannich reaction of aliphatic ketone, aldehyde and amine was described in the presence of a catalytic amount of nano-$Mn(HSO_4)_2$ (10 mol%) and a surfactant, for example sodium dodecyl sulfate (10 mol%) in the water as a green solvent. β-amino carbonyl compounds were obtained regioselectively as a less-substituted product from a one-pot three component Mannich reaction of 2-butanone in the above conditions. On the other hand, 3-pentanone as a symmetric ketone in the Mannich reactions gave β-amino carbonyl compounds with moderate to high *syn* diasterioselectivity. Control of regioselectivity and/or diasterioselectivity of the most products is related to micelle formation of organic substrates and SDS in water. Hydrophobic groups of substrates self-assembled in these microreactors whereas, hydrophilic groups were solvated with water or chelated with $Mn(HSO_4)$. The above interactions forwarded to these observed selectivity.

Graphical abstract



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Keywords Kinetic controlled · *syn*-diastereoselective · Unfunctionalized ketones · Nano-$Mn(HSO_4)_2$ · Mannich reaction · Micelle

Introduction

Mannich reactions are among the most important carbon–carbon bond forming reactions in organic synthesis [1–3]. They provide β-amino carbonyl compounds, which are important synthetic intermediates for various pharmaceuticals and natural products [4]. The increasing popularity of the Mannich reaction has been fueled by the ubiquitous nature of nitrogen-containing compounds in drugs and natural products [5, 6].

Carrying out organic reactions in water has become highly desirable in recent years to meet environmental considerations [7–12]. The use of water as a sole medium for organic reactions would greatly contribute to the development of environmentally friendly processes. Indeed, industry prefers to use water as a solvent rather than toxic organic solvents [13]. In this context, in recent years, much attention has been focused on Lewis acid catalyzed organic reactions in water.

Nanoparticles have recently attracted much interest because of their many applications in a variety of disciplines, for example chemistry, materials science, and the biomedical sciences [14, 15]. Metal nanoparticles are of fundamental interest because of their unique performance in ultrasensitive chemical and biological sensors and their selectivity as catalysts in chemical and photochemical reactions [16–21]. Because of their high surface-to-volume ratio, metal nanoparticles have more active sites per unit area than traditional catalysts [22]. Hydrophilic nanoparticles with high dispersity in environmentally benign solvents are extremely important

in biological applications [23]. These nanoparticles are soluble in water in a pH range of approximately 5–9 [24].

Several three-component Mannich reaction are available for the diastereoselective synthesis of β-amino carbonyl compounds [25–32]. However, a systematic study of acyclic ketones and/or a *syn* diastereoselectivity was not reported in the literature. Therefore, to achieve a *syn* diastereoselective synthesis of β-aminoketones, we chose nano-$Mn(HSO_4)_2$ (10 mol%) as catalyst and sodium dodecyl sulfate (10 mol%) as surfactant in water for three-component Mannich reaction of aliphatic ketones, aldehydes and amines.

Experimental

General

Chemicals were either prepared in our laboratories or purchased from Merck, Fluka, and Aldrich. All yields refer to isolated products. The reactions were monitored by thin-layer chromatography conducted on silica plates. The products were characterized by comparison of their physical or spectral properties with those of authentic samples. IR spectra were recorded on a Thermo Nicolet Avatar-370 FTIR spectrophotometer. NMR spectra were recorded on ASPECT 3000 Brucker-100 MHz and Avance Brucker-400 MHz spectrometers in $CDCl_3$ as the solvent and with TMS as internal standard. General procedure for synthesis of manganese hydrogen sulfate and data related to nanostructure characterization (XRD and TEM) reported in our recent article [25].

General procedure for the Mannich reaction (1–18)

The aromatic aldehyde (1 mmol), aromatic amine (1 mmol), aliphatic ketone (2-butanone, 3-pantanone, *iso*-butyl methyl ketone) (1.2 mmol), $Mn(HSO_4)_2$ (10 mol%, 25 mg), and SDS (10 mol%, 28.8 mg) were added to water (0.5 mL). The reaction mixture was stirred at room temperature for the appropriate time. The progress of reaction was monitored by TLC. After completion of the reaction, the solid mixture was isolated by filtration to eliminate the catalyst, then the crude product was extracted with *n*-hexane or petroleum ether. The extract was dried over anhydrous Na_2SO_4 then evaporated to dryness. The residue was purified by recrystallization from ethanol.

1-Phenyl-1-(phenylamino) pentan-3-one (1)

^{1}H NMR ($CDCl_3$, 100 MHz, δ ppm): 0.95 (t, 3H, $J = 7.0$ Hz), 2.3 (q, 2H, $J = 7.0$ Hz), 2.85 (d, 2H, $J = 7.0$ Hz), 4.5 (br, NH), 4.85 (t, 1H, $J = 7.0$ Hz), 6.4–6.8 (m, 3H), 7–7.4 (m, 7H); IR (KBr disk): 3387 (s, NH), 3023 (w), 2990 (w), 1707 (s, C=O), 1602 (s), 1514 (s), 1283 (m), 1106 (m), 749 (s), 551 (m) cm^{-1}.

1-Phenyl-1-(*p*-tolylamino) pentan-3-one (2)

^{1}H NMR ($CDCl_3$, 100 MHz, δ ppm): 1.0 (t, 3H, $J = 7.0$ Hz), 2.2 (s, 3H), 2.35 (q, 2H, $J = 7.0$ Hz), 2.85 (d, 2H, $J = 7.0$ Hz), 4.3–4.6 (br, NH), 4.8 (t, 1H, $J = 7.0$ Hz), 6.4 (d, 2H, $J = 8.0$ Hz), 6.9 (d, 2H, $J = 8.0$ Hz), 7.1–7.5 (m, 5H); IR (KBr disk): 3372 (s, NH), 2970 (w), 2937 (w), 1704 (s, C=O), 1620 (s), 1521 (s), 1278 (s), 807 (s), 603 (m) cm^{-1}.

1-((4-Bromophenyl)amino)-1-phenylpentan-3-one (3)

^{1}H NMR ($CDCl_3$, 100 MHz, δ ppm): 0.95 (t, 3H, $J = 7.0$ Hz), 2.3 (q, 2H, $J = 7.0$ Hz), 2.9 (d, 2H, $J = 7.0$ Hz), 4.65 (br, NH), 4.75 (t, 1H, $J = 7.0$ Hz), 6.4 (d, 2H, $J = 8.0$ Hz), 7.15 (d, 2H, $J = 8.0$ Hz), 7.2–7.4 (m, 5H); IR (KBr disk): 3379 (s, NH), 2982 (w), 2896 (w), 1709 (s, C=O), 1663 (s), 1595 (s), 1486 (s), 1376 (w), 1279 (m), 1176 (w), 988 (w), 804 (w), 649 (m) cm^{-1}.

1-(4-Methoxyphenyl)-1-(phenylamino) pentan-3-one (4)

IR (KBr disk): 3337 (s, NH), 2967 (w), 2934 (w), 2906 (w), 1705 (s, C=O), 1601 (s), 1513 (s), 1441 (m), 1249 (s), 1106 (w), 1024 (s), 832 (s), 697 (m), 592 (w) cm^{-1}.

1-(4-Methoxyphenyl)-1-(*p*-tolylamino) pentan-3-one (5)

^{1}H NMR ($CDCl_3$, 100 MHz, δ ppm): 0.95 (t, 3H, $J = 7.0$ Hz), 2.2 (s, 3H), 2.3 (q, 2H, $J = 7.0$ Hz), 2.8 (d, 2H, $J = 7.0$ Hz), 3.75 (s, 3H), 4.1–4.5 (br, NH), 4.75 (t, 1H, $J = 7.0$ Hz), 6.45 (d, 2H, $J = 8.0$ Hz), 6.7–7 (m, 4H), 7.1–7.3 (m, 2H); IR (KBr disk): 3370 (s, NH), 2975 (w), 2839 (m), 1711 (s, C=O), 1615 (s), 1521 (s), 1373 (w), 1249 (s), 1178 (s), 808 (s), 592 (w) cm^{-1}.

1-((4-Chlorophenyl)amino)-1-(4-methoxyphenyl) pentan-3-one (6)

^{1}H NMR ($CDCl_3$, 100 MHz, δ ppm): 1.0 (t, 3H, $J = 7.0$ Hz), 2.3 (q, 2H, $J = 7.0$ Hz), 2.8 (d, 2H, $J = 7.0$ Hz), 3.8 (s, 3H), 4.6–4.8 (m, 1H which masked with NH), 6.45 (d, 2H, $J = 8.0$ Hz), 6.85 (d, 2H, $J = 8.0$ Hz), 7.05 (d, 2H, $J = 8.0$ Hz),7.2 (d, 2H, $J = 8.0$ Hz) IR (KBr disk): 3370 (s, NH), 3002 (w), 2966 (w), 2835 (w), 1710 (s, C=O), 1602 (s), 1513 (s), 1254 (s), 1171 (s), 1115 (m), 931 (w), 820 (s), 686 (m), 600 (w) cm^{-1}.

1-((4-Bromophenyl)amino)1-(4-methoxyphenyl) pentan-3-one (7)

^{1}H NMR ($CDCl_3$, 100 MHz, δ ppm): 0.95 (t, 3H, J = 7.0 Hz), 2.3 (q, 2H, J = 7.0 Hz), 2.85 (d, 2H, J = 7.0 Hz), 3.8 (s, 3H), 4.6–4.8 (m, 1H which masked with NH), 6.4 (d, 2H, J = 8.0 Hz), 6.85 (d, 2H, J = 8.0 Hz), 7–7.4 (m, 4H); IR (KBr disk): 3371 (s, NH), 2958 (w), 2892 (w), 1709 (s, C=O), 1604 (s), 1572 (s), 1510 (s), 1254 (s), 1160 (m), 1029 (m), 845 (m), 657 (w) cm^{-1}.

1-(4-Isopropylphenyl)-1-(phenylamino) pentan-3-one (8)

^{1}H NMR (DMSO, 300 MHz, δ ppm): 0.90 (t, 3H, J = 7.2 Hz), 1.16 (d, 6H, J = 6.9 Hz), 2.37–2.54 (m, 2H), 2.66–2.97 (m, 3H), 4.82 (dd, 1H, J_1 = 9.0 Hz, J_2 = 4.8 Hz), 6.45–7.02 (m, 5H), 7.16 (d, 2H, J = 8.1 Hz), 7.32 (d, 2H, J = 8.1 Hz); ^{13}C NMR (DMSO, 75 MHz, δ ppm): 7.85, 24.43, 33.49, 35.85, 50.74, 52.83, 113.32, 116.30, 126.68, 126.84, 129.19, 141.77, 147.10, 148.23, 209.05; IR (KBr disk): 3375 (s, NH), 3043 (w), 2961 (m), 1704 (s, C=O), 16.1 (s), 1513 (m), 1279 (m), 829 (m), 753 (s), 695 (w) cm^{-1}.

1-(4-Isopropylphenyl)-1-(*p*-tolylamino) pentan-3-one (9)

^{1}H NMR (DMSO, 300 MHz, δ ppm): 0.99 (t, 3H, J = 7.2 Hz), 1.19 (d, 6H, J = 11.1 Hz), 2.32 (s, 3H) 2.41–2.51 (m, 2H), 2.94–2.91 (m, 1H), 2.96–3.42 (m, 2H) 4.72 (dd, 1H, J_1 = 9.0 Hz, J_2 = 4.5 Hz), 7.12 (d, 2H, J = 8.4 Hz), 7.29 (d, 2H, J = 7.8 Hz), 7.49 (d, 2H, J = 8.4 Hz), 7.76 (d, 2H, J = 7.8 Hz); ^{13}C NMR (DMSO, 75 MHz, δ ppm): 19.99, 20.99, 24.60, 26.86, 42.71, 47.57, 58.63, 123.34, 129.46, 130.61, 138.07, 216.67; IR (KBr disk): 3371 (s, NH), 2957 (m), 2884 (w), 1703 (s, C=O), 1619 (m), 1521 (s), 1370 (m), 1277 (s), 1112 (m), 772 (s), 692 (m), 506 (w) cm^{-1}; MS (EI): 309 [M^+], 308, 307, 306, 305, 236 (base peak), 221, 183, 107, 57.

1-((4-Bromophenyl)amino)-1-(4-isopropylphenyl) pentan-3-one (10)

^{1}H NMR (DMSO, 300 MHz, δ ppm): 1.07 (t, 3H, J = 6.9 Hz), 1.24 (d, 6H, J = 6.9 Hz), 2.51 (m, 2H), 2.91–3.01 (m, 1H), 3.41–3.50 (m, 2H), 4.38 (t, 1H, J = 4.8 Hz), 7.22 (d, 2H, J = 8.4 Hz), 7.40 (d, 2H, J = 7.8 Hz), 7.58 (d, 2H, J = 8.4 Hz), 7.86 (d, 2H, J = 7.8 Hz); ^{13}C NMR (DMSO, 75 MHz, δ ppm): 19.98, 20.46, 24.60, 26.85, 42.56, 42.70, 47.27, 47.6, 58.59, 119.92, 124.96, 133.01, 133.39, 216.59; IR (KBr disk): 3376 (s, NH), 2962 (w), 2872 (W), 1708 (s, C=O), 1598 (s), 1487 (s), 1415 (w), 1318 (m), 1188 (m), 1073 (w), 808 (s), 600 (w) cm^{-1}; MS (EI): 375, 374 [M^+], 373, 372, 371, 370, 301 (base peak), 221, 172, 130, 92, 65, 57 (base peak), 43.

1-((4-Bromophenyl)amino)-1-(4-chlorophenyl) pentan-3-one (11)

^{1}H NMR (DMSO, 300 MHz, δ ppm): 1.09 (t, 3H, J = 7.2 Hz), 2.42–2.52 (m, 2H), 2.66–2.67 (m, 1H), 2.91–3.46 (m, 2H), 3.41–3.50 (m, 2H), 4.35 (d, 1H, J = 5.4 Hz), 6.53 (d, 2H, J = 8.7 Hz), 7.13 (d, 2H, J = 8.7 Hz), 7.29 (d, 2H, J = 6.9 Hz), 7.97 (d, 2H, J = 6.9 Hz); ^{13}C NMR (DMSO, 75 MHz, δ ppm): 18.99, 24.61, 42.71, 58.61, 123.74, 126.71, 129.51, 130.88, 132.83, 134.13, 135.51, 141.98, 216.61; IR (KBr disk): 3382 (s, NH), 2974 (w), 2913 (w), 1708 (s, C=O), 1598 (s), 1511 (s), 1413 (m), 1317 (m), 1102 (w), 914 (w), 808 (s), 498 (m) cm^{-1}.

5-Methyl-1-phenyl-1-(phenylamino)hexan-3-one (12)

^{1}H NMR ($CDCl_3$, 100 MHz, δ ppm): 0.9 (d, 6H, J = 6.0 Hz), 2–2.3 (m, 3H), 2.95 (d, 2H, J = 7.0 Hz), 4.5–4.7 (br, NH), 4.85 (t, 1H, J = 7.0 Hz), 6.5–6.8 (m, 3H), 7–7.5 (m, 7H); IR (KBr disk): 3381 (s, NH), 3023 (w), 2954 (m), 1703 (s, C=O), 1602 (s), 1515(m), 1369 (w), 1074 (m), 746 (m), 693 (m), 551 (w) cm^{-1}.

2-Methyl-1-phenyl-1-(phenylamino) pentan-3-one (13)

1H NMR ($CDCl_3$, 100 MHz, δ ppm): 0.8–1.0 (m, 3H), 1.0–1.3 (m, 3H) 2.4 (q, 2H, J = 7.0 Hz), 2.9–3.2 (m, 1H), 4.5 (d, 0.4H, J = 5.0 Hz, anti), 4.7 (d, 0.6H, J = 4.0 Hz, syn), 6.4–6.8 (m, 5H), 6.9–7.4 (m, 5H); IR (KBr disk): 3399 (s, NH), 3051 (w), 3027 (w), 2971 (w), 1707 (s, C=O), 1603 (s), 1520 (m), 1374 (m), 1325 (s), 1107 (w), 979 (m), 860 (m), 746 (s), 510 (m) cm^{-1}.

2-Methyl-1-phenyl-1-(p-tolylamino) pentan-3-one (14)

^{1}H NMR (DMSO, 300 MHz, δ ppm): 0.72 (d, 3H, J = 6.3 Hz), 0.93 (d, 3H, J = 6.6 Hz), 2.07 (s, 3H), 2.39–2.67 (m, 2H), 2.99 (t, 1H, J = 6.3 Hz), 4.63 (t, 1H, J = 7.5 Hz), 6.49 (d, 2H, J = 5.7 Hz), 7.8 (d, 2H, J = 6.3 Hz), 7.16–7.43 (m, 5H); ^{13}C NMR (DMSO, 75 MHz, δ ppm): 7.96, 13.12, 15.29, 20.45, 34.99, 40.04, 51.93, 52.55, 58.92, 60.02, 113.58, 113.98, 124.77, 125.03, 127.13, 127.97, 129.62, 143.09, 146.01, 212.73, 213.91; IR (KBr disk): 3384 (s, NH), 2971 (w), 2935 (w), 1703 (s, C=O), 1617 (s), 1520 (s), 1454 (s), 1360 (w), 1302 (m), 1106 (m), 976 (m), 804 (s), 791 (m), 702 (s), 612 (w), 510 (w) cm^{-1}.

1-((4-Bromophenyl)amino)-2-methyl-1-phenylpentan-3-one (15)

^{1}H NMR (DMSO, 300 MHz, δ ppm): 0.70 (d, 3H, J = 7.2 Hz), 1.10 (d, 3H, J = 6.9 Hz), 1.91–2.48 (m, 2H), 2.96–3.06 (m, 1H), 4.62 (d, 1H, J = 7.8 Hz), 6.56 (d, 2H, J = 9.0 Hz), 7.12 (d, 2H, J = 9.0 Hz), 7.18–7.33 (m, 5H); ^{13}C NMR (DMSO, 75 MHz, δ ppm): 7.82, 13.25, 35.09, 52.42, 58.67, 107.14, 115.33, 127.55, 128.63, 131.69, 142.47, 147.56, 212.59; IR (KBr disk): 3386 (s, NH), 3023 (w), 2921 (w), 1671 (s, C=O), 1600 (s), 1511 (s), 1448 (m), 1368 (m), 1291 (s), 1217 (m), 1090 (m), 1000 (m), 857 (m), 744 (s), 688 (s), 579 (m), 514 (m) cm^{-1}; MS (EI): 346 [M$^+$], 344, 343, 342, 341, 260 (base peak), 169.

1-(4-Isopropylphenyl)-2- methyl-1-(phenylamino) pentan-3-one (16)

^{1}H NMR (DMSO, 300 MHz, δ ppm): 0.70 (d, 3H, J = 7.2 Hz), 1.08 (d, 3H, J = 6.9 Hz), 1.15 (d, 6H, J = 6.9 Hz), 1.92–2.52 (m, 2H), 2.77–2.86 (m, 1H), 2.93–3.03 (m, 1H), 4.62 (d, 1H, J = 7.8 Hz), 6.43–7.00 (m, 5H), 7.14 (d, 2H, J = 8.1 Hz), 7.23 (d, 2H, J = 8.1 Hz); ^{13}C NMR (DMSO, 75 MHz, δ ppm): 7.81, 13.18, 24.35, 33.45, 35.03, 52.52, 58.32, 113.32, 116.33, 126.45, 127.49, 129.20, 140.28, 147.20, 148.32, 212.84; IR (KBr disk): 3381 (s, NH), 2958 (m), 2873 (w), 2971 (w), 1703 (s, C=O), 1602 (s), 1515 (s), 1374 (m), 1319 (m), 1105 (m), 972 (m), 750 (s), 693 (s), 592 (w) cm^{-1}; MS (EI): 309 [M$^+$], 308, 307, 306, 305, 222 (base peak), 208, 161, 144, 104, 57.

1-((4-Bromophenyl)amino)-1-(4-isopropylphenyl)-2-methylpentan-3-one (17)

^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 0.95 (t, 3H, J = 7.2 Hz), 1.13 (d, 3H, J = 6.8 Hz), 1.25 (d, 6H, J = 7.2 Hz), 2.35 (m, 2H), 2.90 (m, 1H), 3.00 (m, 1H), 4.6 (d, 1H, J = 5.6 Hz, syn), 6.41 (d, 2H, J = 8.8 Hz), 7.1–7.25 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 7.49, 11.65, 23.92, 33.69, 35.53, 52.07, 59.19, 109.47, 115.41, 126.70, 126.71, 131.77, 137.66, 145.95, 148.11, 213.46; IR (KBr disk): 3402 (s, NH), 2961 (w), 2927 (w), 1707 (s, C=O), 1598 (s), 1512 (s), 1376 (w), 1321 (m), 980 (m), 822 (s), 509 (m) cm^{-1}.

1-((4-Chlorophenyl)amino)-1-(4-methoxyphenyl)-2-methylpentan-3-one (18)

^{1}H NMR (DMSO, 300 MHz, δ ppm): 0.72 (d, 3H, J = 7.2 Hz), 1.10 (d, 3H, J = 6.9 Hz), 2.37–2.48 (m, 2H), 2.96–3.06 (m, 1H), 3.84 (s, 1H), 4.63 (d, 1H, J = 7.8 Hz), 7.07 (d, 2H, J = 8.7 Hz), 7.19 (d, 2H, J = 6.6 Hz), 7.56 (d, 2H, J = *6.6 Hz*), 7.90 (d, 2H, J = 8.7 Hz); ^{13}C NMR (DMSO, 75 MHz, δ ppm): 7.85, 13.27, 24.18, 33.43, 35.14, 55.80, 114.76, 118.49, 123.63, 129.18, 131.12, 132.45, 151.41, 212.91; IR (KBr disk): 3389 (s, NH), 2978 (w), 2933 (w), 1702 (s, C=O), 1603 (s), 1514 (s), 1458 (m), 1320 (m), 1255 (s), 1179 (m), 1033(m), 976 (m), 825 (m), 686 (w), 502 (m) cm^{-1}.

Results and discussion

Recently, we have modified an efficient method for preparation of Mannich products, in water, from aldehydes, aromatic amines, and cyclohexanone under very mild conditions using manganese hydrogen sulfate and sodium dodecyl sulfate [25]. Herein, we wish to improve the regioselectivity and diastereoselectivity of this reaction in the case of acyclic ketones (Scheme 1).

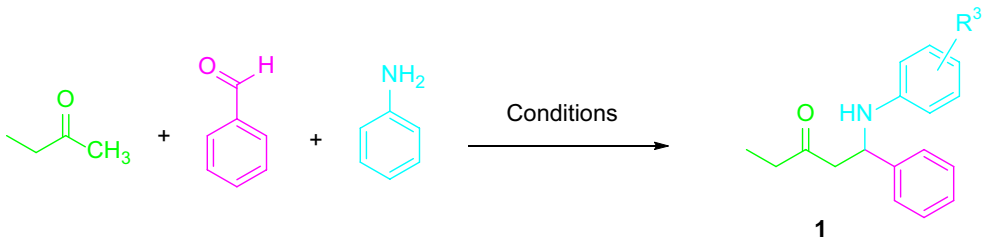
Using benzaldehyde, aniline and 2-butanone as an acyclic ketone, we initially screened different conditions. The results are summarized in Table 1.

First, we used ethanol as solvent (Table 1, entry 1). After 6 h in room temperature, the only product **1** was obtained in 75 % yield. Using H_2O:Ethanol (1:1) as a solvent in the presence of $Mn(HSO_4)_2$ (10 mol%) did not observe any notable difference in regioselectivity, reaction time and yield of the reaction (Table 1, entry 2).

Shifting of the solvent from ethanol to water, resulted in low yield, increasing the time of the reaction, without any difference in regioselectivity (Table 1, entry 3). Adding sodium dodecyl sulfate (10 mol%), in the presence of $Mn(HSO_4)_2$ (10 mol%) and water as solvent, resulted yield (85 %) and short reaction time (3 h) (Table 1, entry 4). Next, the lower catalyst loading (5 and 2.5 mol%) yield of the reaction decrease and time of the reaction become high, with the same regioselectivity (Table 1, entries 5, 6). Also, In the present of different amount of sodium dodecyl sulfate (5 and 2.5 mol%) yield of the reaction become low and time of the reaction increased (Table 1, entries 7, 8). After that, by increasing the temperature of the reaction into 50 and 70 °C in 3 h, did not observe difference in regioselectivity (Table 1, entry 9, 10).

This reaction with other acid catalysts such as $Fe(HSO_4)_3$ and $Fe(HSO_4)_3{\cdot}SiO_2$ in the presence of sodium dodecyl sulfate (10 mol%) and water as solvent, did not have any product (Table 1, entry 11, 12). Whereas, $Fe(HSO_4)_3{\cdot}SiO_2$ can be catalyzed this reaction in ethanol [26].

Eventually, we chose manganese hydrogen sulfate (10 %) with SDS (10 %) as the best catalyst system, in water as green solvent for this three component Mannich reaction. The most important ability of this catalyst is producing the kinetic controlled β-amino carbonyl, although other papers reported thermodynamic stable β-amino carbonyls [25].



Scheme 1 Synthesis of β-amino ketones via direct Mannich reaction

Table 1 Catalyst screening and condition optimizations for the three-component direct Mannich reaction

Entry	Cat (mol%)	SDS (mol%)	Solvent	T (°C)	Time (h)	Yield (%)
1	$Mn(HSO_4)_2$ (10 mol%)	–	EtOH	25	6	75
2	$Mn(HSO_4)_2$ (10 mol%)	–	EtOH + H_2O	25	6	75
3	$Mn(HSO_4)_2$ (10 mol%)	–	H_2O	25	10	70
4	$Mn(HSO_4)_2$ (10 mol%)	10	H_2O	25	3	85
5	$Mn(HSO_4)_2$ (5 mol%)	10	H_2O	25	4	75
6	$Mn(HSO_4)_2$ (2.5 mol%)	10	H_2O	25	5	75
7	$Mn(HSO_4)_2$ (10 mol%)	5	H_2O	25	5	77
8	$Mn(HSO_4)_2$ (10 mol%)	2.5	H_2O	25	7	70
9	$Mn(HSO_4)_2$ (10 mol%)	10	H_2O	50	3	72
10	$Mn(HSO_4)_2$ (10 mol%)	10	H_2O	70	3	65
11	$Fe(HSO_4)_3$ (10 mol%)	10	H_2O	25	24	n.r
12	$Fe(HSO_4)_3.SiO_2$ (10 mol%)	10	H_2O	25	24	n.r

2-Butanone (1.2 mmol), benzaldehyde (1 mmol), aniline (1 mmol) and $Mn(HSO_4)_2$ (0.1 mmol) in water (0.5 ml) was stirred

Using the optimized reaction conditions, the scope of the reaction was assessed. Excellent results were obtained when different combinations of aldehydes, amines, and 2-butanone and iso-butyl methyl ketone were used. In all the cases, kinetic product with good result (67–90 %) was synthesized (Table 2, entry 1–12). The 1H NMR spectra of compounds, recorded in $CDCl_3$ solution, exhibit the characteristic signal of CH proton as a doublet of doublet at 4.7–4.8 ppm for compound **8** and **9** with high-resolution NMR instrument (300 MHz) whereas, in other compounds a triplet was observed with low-resolution NMR instrument (100 MHz).

The generality of this method can be deduced from the results summarized in Table 2. In the presence of electron donating groups, for example Me and Br, at the 4-position of aniline, corresponding β-amino ketones were obtained in good yields (Table 2, entry 2, 3).

On the other hand, in the presence of methoxy, isopropyl and Cl, at the para position of the benzaldehyde resulted in good yields (Table 2, entry 4–11). In the reaction of these benzaldehyde with substituent at the para position of anilines did not change the yield and time of the reactions. The presence of a strong electron-withdrawing group, for example NO_2, in the benzaldehyde and aniline caused precipitation of the corresponding imine and prevented completion of the reaction [26].

We tried this reaction with other ketones such as cyclopentanone and *iso*-butyl methyl ketone. Cyclopentanone with aniline and aldehyde did not give any product, but *iso*-butyl methyl ketone caused kinetic product with 72 % yield (Table 2, entry 12).

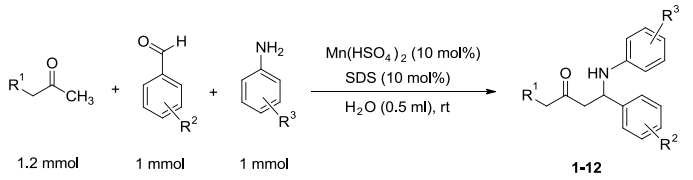
To indicate the sufficiency of our catalytic system and check out the diastereoselectivity of the Mannich reaction, this reaction was performed with 3-pentanone under same conditions. Products synthesized in good yields and the results are summarized in Table 3.

In the presence of electron donating groups, for example Me and Br, at the 4-position of aniline, reactions proceeded in good yields (65–70 %) with diastereoselectivity 60:40 in that prefer *syn* isomer to *anti* (Table 3, entry 1–3).

The presence of lipophilic electron donating group, such as isopropyl at the para position of benzaldehyde resulted syn isomer with high diastereoselectivity (Table 3, entry 4, 5).

Next, the presence of a hydrophilic electron donating group such as methoxy group at the 4-position of

Table 2 Synthesis of kinetic controlled β-amino ketones derivatives by use of $Mn(HSO_4)_2$—SDS under aqueous conditions



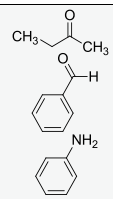
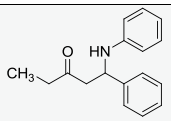
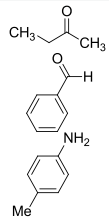
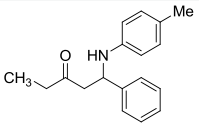
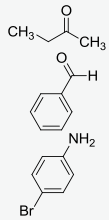
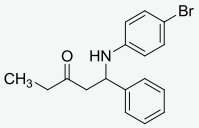
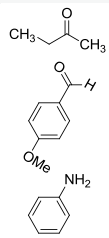
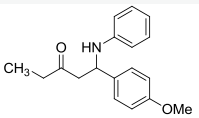
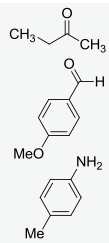
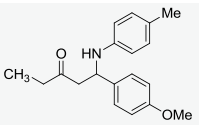
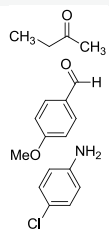
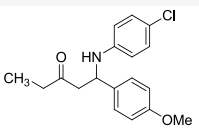
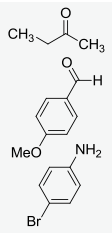
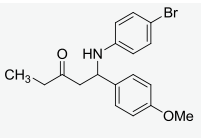
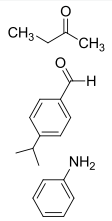
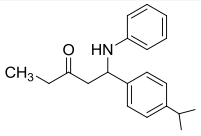
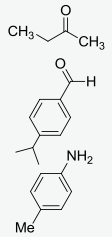
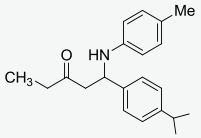
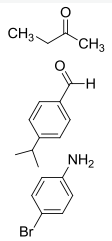
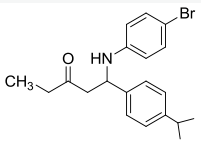
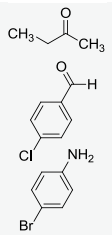
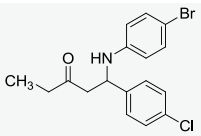
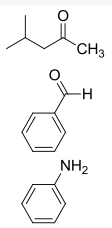
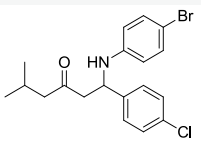
Entry	Substrates	Product	Time (h)	Yield (%)[a]	mp(°C)/lit
1		 **1**	3	85	118-119/118-120[27-29]
2		 **2**	4.5	90	110-112/ 111-112[28,30]
3		 **3**	2	85	113-115/114-116[28,30]
4		 **4**	1	80	86/84-86[28,31]
5		 **5**	3	77	86-87/84-86[28,31]
6		 **6**	5	85	104-105/104-105[28]

Table 2 continued

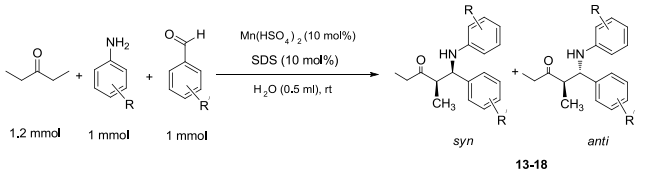
7		 **7**	1.5	74	110-111/109-111[28]
8		 **8**	5	70	112
9		 **9**	3.5	67	109.2
10		 **10**	2	80	91-92
11		 **11**	3.5	75	82-83
12		 **12**	3.5	72	81-82/80-81[30]

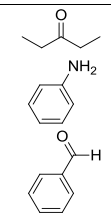
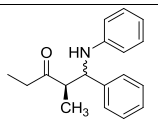
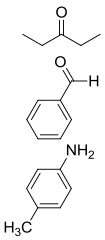
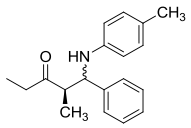
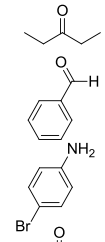
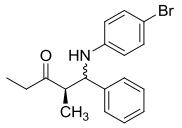
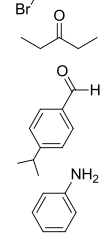
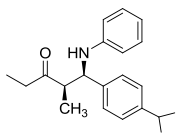
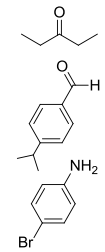
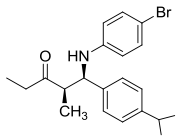
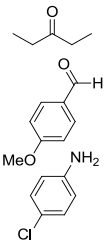
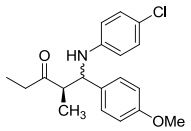
[a] Isolated yielded

benzaldehyde decreased the *syn* diastereoselectivity from 98:2 to 70:30 (Table 3, entry 6). Most of the reported catalysts for Mannich reactions gave *anti* isomer preferentially, but the unique characteristic of this catalyst is that, prefer the *syn* diastereoisomer.

According to Tables 2 and 3, although, in the presence of a strong electron-withdrawing group, as a result of precipitation of imine, this reaction did not progress, effects of other substituents did not have any electronic rule. This phenomenon can mainly be attributed to the formation of

Table 3 Synthesis of diastereoselective β-amino ketones derivatives via 3-pentanone, aldehyde and aniline by use of $Mn(HSO_4)_2$—SDS under aqueous conditions



Entry	Substance	Product	Time (h)	Yield (%)[a]	*syn:anti*	mp(°C)/lit
1		 **13**	5.5	72	60:40	127-128/128-130[32]
2		 **14**	7	77	70:30	99.2
3		 **15**	6	70	60:40	140
4		 **16**	5	75	98:2	120.2
5		 **17**	6.5	67	100	120
6		 **18**	8	65	70:30	123

[a] Isolated yielded

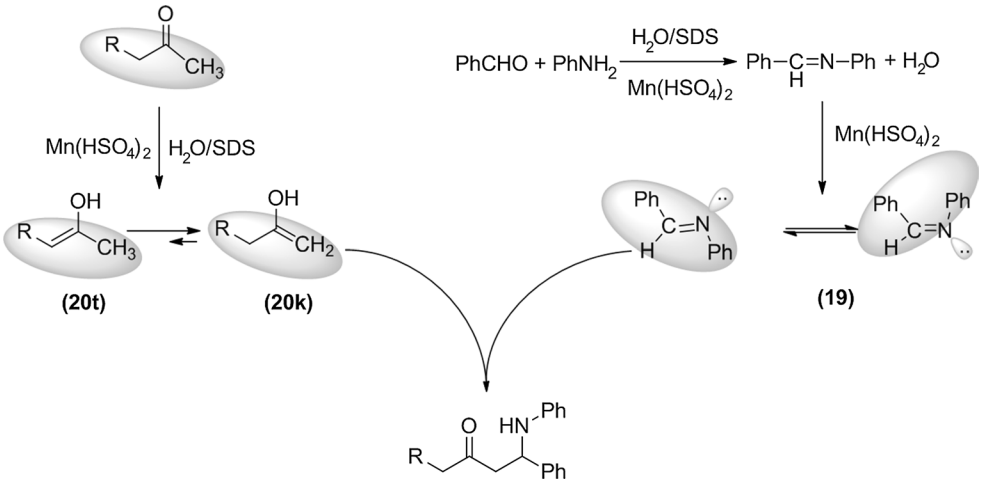


Fig. 1 The proposed mechanism of synthesis of Kinetic product β-amino ketones by use of $Mn(HSO_4)_2$—SDS as catalyst system under aqueous conditions

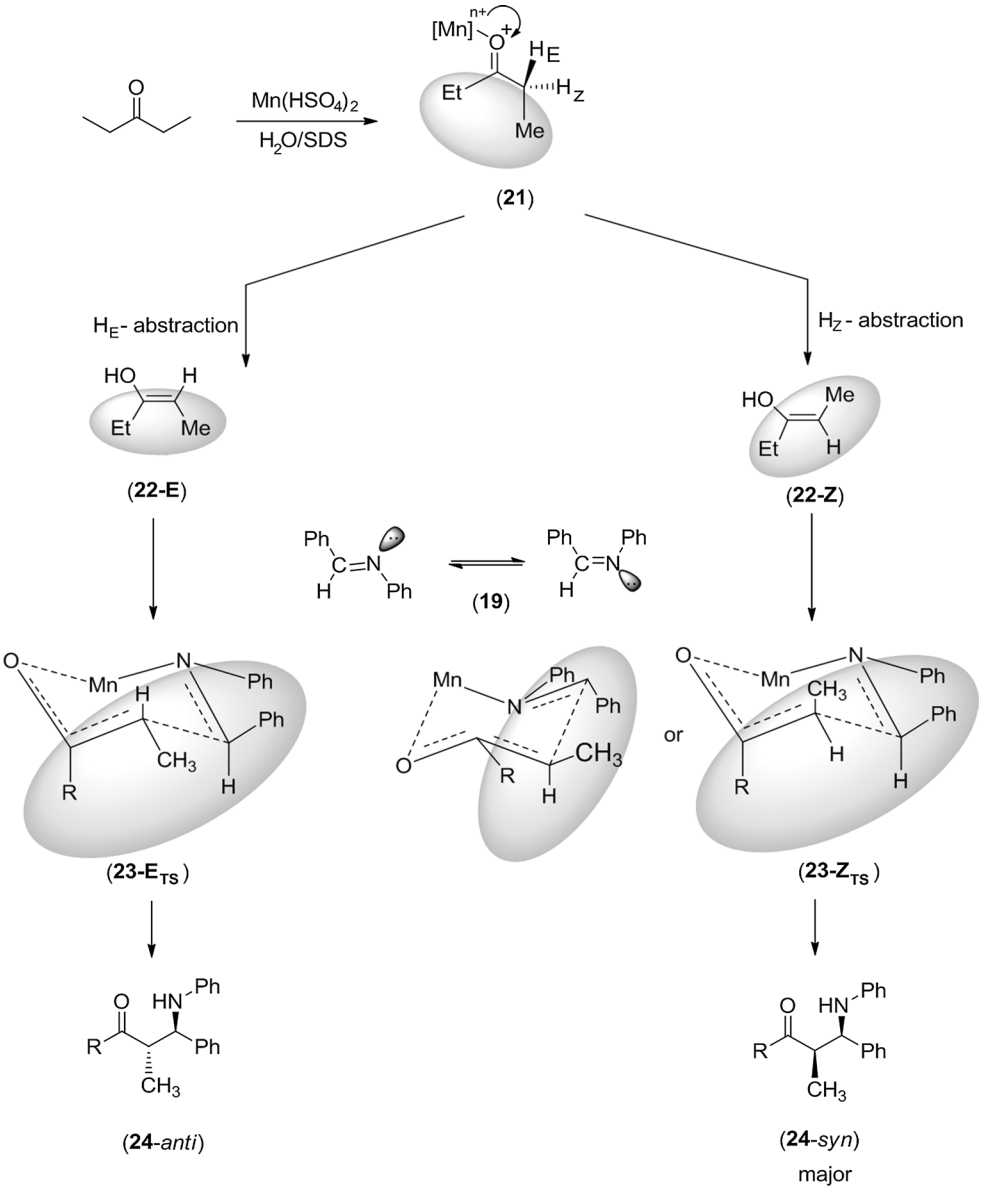


Fig. 2 The proposed mechanism of synthesis of *syn*-diastereoselective β-amino ketones by use of $Mn(HSO_4)_2$—SDS as catalyst system under aqueous conditions

micelles from the starting materials and intermediates in the presence of H_2O and SDS. In other words, the smooth progress of the reaction in the presence of alkyl or halogen substitutions of the aniline or benzaldehyde is the result of the tendency to form micelles, as a result of the alkyl groups and the lipophilic properties of SDS, with the result that hydrogen bond formation by halogen and methoxy groups is disrupted. One possible reaction mechanism is that micelle formation is essential to gather all the components, i.e. ketone, amine, aldehyde, and catalyst. In these micelles, reaction proceeded via formation of imine (**19**), followed by nucleophilic addition of enol to imine to synthesized of β-amino ketones. Kinetic product formed by the preferential formation of kinetic enol (**20k**) under acidic conditions imposed in micelle, the way that prefers the lipophilic part of molecules (larger alkyl) did not participate in the reaction (Fig. 1).

When the ketone is 3-pentanone, two isomeric enols (**E**, **Z-22**) can be formed. According to the following mechanism seems, preferably Z-enol formed and produced *syn* product (Fig. 2).

In the micelle (**21**), seems H_z is more accessible for water molecules that act as base and then mainly Z-enol (**Z-22**) produce. According to Fig. 2, Z-enol through the transition state **23-Z**, produced *syn* product (**24-syn**) and E-enol through the transition state **23-E**, produced *anti* product (**24-anti**). By using isopropyl benzaldehyde that is more easily placed inside the micelle, *syn* product (100 %) is achieved. A similar rule can be made about the stereochemistry of imine.

Conclusion

We report an environmentally benign, novel, and easy procedure for *syn*- diastereoselective synthesis of Mannich products by use of nano-manganese hydrogen sulfate and SDS in water. The procedure has several advantages, for example high diastereoselectivity, high yields, and mild reaction conditions, use of inexpensive reagents, low temperature, and very simple work-up procedures. Low loading and ready accessibility are the main features of the new catalyst.

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