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Article

Efficient Synthesis of Rhodanine-Based Amides via Passerini Reaction using Tetramethylguanidine-Functionalized Silica Nanoparticles as Reusable Catalyst

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Novel rhodanine-based amide derivatives were prepared in good yields via Passerini reaction of rhodanine-*N*-acetic acid with aromatic aldehydes and *tert*-butyl isocyanide in the presence of tetramethylguanidine immobilized on silica nanoparticles (TMG-SiO_2 NPs) as a heterogeneous base catalyst. The synthesized compounds were evaluated for their antibacterial effects against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Bacillus subtilis*.

Keywords: Passerini reaction, rhodanine-*N*-acetic acid, tetramethylguanidine, heterogeneous catalysis, antibacterial agents

Introduction

Multicomponent reactions (MCRs) are valuable synthetic tool to prepare diverse and complex molecular structures from simple building blocks and offer high efficiency and atom economy.[1] Among them, the Passerini reaction is classified as an isocyanide multicomponent reaction (IMCR), and deals with the condensation of an isocyanide, an aldehyde and a carboxylic acid.[2,3] Subsequently, several optimizations have been performed to improve the yield, the ecological impact, and the reaction times of the Passerini reaction. These processes have been described in aqueous solution,[4] ionic liquids,[5,6] solvent-free,[7-9] under microwave irradiation,[10] and in the presence of molecular sieves as drying agents.[11] Despite the efficiency of the reported protocols, some of them suffer from drawbacks such as harsh reaction conditions, excessive use of reactants, use of expensive catalyst and hard separation. Thus, the development of a new and simple methodology for the synthesis of α-acyloxy amides via Passerini reaction has become an interesting challenge.

Along with other reaction parameters, the nature of the catalyst plays a significant role in determining yield, selectivity and general applicability. Solid catalysts are generally preferable in catalysis related to their easy separation, recyclability, high thermal stability and low pollution effects.[12] The surface modification of silica with homogenous catalysts is an excellent method for development of heterogeneous reusable catalysts for organic reactions.[13-15] Silica nanoparticles have enormously large and highly reactive surface area and therefore are a good option to use as support for immobilization of organic materials.[16]

On the other hand, 4-thiazolidinones are important scaffolds because of their biological properties including antitubercular,[17] anticancer,[18,19] anticonvulsant,[20] antifungal,[21] antibacterial,[21] and hypnotic activities.[22] Thus, in continuation of our investigations on the synthesis of biological compounds[23,24] and the use of heterogeneous catalysts for chemical preparation,[25,26] we herein disclose a Passerini reaction for the synthesis of rhodanine-based amides in good yields by the condensation of rhodanine-*N*-acetic acid with aromatic aldehydes and *tert*-butyl isocyanide in the presence of tetramethylguanidine-functionalized silica nanoparticles (TMG-SiO_2 NPs) as a heterogeneous basic catalyst. The synthesized α-acyloxy amides were also screened for their antibacterial activity by the disc diffusion method.

Experimental

General information

All chemicals and reagents were purchased from Merck or Aldrich, and used without purification. Nano silica-supported tetramethylguanidine solid base catalyst was synthesized according to reported procedure in the literature.[15] Melting points were measured on

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an Electrothermal 9100 apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 AVANCE spectrometer at 400.13 and 100.61 MHz, respectively. Chemical shifts are given in parts per million (δ) relative to internal tetramethylsilane standard, and coupling constants (J) are reported in hertz (Hz). IR spectra were recorded on a Bruker Tensor 27 spectrometer. Mass spectra were determined on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were carried on a Perkin-Elmer 2400II CHNS/O Elemental Analyzer. Thermogravimetric analysis (TGA) was recorded on a Stanton Redcraft STA-780. X-ray powder diffraction (XRD) patterns were recorded by an X-ray diffractometer (XRD, GBC MMA Instrument) with Be-filtered Cu Kα radiation (λ 1.54 Å). Field emission scanning electron microscopy (FE-SEM) images were obtained on a Hitachi S-1460 field emission scanning electron microscope using an ACC voltage of 15 kV.

General procedure for the synthesis of rhodanine-based amides

A mixture of rhodanine-*N*-acetic acid (1.0 mmol), aldehydes (2.0 mmol), *tert*-butyl isocyanide (1.0 mmol) and TMG-SiO_2 NPs (0.20 g, 10 mol%) in tetrahydrofuran (10.0 mL) was stirred at 70 ºC. Upon compilation, monitored by TLC, the catalyst was filtered from hot reaction mixture and washed with acetone. The filtrate was evaporated under vacuum to afford the product precipitates, which was purified by recrystallization in methanol. It was found that the recovered catalyst could be used directly for five cycles without noticeable drop in the catalytic activity. The structure of products **4a**-**4j** was determined on the basis of their elemental analysis, ^{1}H NMR, ^{13}C NMR, IR and mass spectra.

Physical and spectral data for the synthesized compounds (**4a-4j**)

2-(*Tert*-butylamino)-2-oxo-1-phenylethyl[(5*Z*)-5-benzylidene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]acetate (**4a**)

Yellow powder; mp: 154-156 ºC; yield: (0.32 g, 70%); IR (KBr) ν / cm^{-1} 3373 (NH), 2926 (C_{sp3}–H), 1755, 1701 and 1661 (C=O), 1598 (C=C), 1208 (C_{sp2}–O and C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H, CMe_3), 4.98 and 5.02 (2d, 2H, *J* 16.8, AB-system, CH_2), 6.02 (br s, 1H, NH), 6.05 (s, 1H, CH), 7.36-7.40 (m, 5H, 5Ar-H), 7.51-7.55 (m, 5H, 5Ar-H), 7.83 (s, 1H, CH vinylic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7 (C*Me*$_3$), 45.0 (N–CH_2), 51.4 (*C*Me$_3$), 77.0 (CH), 122.3, 127.3, 128.7, 129.5, 130.0, 130.2, 130.8, 131.2, 133.0, 134.7, 166.4 (C=O), 166.5 (C=O), 167.0 (C=O), 192.9 (C=S); MS (EI, 70 eV) *m/z*: 468.1 (M$^+$); anal. calcd. for $C_{24}H_{24}N_2O_4S_2$ (468.59): C, 61.52; H, 5.16; N, 5.98; S, 13.69%; found: C, 61.58; H, 5.09; N, 6.05; S, 13.62%.

2-(*Tert*-butylamino)-1-(4-chlorophenyl)-2-oxoethyl[(5*Z*)-5-(4-chlorobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl] acetate (**4b**)

Yellow powder; mp: 180-182 ºC; yield: (0.42 g, 80%); IR (KBr) ν / cm^{-1} 3307 (NH), 2969 (C_{sp3}–H), 1756, 1731 and 1658 (C=O), 1601 (C=C), 1189 (C_{sp2}–O and C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 9H, CMe_3), 4.98 and 5.01 (2d, 2H, *J* 16.8, AB-system, CH_2), 6.00 (s, 1H, CH), 6.01 (br s, 1H, NH), 7.31-7.37 (m, 4H, 4Ar-H), 7.47 (d, 2H, *J* 8.8, 2Ar-H), 7.51 (d, 2H, *J* 8.8, 2Ar-H), 7.76 (s, 1H, CH vinylic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6 (C*Me*$_3$), 44.9 (N-CH_2), 51.9 (*C*Me$_3$), 76.2 (CH), 122.7, 128.6, 129.0, 129.9, 131.4, 131.8, 133.2, 133.4, 135.1, 137.6, 164.2 (C=O), 166.0 (C=O), 166.8 (C=O), 192.3 (C=S); MS (EI, 70 eV) *m/z*: 537.0 (M$^+$); anal. calcd. for $C_{24}H_{22}Cl_2N_2O_4S_2$ (537.48): C, 53.63; H, 4.13; N, 5.21; S, 11.93%; found: C, 53.69; H, 4.18; N, 5.17; S, 11.87%.

2-(*Tert*-butylamino)-1-(4-bromophenyl)-2-oxoethyl [(5*Z*)-5-(4-bromobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl] acetate (**4c**)

Yellow powder; mp: 188-190 ºC; yield: (0.42 g, 68%); IR (KBr) ν / cm^{-1} 3296 (NH), 2926 (C_{sp3}–H), 1748, 1722 and 1658 (3C=O), 1603 (C=C), 1202 (C_{sp2}–O and C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 9H, CMe_3), 4.97 and 5.02 (2d, 2H, *J* 16.8, AB-system, CH_2), 5.98 (s, 1H, CH), 6.00 (br s, 1H, NH), 7.27 (d, 2H, *J* 8.4, 2Ar-H), 7.39 (d, 2H, *J* 8.4, 2Ar-H), 7.51 (d, 2H, *J* 6.8, 2Ar-H), 7.67 (d, 2H, *J* 6.8, 2Ar-H), 7.74 (s, 1H, CH vinylic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6 (C*Me*$_3$), 44.9 (N-CH_2), 51.9 (*C*Me$_3$), 76.2 (CH), 122.9, 128.9, 129.7, 130.0, 130.2, 131.8, 131.9, 132.8, 133.2, 133.9, 164.2 (C=O), 165.9 (C=O), 166.8 (C=O), 192.2 (C=S); MS (EI, 70 eV) *m/z*: 626.3 (M$^+$); anal. calcd. for $C_{24}H_{22}Br_2N_2O_4S_2$ (626.38): C, 46.02; H, 3.54; N, 4.47; S, 10.24%; found: C, 46.11; H, 3.48; N, 4.39; S, 10.32%.

2-(*Tert*-butylamino)-1-(4-fluorophenyl)-2-oxoethyl[(5*Z*)-5-(4-fluorobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl] acetate (**4d**)

Yellow powder; mp: 162-164 ºC; yield (0.41 g, 82%); IR (KBr) ν / cm^{-1} 3304 (NH), 2926 (C_{sp3}–H), 1758, 1703 and 1661 (C=O), 1596 (C=C), 1192 (C_{sp2}–O and C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H, CMe_3), 4.96 and 5.02 (2d, 2H, *J* 16.8, AB-system, CH_2), 6.02 (s, 2H, CH and NH), 7.04-7.09 (m, 2H, 2Ar-H), 7.20-7.25 (m, 2H, 2Ar-H), 7.36-7.39 (m, 2H, 2Ar-H), 7.53-7.57 (m, 2H, 2Ar-H), 7.79 (s, 1H, CH vinylic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6 (C*Me*$_3$), 44.9 (N-CH_2), 51.9 (*C*Me$_3$), 76.2 (CH), 115.8

(d, *J* 21.5, CH_{Ar}), 116.9 (d, *J* 22.0, CH_{Ar}), 121.8, 129.3 (d, *J* 8.3, CH_{Ar}), 130.9 (d, *J* 3.4, C_{Ar}), 132.9 (d, *J* 8.8, CH_{Ar}), 133.4, 163.1 (d, *J* 248.8, CF), 164.1 (d, *J* 254.0, CF), 164.3 (C=O), 166.3 (C=O), 166.9 (C=O), 192.5 (C=S); MS (EI, 70 eV) *m/z*: 504.1 (M^+); anal. calcd. for $C_{24}H_{22}F_2N_2O_4S_2$ (504.57): C, 57.13; H, 4.39; N, 5.55; S, 12.71%; found: C, 57.21; H, 4.31; N, 5.47; S, 12.68%.

2-(*Tert*-butylamino)-1-(4-nitrophenyl)-2-oxoethyl [(5*Z*)-5-(4-nitrobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl] acetate (**4e**)

Yellow powder; mp: 188-190 ºC; yield: (0.47 g, 85%); IR (KBr) ν / cm^{-1} 3385 (NH), 2926 (C_{sp3}–H), 1758, 1725 and 1699 (C=O), 1607 (C=C), 1519 and 1344 (NO_2), 1201(C_{sp2}–O and C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H, CMe_3), 5.05 and 5.07 (2d, 2H, *J* 16.8, AB-system, CH_2), 6.05 (br s, 1H, NH), 6.12 (s, 1H, CH), 7.61 (d, 2H, *J* 8.4, 2Ar-H), 7.70 (d, 2H, *J* 8.8, 2Ar-H), 7.84 (s, 1H, CH vinylic), 8.25 (d, 2H, *J* 7.0, 2Ar-H), 8.38 (d, 2H, *J* 7.2, 2Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6 (C*Me*$_3$), 44.9 (N-CH_2), 52.2 (*C*Me_3), 75.8 (CH), 123.9, 124.6, 126.6, 128.0, 131.1, 131.2, 138.7, 141.6, 148.2, 148.4, 164.0 (C=O), 165.1 (C=O), 166.5 (C=O), 191.5 (C=S); MS (EI, 70 eV) *m/z*: 559.0 (M^+ + 1); anal. calcd. for $C_{24}H_{22}N_4O_8S_2$ (558.58): C, 51.60; H, 3.97; N, 10.03; S, 11.48%; found: C, 51.68; H, 3.91; N, 10.11; S, 11.53%.

2-(*Tert*-butylamino)-1-(4-methylphenyl)-2-oxoethyl [(5*Z*)-5-(4-methylbenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl] acetate (**4f**)

Yellow powder; mp: 207-209 ºC; yield: (0.33 g, 67%); IR (KBr) ν / cm^{-1} 3417 (NH), 2926 (C_{sp3}–H), 1757, 1699 (C=O), 1593 (C=C), 1198 (C_{sp2}–O and C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H, CMe_3), 2.35 and 2.45 (2s, 6H, $2CH_3$), 4.95 and 5.01 (2d, 2H, *J* 16.8, AB-system, CH_2), 6.01 (s, 2H, CH and NH), 7.17 (d, 2H, *J* 8.0, 2Ar-H), 7.27 (d, 2H, *J* 8.0, 2Ar-H), 7.33 (d, 2H, *J* 8.0, 2Ar-H), 7.44 (d, 2H, *J* 8.4, 2Ar-H), 7.80 (s, 1H, CH vinylic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 and 21.7 ($2CH_3$), 28.7 (C*Me*$_3$), 45.0 (N-CH_2), 51.7 (*C*Me_3), 76.9 (CH), 127.3, 129.4, 130.2, 130.3, 130.9, 132.0, 134.9, 139.0, 164.4 (C=O), 166.7 (C=O), 167.1(C=O), 193 (C=S); MS (EI, 70 eV) *m/z*: 497.2 (M^+ + 1); anal. calcd. for $C_{26}H_{28}N_2O_4S_2$ (496.64): C, 62.88; H, 5.68; N, 5.64; S, 12.91%; found: C, 62.79; H, 5.72; N, 5.69; S, 12.84%.

2-(*Tert*-butylamino)-1-(2-chlorophenyl)-2-oxoethyl [(5*Z*)-5-(2-chlorobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl] acetate (**4g**)

Yellow powder; mp: 148-150 ºC; yield: (0.42 g, 78%); IR (KBr) ν / cm^{-1} 3397 (NH), 2925 (C_{sp3}–H), 1739 and 1688 (C=O), 1599 (C=C), 1199 (C_{sp2}–O and C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H, CMe_3), 4.98 and 5.02 (2d, 2H, *J* 16.8, AB-system, CH_2), 6.11 (br s, 1H, NH), 6.38 (s, 1H, CH), 7.30-7.33 (m, 2H, 2Ar-H), 7.40-7.46 (m, 4H, 4Ar-H), 7.51-7.55 (m, 2H, 2Ar-H), 8.18 (s, 1H, CH vinylic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6 (C*Me*$_3$), 44.8 (N-CH_2), 52.0 (*C*Me_3), 74.3 (CH), 125.3, 127.2, 127.5, 129.3, 130.0, 130.1, 130.4, 130.5, 130.7, 131.5, 131.9, 133.0, 133.9, 136.4, 164.4 (C=O), 165.6 (C=O), 166.5 (C=O), 192.6 (C=S); MS (EI, 70 eV) *m/z*: 537.1 (M^+); anal. calcd. for $C_{24}H_{22}Cl_2N_2O_4S_2$ (537.48): C, 53.63; H, 4.13; N, 5.21; S, 11.93%; found: C, 53.58; H, 4.19; N, 5.26; S, 11.89%.

2-(*Tert*-butylamino)-1-(2-nitrophenyl)-2-oxoethyl [(5*Z*)-5-(2-nitrobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl] acetate (**4h**)

Yellow powder; mp: 150-152 ºC; yield: (0.45 g, 81%); IR (KBr) ν / cm^{-1} 3405 (NH), 2968 (C_{sp3}–H), 1725 (C=O), 1607 (C=C), 1529 and 1340 (NO_2), 1215 (C_{sp2}–O and C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H, CMe_3), 4.99 and 5.02 (2d, 2H, *J* 16.8, AB-system, CH_2), 6.22 (br s, 1H, NH), 6.61 (s, 1H, CH), 7.53-7.57 (m, 1H, Ar-H), 7.65-7.70 (m, 4H, 4Ar-H), 7.79 (t, 1H, *J* 6.8, Ar-H), 8.05 (d, 1H, *J* 8.4, Ar-H), 8.19 (s, 1H, CH vinylic), 8.23 (d, 1H, *J* 7.8 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6 (C*Me*$_3$), 44.8 (N-CH_2), 52.1 (*C*Me_3), 73.3 (CH), 125.2, 125.8, 127.7, 129.2, 129.5, 129.9, 130.0, 130.3, 130.7, 131.2, 133.7, 134.2, 147.8, 148.0, 164.6 (C=O), 164.9 (C=O), 165.8 (C=O), 192.5 (C=S); MS (EI, 70 eV) *m/z*: 558.0 (M^+); anal. calcd. for $C_{24}H_{22}N_4O_8S_2$ (558.58): C, 51.60; H, 3.97; N, 10.03; S, 11.48%; found: C, 51.54; H, 3.92; N, 10.10; S, 11.55%.

2-(*Tert*-butylamino)- 1-(3-chlorophenyl)-2-oxoethyl [(5*Z*)-5-(3-chlorobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl] acetate (**4i**)

Yellow powder; mp: 136-138 ºC; yield: (0.40 g, 74%); IR (KBr) ν / cm^{-1} 3274 (NH), 2926 (C_{sp3}–H), 1747, 1718 and 1658 (C=O), 1604 (C=C), 1197 (C_{sp2}–O and C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 9H, CMe_3), 4.98 and 5.04 (2d, 2H, *J* 16.8, AB-system, CH_2), 5.99 (s, 1H, CH), 6.03 (br s, 1H, NH), 7.28-7.36 (m, 4H, 4Ar-H), 7.40-7.51 (m, 4H, 4Ar-H), 7.74 (s, 1H, CH vinylic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6 (C*Me*$_3$), 44.9 (N-CH_2), 51.9 (*C*Me_3), 76.1 (CH), 123.8, 125.5, 127.1, 128.5, 129.2, 129.7, 130.0, 130.4, 130.7, 131.1, 132.8, 134.7, 135.6, 136.8, 164.1 (C=O), 165.8 (C=O), 166.8 (C=O), 192.3 (C=S); MS (EI, 70 eV) *m/z*: 537.1 (M^+); anal. calcd. for $C_{24}H_{22}Cl_2N_2O_4S_2$ (537.48): C, 53.63; H, 4.13; N, 5.21; S, 11.93%; found: C, 53.67; H, 4.19; N, 5.15; S, 11.89%.

2-(*Tert*-butylamino)-1-(3-bromophenyl)-2-oxoethyl [(5*Z*)-5-(3-bromobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl] acetate (**4j**)

Yellow powder; mp: 140-142 ºC; yield: (0.44 g, 71%); IR (KBr) ν / cm^{-1} 3285 (NH), 2926 (C_{sp3}-H), 1750, 1714 and 1655 (C=O), 1601 (C=C), 1191 (C_{sp2}-O), 1210 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H, CMe_3), 4.99 and 5.05 (2d, 2H, *J* 16.8, AB-system, CH_2), 5.98 (s, 1H, CH), 6.01 (br s, 1H, NH), 7.25 (t, 1H, *J* 8.0 Hz, Ar-H), 7.35 (br d, 1H, *J* 7.6, Ar-H), 7.40 (t, 1H, *J* 8.0, Ar-H), 7.46-7.51 (m, 3H, 3Ar-H), 7.61-7.64 (m, 1H, Ar-H), 7.68 (t, 1H, *J* 1.6, Ar-H), 7.74 (s, 1H, CH vinylic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6 (CMe_3), 44.9 (N-CH_2), 52.0 (CMe_3), 76.0 (CH), 122.7, 126.0, 128.9, 129.7, 129.9, 130.0, 130.3, 130.9, 132.1, 132.8, 133.4, 134.0, 134.9, 137.0, 164.1(C=O), 165.8 (C=O), 166.7 (C=O), 192.3 (C=S); MS (EI, 70 eV) *m/z*: 626.9 (M^+); anal. calcd. for $C_{24}H_{22}Br_2N_2O_4S_2$ (626.38): C, 46.02; H, 3.54; N, 4.47; S, 10.24%; found: C, 46.08; H, 3.59; N, 4.41; S, 10.29%.

Antibacterial activity assay

The antibacterial activity of the synthesized compounds was assayed using Kirby–Bauer disk diffusion method where a filter disc was impregnated with the compounds and placed on the surface of inoculated agar plates.[24,27] The compounds **4a**-**4j** were dissolved into dimethyl sulfoxide (DMSO) to achieve 20 mg mL^{-1} solution, then filter sterilized using a 0.22 µm Ministart (Sartorius). The antibacterial activity of the compounds was investigated against four bacterial species. Test organisms included *Escherichi coli* PTCC 1330, *Pseudomonas aeruginosa* PTCC 1074, *Staphylococcus aureus* ATCC 35923 and *Bacillus subtilis* PTCC 1023. Late exponential phase of the bacteria were prepared by inoculating 1% (v/v) of the cultures into the fresh Muller-Hinton broth (Merck) and incubating on an orbital shaker at 37 °C and 100 rpm overnight. Before using the cultures, they were standardized with a final cell density of approximately 10^8 cfu mL^{-1}. Muller-Hinton agar (Merck) was prepared and inoculated from the standardized cultures of the test organisms then spread as uniformly as possible throughout the entire media. Sterile paper discs (6 mm diameter) were impregnated with 20 µL of the compound solution then allowed to dry. The impregnated disc was introduced on the upper layer of the seeded agar plate and incubated at 37 °C for 24 hours. The antibacterial activities of the synthesized compounds were compared with known antibiotic gentamicin (10 µg *per* disc) and chloramphenicol (30 µg *per* disc) as positive control and DMSO (20 µL *per* disc) as negative control. Antibacterial activity was evaluated by measuring the diameter of inhibition zone (mm) on the surface of plates and the results were reported as mean ± SD (standard deviation) after three repeats.

Results and Discussion

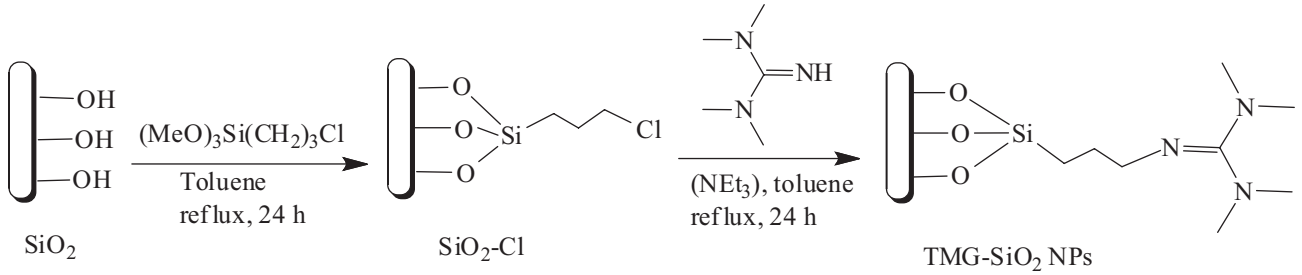
Synthesis and characterization of catalyst

Nano silica-supported tetramethylguanidine was synthesized according to reported procedure in the literature,[15] by silylation/condensation of nano silica with (3-chloro propyl)trimethoxy silane, which was then reacted with tetramethylguanidine to form TMG-SiO_2 NPs catalyst (Scheme 1).

The catalyst structure was characterized by elemental analysis, IR spectroscopy, TGA, XRD and FE-SEM (Supplementary Information (SI) section). The amount of tetramethylguanidine grafted on nano silica was evaluated by the nitrogen content, 0.50 mmol g^{-1}, on the base of elemental analysis (C: 4.83%; H: 1.05%; N: 2.10%), which was in good agreement with the result obtained from TGA analysis.

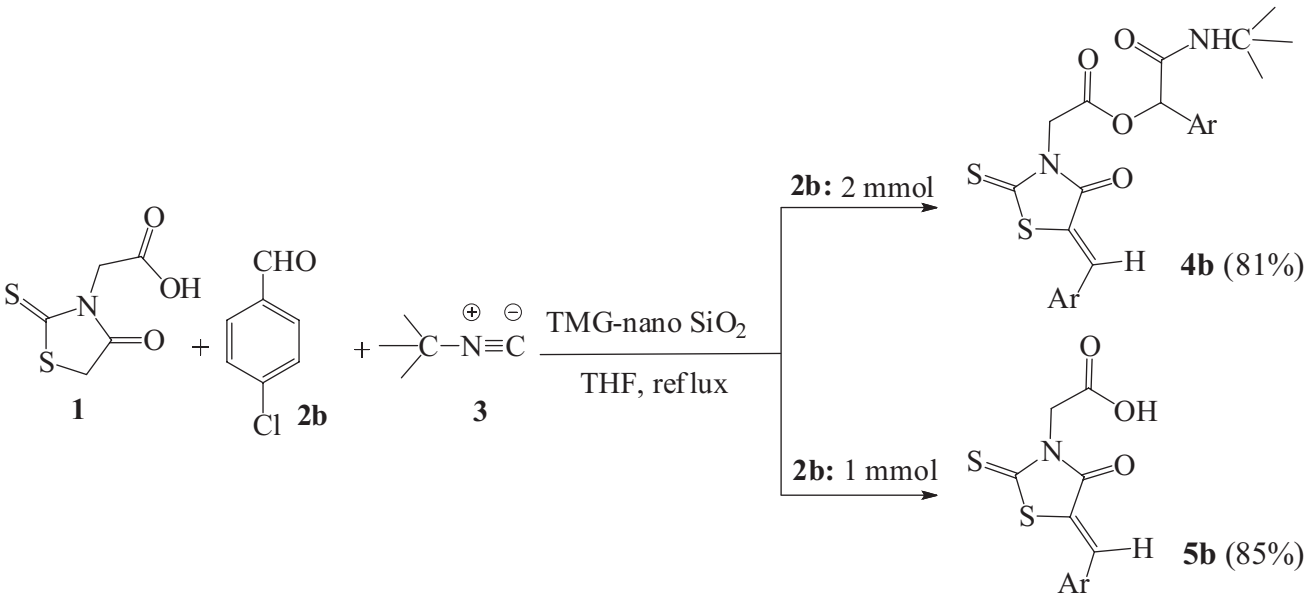
Catalytic study

Initially, the reaction of rhodanine-*N*-acetic acid **1** (1.0 mmol), 4-chlorobenzaldehyde **2b** (1.0 mmol) and *tert*-butyl isocyanide **3** (1.0 mmol) as model substrates in the presence of 15 mol% (0.30 g) TMG-SiO_2 NPs in tetrahydrofuran (THF) under reflux conditions was used to determine suitability of the catalyst for the desired



SiO_2 SiO_2-Cl TMG-SiO_2 NPs

Scheme 1. Synthesis of TMG-SiO_2 NPs.



Scheme 2. Synthesis of rhodanine-based amide using TMG-SiO_2 NPs catalyzed Passerini reaction.

reaction. This condensation reaction did not afford the Passerini product **4b**, while in contrast, benzilidene rhodanine-*N*-acetic acid **5b**, confirmed by NMR spectra, was obtained in 85% yield. Subsequently, by increasing the amount of 4-chlorobenzaldehyde to 2.0 mmol, product **4b** was formed in 81% yield, Scheme 2.

Interestingly, the three-component reaction of benzilidene rhodanine-*N*-acetic acid **5b** (1.0 mmol) with 4-chlorobenzaldehyde **2b** (1.0 mmol) and *tert*-butyl isocyanide **3** (1.0 mmol) in the absence of catalyst, did not convert into **4b** even after 24 h in boiling THF. The results clearly show that, TMG-SiO_2 NPs effectively catalyze the Passerini reaction. Next, we attempted to determine the optimum conditions by examining the influence of catalyst, solvent and temperature variations on the progress of the Passerini reaction. The results of the optimized conditions are summarized in Table 1.

Table 1. Optimization of reaction conditions for the synthesis of rhodanine-based amide **4b**

entry	Catalyst / mol%	Solvent	Temperature / ºC	time / h	Yield[a] / %
1	–	THF	70	24	trace
2	SiO_2 NPs / 0.3 g	THF	70	24	trace
3	TiO_2 NPs / 15	THF	70	24	trace
4	MgO NPs / 15	THF	70	24	trace
5	TMG / 15	THF	70	24	trace
6	DABCO / 15	THF	70	24	trace
7	SBA-15-DABCO / 15	THF	70	24	20
8	DBU- SiO_2 NPs / 15	THF	70	24	30
9	TMG-SiO_2 NPs / 15	THF	70	10	81
10	TMG-SiO_2 NPs / 20	THF	70	10	80
11	TMG-SiO_2 NPs / 10	THF	70	10	80
12	TMG-SiO_2 NPs / 5	THF	70	24	30
13	TMG-SiO_2 NPs / 10	CH_2Cl_2	40	24	35
14	TMG-SiO_2 NPs / 10	EtOH	80	24	–
15	TMG-SiO_2 NPs / 10	H_2O	100	24	–
16	TMG-SiO_2 NPs / 10	THF	40	24	45
17	TMG-SiO_2 NPs / 10	THF	25	24	trace

[a]Yield refer to isolated products.

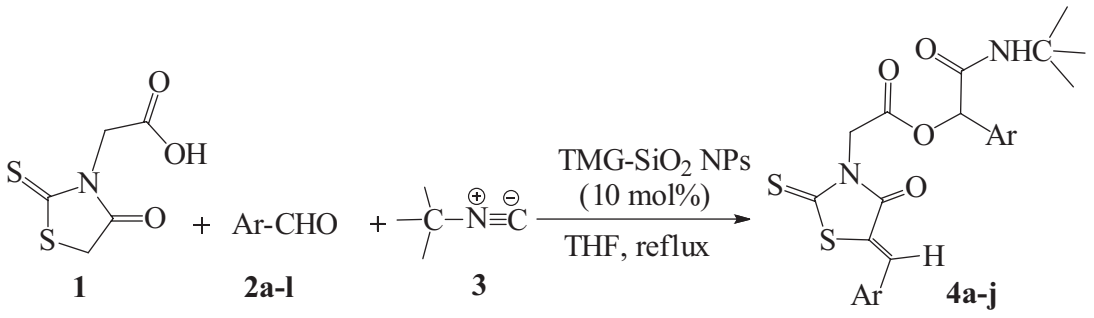
Only a trace amount of the product **4b** could be detected in the absence of catalyst even after 24 h under reflux conditions in THF (Table 1, entry 1). To explore the suitable reaction conditions, the above model reaction was performed in the presence of various catalysts such as SiO_2 NPs, TiO_2 NPs, MgO NPs, TMG, DABCO, SBA-15-DABCO, DBU-SiO_2 NPs in boiling THF (Table 1, entries 2-8). From the results, it is obvious that TMG-SiO_2 NPs demonstrates superior catalytic activity in this reaction and is the best catalyst among those examined (Table 1, entry 9). We also evaluated the amount of catalyst required for this transformation. It was observed that when the model reaction was run in the presence of 10 mol% (0.20 g) TMG-SiO_2 NPs in THF at 70 ºC, good results were obtained with regard to the yield and reaction time (Table 1, entry 11). Increasing the amount of catalyst did not change the yield dramatically (Table 1, entries 9 and 10), whereas reduction of it significantly decreased the product yield (Table 1, entry 12). Next, the model reaction was studied in various solvents such as water, ethanol, and dichloromethane using 10 mol% of TMG-SiO_2 NPs under reflux conditions (Table 1, entries 13-15). As shown in Table 1, the reaction failed completely in protic solvents, and THF provided greater yield and shorter reaction time than CH_2Cl_2. To optimize the reaction temperature, the model reaction was carried out in THF at different temperatures. We observed that, the reaction did not proceed to completion at room temperature (Table 1, entry 17), and the yield of product was improved as the temperature was increased to 70 ºC under the same conditions.

To explore the scope and limitations of this reaction, we applied TMG-SiO_2 NPs (10 mol%) on the reactions of rhodanine-*N*-acetic acid 1 with a variety of aromatic aldehydes **2a**-**2l** and *tert*-butyl isocyanide **3** in boiling THF. Under the optimized reaction conditions, a series of 2-(*tert*-butylamino)-2-oxo-1-phenylethyl[(5*Z*)-5-benzylidene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]acetate derivatives **4a**-**4j** were synthesized in good yields. The yield of products and time taken for maximum conversion of the substrates in each case, are listed in Table 2.

As presented in Table 2, the reaction of aldehydes with electron accepting groups afforded the highest yields and the shortest reaction times (entries 4 and 5), whereas the reaction of aldehydes **2k** and **2l** with strong electron releasing groups did not proceed, so no product could be isolated (entries 11 and 12). The structures of **4a**-**4j** were deduced from ^1H and ^{13}C NMR, IR and mass spectra as well as elemental analyses.

To evaluate the recyclability and stability of our catalyst, we designed a set of experiments by successive condensation

Table 2. TMG-SiO_2 NPs catalyzed synthesis of rhodanine-based amides[a] **4**



entry	Product	Ar	time / h	Yield[b] / %
1	**4a**	C_6H_5	20	70
2	**4b**	4-ClC_6H_4	10	80
3	**4c**	4-BrC_6H_4	19	68
4	**4d**	4-FC_6H_4	8	82
5	**4e**	4-$NO_2C_6H_4$	3	85
6	**4f**	4-MeC_6H_4	18	67
7	**4g**	2-ClC_6H_4	9	78
8	**4h**	2-$NO_2C_6H_4$	10	81
9	**4i**	3-ClC_6H_4	22	74
10	**4j**	3-BrC_6H_4	24	71
11	**4k**	4-$OMeC_6H_4$	24	–
12	**4l**	4-$Me_2NC_6H_4$	24	–

[a]Reaction conditions: rhodanine-*N*-acetic acid (1.0 mmol), aldehydes (2.0 mmol), and *tert*-butyl isocyanide (1.0 mmol) in THF (10.0 mL); TMG-SiO_2 NPs (10 mol%); temperature (70 °C); [b]yield refer to isolated products.

of model substrates using recovered TMG-SiO_2 NPs under optimized conditions. After the completion of the first reaction run with 80% yield, the catalyst was filtered from hot reaction mixture, washed with acetone and finally dried at 50 ºC for 1 h. The recycled catalyst was employed in another cycle under the similar conditions. It was found that the catalyst could be used directly for at least five reaction cycles without noticeable drop in the product yield and its catalytic activity (Figure 1). The reactants were taken with respect to the amount of the catalyst recovered after each reaction cycle. The elemental analysis of recycled catalyst after the 5th reaction run revealed slightly decrease in the content of elements (C: 4.65%; H: 0.95%; N: 2.0%), which can be related to catalyst leaching.

A proposed mechanism for the synthesis of α-acyloxy amides **4** is outlined in Scheme 3. The efficiency of

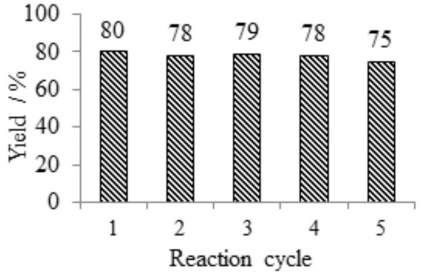
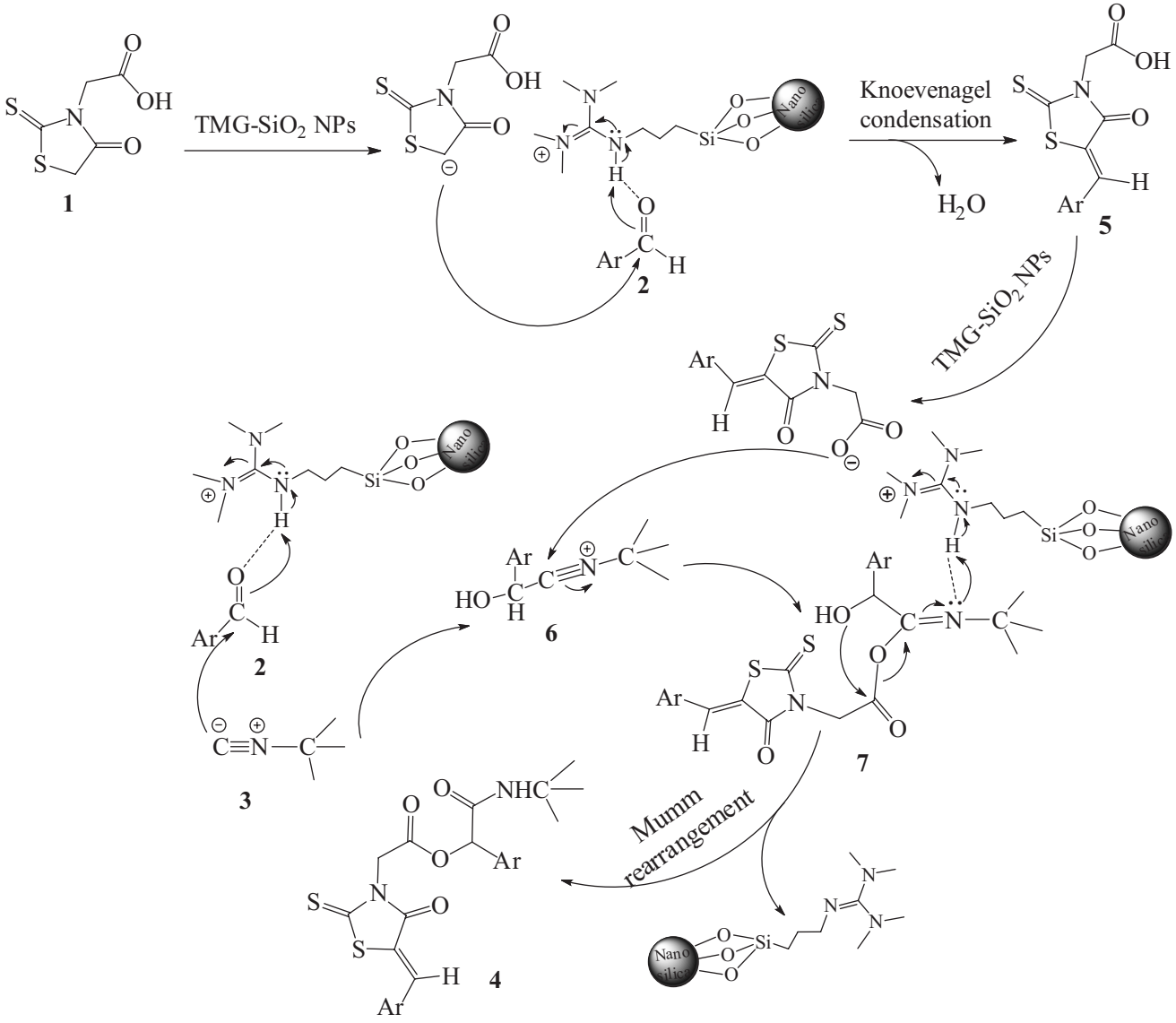


Figure 1. Reusability of the catalyst. Reaction conditions: rhodanine-*N*-acetic acid **1** (1.0 mmol), 4-chlorobenzaldehyde **2b** (2.0 mmol) and *tert*-butyl isocyanide **3** (1.0 mmol) in THF (10.0 mL), TMG-SiO_2 NPs (10 mol%, 0.20 g), temperature (70 ºC), reaction time (10 h).

TMG-SiO_2 NPs is better conceived by considering its acid-base bifunctional nature, providing both proton donating and accepting functions during the catalysis process. The reaction is initiated by TMG-SiO_2 NPs, which upon



Scheme 3. Proposed mechanism for the synthesis of rhodanine-based amide derivatives **4**.

Table 3. Antibacterial activity of the compounds **4a**-**4j** using Kirby-Bauer technique (zone of growth inhibition, mm)

Compound	*E. coli* / mm	*P. aeruginosa* / mm	*S. aureus* / mm	*B. subtilis* / mm
4a[a]	10.5 ± 0.7	9.5 ± 0.7	11.5 ± 0.7	9.5 ± 0.7
4b	NE[b]	NE	9.5 ± 0.7	8.5 ± 0.7
4c	NE	NE	NE	NE
4d	NE	NE	8.5 ± 0.7	12.5 ± 0.7
4e	9.5 ± 0.7	NE	NE	7.5 ± 0.7
4f	NE	NE	NE	8.0 ± 0.1
4g	8.5 ± 0.7	NE	NE	NE
4h	12.0 ± 1.4	NE	16.0 ± 1.4	15.5 ± 0.7
4i	NE	NE	NE	NE
4j	NE	NE	NE	NE
Gentamicin (10 μg / disc)	19.6 ± 1.1	15.6 ± 0.5	20.3 ± 1.5	26.0 ± 1.7
Chloramphenicol (30 μg / disc)	20.7 ± 1.5	NE	21.7 ± 0.6	22.3 ± 1.2
DMSO	NE	NE	NE	NE

[a]Concentration of compounds **4a**-**4j**: 20 mg mL^{-1}; [b]no effect.

removing a proton from rhodanine-*N*-acetic acid **1** promotes a Knoevenagel condensation with the aldehyde **2**, activated by hydrogen-bond donor catalyst, resulting in formation of the compound **5**. Then, nucleophilic attack of isocyanide carbon to carbonyl group of activated aldehyde **2**, affords the adduct **6**. The resulting nitrilium intermediate **6** is attacked by the carboxylate of **5** followed by acyl transfer via Mumm rearrangement,[2,3,28] and proton attraction from conjugate acid of the catalyst to form rhodanine-based amide derivatives **4**.

Antibacterial activity

The antibacterial activity of compounds **4a**-**4j** was evaluated against Gram positive (*S. aureus* and *B. subtilis*) and Gram negative bacteria (*E. coli* and *P. aeruginosa*) by the disc diffusion method; the results were collected in Table 3. In addition, the finding towards inhibition of microorganisms was compared with that of positive controls, gentamicin and chloramphenicol, and DMSO as a negative control. According to Table 3, compound **4a** showed moderate growth inhibitory effect against all tested bacteria, whereas compounds **4c**, **4i** and **4j** exhibited no activity. Also, compounds **4b**, **4d**, **4e**, **4f** and **4g** displayed moderate activity against some microorganisms. Moreover, compound **4h** showed good activity against bacteria except *P. aeruginosa*.

Conclusions

In summary, nano silica functionalized with basic organocatalyst was synthesized, and used as an efficient heterogeneous catalyst for the MCR synthesis of rhodanine-based amides as antibacterial agents. Environmental acceptability, good yields, simple work-up, easy removal and recyclability of catalyst are the important features of this atom economical protocol.

Supplementary information

Supplementary information is available free of charge at http://jbcs.sbq.org.br as a PDF file.

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