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CATALYTIC-FREE HIGHLY EFFICIENT AND ECO-FRIENDLY PROTOCOL FOR THE SYNTHESIS OF SEMICARBAZONES AT AMBIENT TEMPERATURE

JANARDHAN BANOTHU and RAJITHA BAVANTULA*

Department of Chemistry, National Institute of Technology, WARANGAL – 506004 (A.P.) INDIA

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ABSTRACT

Highly efficient procedure for the synthesis of semicarbazones has been developed by the reaction of arylaldehydes/acetophenones/3-acetyl coumarins with semicarbazide hydrochloride under catalytic free conditions in aqueous methanol at ambient temperature in excellent yields. All the compounds were characterized by their analytical and spectral data.

Key words: 3-Acetyl coumarins, Ambient temperature, Catalytic free conditions, Semicarbazones.

INTRODUCTION

Nowadays, green chemistry playing an important role and attracting the researchers both from academia and industries because it involves environmentally clean synthesis, improvement in selectivity, high atom efficiency, elimination of hazardous reagents, easy separation from the reaction mixture and reuse of the reagent. As a result, volatile organic solvents are being replaced by non-toxic, non-volatile media such as ionic liquids, polyethylene glycol and water[1].

Semicarbazone derivatives were found to posses various pharmacological properties such as antimicrobial[2,3], anticonvulsant[4-6], antiepileptic[7], anti-inflammatory[8], antioxidant[9] and antiproliferative[10] activities. These are useful for the protection, purification and characterization of carbonyl compounds[11], and also act as intermediate for the synthesis of biologically important heterocyclic moieties such as 1,3,4-oxadiazoles[12,13], 1,2,3- triazoles, 1,2,4-triazoles[14,15] and metal complexes[16,17].

The common method for the synthesis of semicarbazone derivatives is the reaction of aldehydes/ ketones with semicarbazide in the presence of base or acid as catalyst[11]. Recently many methods have been developed using SiO_2/NaOH[18], sodium acetate supported on silica gel[19] and basic alumina[20] as catalysts. In the present paper and for continuation of our work on the synthesis of biologically interesting molecules using novel methodologies[21-23], we have reported the synthesis of semicarbazone derivatives of aryl aldehydes/aryl ketones/3-acetyl coumarins under catalytic free conditions at ambient temperatures.

Available online at www.sadgurupublications.com
*Author for correspondence; E-mail: rajitha_nitw@yahoo.com; Ph.: 0870-2459445, Fax: 0091-0870-2459547

EXPERIMENTAL

Materials and methods

The melting points were determined in open capillaries using Stuart SMP30 melting point apparatus, and are uncorrected. The progress of the reaction was monitored by TLC and visualized with UV light and iodine vapors. IR spectra were recorded on Perkin–Elmer 237 spectrophotometer using KBr pellet, values are expressed in cm^{-1}. The C, H and N analysis of the compounds were done on a Carlo Erba modal EA1108, NMR spectra were recorded on Brucker 300-MHz spectrometer using TMS as an internal standard and chemical shifts are expressed in ppm. Mass spectra were recorded on a Jeol JMSD-300 spectrometer.

General procedure for the synthesis of semicarbazones 2(a-p), 3(a-h), 4(a-e) and 5

Semicarbazide hydrochloride (1.2 mmol), which was dissolved in 2mL of water was added slowly to 1 mL of methanol containing arylaldehyde/ketone/3-acetyl coumarins (1 mmol) and stirred at room temperature for an appropriate time as indicated in Table 2. After completion of the reaction shown by TLC, the solid separated out was filtered, washed with water and purified by recrystallization from a mixture of methanol : water (1 : 1).

Characterization data

1-Benzylidenesemicarbazide (2a): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3485, 3378, 1669, 1620, 1589; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.28 (s, 2H), 7.13-7.65 (m, 3H), 7.81 (d, 2H), 7.96 (s, 1H), 10.19 (s, 1H); MS (ESI), 70 eV, *m/z*: 164 (M+1).

1-(2-Chlorobenzylidene) semicarbazide (2b): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3476, 3382, 1662, 1620, 1599, 754; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.29 (s, 2H), 7.46 (t, 2H), 7.58 (d, 1H), 7.83 (d, 1H), 7.92 (s, 1H), 10.16 (s, 1H); MS (ESI), 70 eV, *m/z*: 198 (M+1).

1-(4-Chlorobenzylidene) semicarbazide (2c): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3478, 3381, 1675, 1618, 1591, 782; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.29 (s, 2H), 7.57 (d, 2H), 7.82 (d, 2H), 7.95 (s, 1H), 10.22 (s, 1H); MS (ESI), 70 eV, *m/z*: 198 (M+1).

1-(4-Methoxybenzylidene) semicarbazide (2d): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3482, 3378, 1665, 1616, 1591, 1255; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.74 (s, 3H), 6.29 (s, 2H), 7.12 (d, 2H), 7.75 (d, 2H), 7.92 (s, 1H), 10.23 (s, 1H); MS (ESI), 70 eV, *m/z*: 194 (M+1).

1-(3,4-Dimethoxybenzylidene) semicarbazide (2e): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3474, 3380, 1669, 1620, 1585, 1282; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.74 (s, 6H), 6.28 (s, 2H), 6.92 (d, 1H), 7.17 (s, 1H), 7.49 (d, 1H), 7.94 (s, 1H), 10.21 (s, 1H); MS (ESI), 70 eV, *m/z*: 224 (M+1).

1-(2-Nitrobenzylidene) semicarbazide (2f): Yellow solid, IR (KBr, υ_{max}, cm^{-1}): 3457, 3380, 1667, 1622, 1585, 1474; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.30 (s, 2H), 7.64-7.73 (m, 2H), 7.90 (s, 1H), 8.15 (d, 1H), 8.22 (d, 1H), 10.22 (s, 1H); MS (ESI), 70 eV, *m/z*: 209 (M+1).

1-(3-Nitrobenzylidene) semicarbazide (2g): Yellow solid, IR (KBr, υ_{max}, cm^{-1}): 3467, 3371, 1665, 1620, 1589, 1476; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.29 (s, 2H), 7.57 (m, 1H), 7.92 (s, 1H), 8.11 (d, 1H), 8.35 (d, 1H), 8.49 (d, 1H), 10.12 (s, 1H); MS (ESI), 70 eV, *m/z*: 209 (M+1).

1-(2-Hydroxybenzylidene) semicarbazide (2h): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3475, 3363, 3345, 1660, 1617, 1601; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.28 (s, 2H), 7.08-7.47 (m, 3H), 7.56 (d, 1H), 7. 98 (s, 1H), 9.14 (s, 1H), 10.23 (s, 1H); MS (ESI), 70 eV, *m/z*: 180 (M+1).

1-(4-Hydroxybenzylidene) semicarbazide (2i): Brown solid, IR (KBr, υ_{max}, cm^{-1}): 3482, 3364, 3352, 1662, 1618, 1599; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.23 (s, 2H), 7.14 (d, 2H), 7.68 (d, 2H), 7.92 (s, 1H), 9.15 (s, 1H), 10.21 (s, 1H); MS (ESI), 70 eV, *m/z*: 180 (M+1).

1-(4-Hydroxy-3-methoxybenzylidene) semicarbazide (2j): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3458, 3372, 3359, 1654, 1619, 1587, 1244; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.75 (s, 3H), 6.29 (s, 2H), 6.80 (d, 1H), 7.16 (s, 1H), 7.33 (d, 1H), 7.93 (s, 1H), 9.15 (s, 1H), 10.22 (s, 1H); MS (ESI), 70 eV, *m/z*: 210 (M+1).

1-(5-Chloro-2-hydroxybenzylidene) semicarbazide (2k): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3478, 3371, 3367, 1662, 1618, 1601, 744; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.25 (s, 2H), 7.19 (d, 1H), 7.34 (d, 1H), 7.67 (s, 1H), 7.90 (s, 1H), 9.17 (s, 1H), 10.19 (s, 1H); MS (ESI), 70 eV, *m/z*: 214 (M+1).

1-(5-Bromo-2-hydroxybenzylidene) semicarbazide (2l): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3475, 3389, 3351, 1660, 1624, 1589, 682; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.26 (s, 2H), 7.23 (d, 1H), 7.35 (d, 1H), 7.63 (s, 1H), 7.98 (s, 1H), 9.18 (s, 1H), 10.20 (s, 1H); MS (ESI), 70 eV, *m/z*: 259 (M+1).

1-(3,5-Dibromo-2-hydroxybenzylidene) semicarbazide (2m): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3465, 3382, 3362, 1674, 1626, 1605, 690; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.30 (s, 2H), 7.73 (s, 1H), 7.90 (s, 1H), 7.92 (s, 1H), 9.17 (s, 1H), 10.22 (s, 1H); MS (ESI), 70 eV, *m/z*: 337 (M+1).

1-(4-(Dimethylamino) benzylidene) semicarbazide (2n): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3476, 3367, 1674, 1624, 1608; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.82 (s, 6H), 6.29 (s, 2H), 7.10 (d, 2H), 7.72 (d, 2H), 7.92 (s, 1H), 10.17 (s, 1H); MS (ESI), 70 eV, *m/z*: 207 (M+1).

1-(-3-Phenylallylidene) semicarbazide (2o): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3457, 3372, 1667, 1622, 1586; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.28 (s, 2H), 6.87 (t, 2H), 7.29-7.38 (m, 3H), 7.52 (d, 2H), 7.67-7.69 (m, 1H), 10.19 (s, 1H); MS (ESI), 70 eV, *m/z*: 190 (M+1).

1-((Furan-2-yl)methylene) semicarbazide (2p): Brown solid, IR (KBr, υ_{max}, cm^{-1}): 3454, 3379, 1652, 1624, 1597, 1094; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.31 (s, 2H), 6.57 (t, 1H), 6.80 (s, 1H), 7.75 (d, 2H), 10.23 (s, 1H); MS (ESI), 70 eV, *m/z*: 154 (M+1).

1-(1-Phenylethylidene) semicarbazide (3a): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3484, 3379, 1685, 1620, 1592; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24 (s, 3H), 6.64 (s, 2H), 7.47-7.68 (m, 3H), 7.84 (d, 2H), 9.67 (s, 1H); MS (ESI), 70 eV, *m/z*: 178 (M+1).

1-(1-(4-Chlorophenyl) ethylidene) semicarbazide (3b): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3480, 3382, 1674, 1618, 1593, 786; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.25 (s, 3H), 6.63 (s, 2H), 7.55 (d, 2H), 7.79 (d, 2H), 9.65 (s, 1H); MS (ESI), 70 eV, *m/z*: 212 (M+1).

1-(1-(4-Bromophenyl) ethylidene) semicarbazide (3c): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3480, 3378, 1678, 1620, 1586, 695; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27 (s, 3H), 6.64 (s, 2H), 7.78 (d, 2H), 7.92 (d, 2H), 9.72 (s, 1H); MS (ESI), 70 eV, *m/z*: 257 (M+1).

1-(1-*p*-Tolylethylidene) semicarbazide (3d): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3472, 3376, 1685, 1621, 1597; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.23 (s, 3H), 2.32 (s, 3H), 6.65 (s, 2H), 7.32 (d, 2H), 7.74 (d, 2H), 9.64 (s, 1H); MS (ESI), 70 eV, *m/z*: 192 (M+1).

1-(1-(4-Methoxyphenyl) ethylidene) semicarbazide (3e): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3487, 3381, 1679, 1620, 1598, 1210; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24 (s, 3H), 3.75 (s, 3H), 6.64 (s, 2H), 7.12 (d, 2H), 7.75 (d, 2H), 9.65 (s, 1H); MS (ESI), 70 eV, *m/z*: 208 (M+1).

1-(1-(4-Nitrophenyl) ethylidene) semicarbazide (3f): Yellow solid, IR (KBr, υ_{max}, cm^{-1}): 3475, 3380, 1685, 1618, 1583, 1476; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.23 (s, 3H), 6.65 (s, 2H), 8.13 (d, 2H), 8.18 (d, 2H), 9.64 (s, 1H); MS (ESI), 70 eV, *m/z*: 223 (M+1).

1-(1-(2-Hydroxyphenyl) ethylidene) semicarbazide (3g): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3489, 3378, 3210, 1682, 1621, 1594; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.22 (s, 3H), 6.20 (s, 2H), 6.84 (t, 2H), 7.18-7.22 (m, 1H), 7.48-7.50 (m, 1H), 9.63 (s, 1H), 12.72 (s, 1H); MS (ESI), 70 eV, *m/z*: 194 (M+1).

1-(1-(4-Phenylphenyl) ethylidene) semicarbazide (3h): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3474, 3380, 1685, 1620, 1592; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.61 (s, 3H), 6.52 (s, 2H), 7.41-7.53 (m, 3H), 7.75 (d, 2H), 7.83 (d, 2H), 8.04 (d, 2H), 9.36 (s, 1H); MS (ESI), 70 eV, *m/z*: 254 (M+1).

1-(1-(2-Oxo-2*H*-chromen-3-yl) ethylidene) semicarbazide (4a): Colourless solid, IR (KBr, υ_{max}, cm^{-1}): 3484, 3378, 1715, 1685, 1618, 1594; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.59 (s, 3H), 6.54 (s, 2H), 7.60-7.64 (m, 1H), 7.76 (t, 2H), 7.95 (d, 1H), 8.66 (s, 1H), 9.53 (s, 1H); MS (ESI), 70 eV, *m/z*: 246 (M+1).

1-(1-(6-Bromo-2-oxo-2*H*-chromen-3-yl) ethylidene) semicarbazide (4b): Pale yellow solid, IR (KBr, υ_{max}, cm^{-1}): 3472, 3389, 1718, 1676, 1620, 1588, 694; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.61 (s, 3H), 6.53 (s, 2H), 7.12 (d, 1H), 7.45 (d, 1H), 7.98 (s, 1H), 8.65 (s, 1H), 9.52 (s, 1H); MS (ESI), 70 eV, *m/z*: 325 (M+1).

1-(1-(6,8-Dibromo-2-oxo-2*H*-chromen-3-yl) ethylidene) semicarbazide (4c): Pale yellow solid, IR (KBr, υ_{max}, cm^{-1}): 3485, 3384, 1714, 1680, 1619, 1592, 692; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.59 (s, 3H), 6.54 (s, 2H), 7.49 (s, 1H), 7.74 (s, 1H), 8.64 (s, 1H), 9.52 (s, 1H); MS (ESI), 70 eV, *m/z*: 404 (M+1).

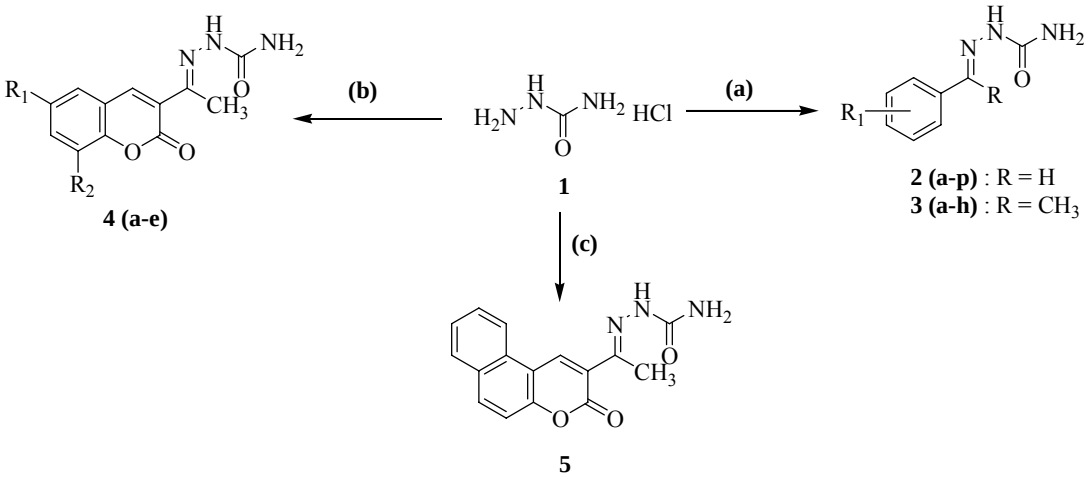
1-(1-(6-Chloro-2-oxo-2*H*-chromen-3-yl) ethylidene) semicarbazide (4d): Pale yellow solid, IR (KBr, υ_{max}, cm^{-1}): 3489, 3380, 1720, 1682, 1611, 1572, 784; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.60 (s, 3H), 6.53 (s, 2H), 7.15 (d, 1H), 7.47 (d, 1H), 8.02 (s, 1H), 8.65 (s, 1H), 9.53 (s, 1H); MS (ESI), 70 eV, *m/z*: 280 (M+1).

1-(1-(8-Methoxy-2-oxo-2*H*-chromen-3-yl) ethylidene) semicarbazide (4e): Pale yellow solid, IR (KBr, υ_{max}, cm^{-1}): 3496, 3384, 1713, 1680, 1601, 1560, 1097; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.58 (s, 3H), 3.91 (s, 3H), 6.53 (s, 2H), 7.35 (d, 1H), 7.42 (d, 1H), 7.48 (t, 1H), 8.62 (s, 1H), 9.52 (s, 1H); MS (ESI), 70 eV, *m/z*: 276 (M+1).

1-(1-(3-Oxo-3*H*-benzo[*f*]chromen-2-yl) ethylidene) semicarbazide (5): Yellow solid, IR (KBr, υ_{max}, cm^{-1}): 3484, 3389, 1721, 1669, 1605, 1575; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.65 (s, 3H), 6.57 (s, 2H), 7.61-7.80 (m, 3H), 8.09 (d, 1H), 8.33 (d, 1H), 8.62 (d, 1H), 8.66 (s, 1H), 9.27 (s, 1H); MS (ESI), 70 eV, *m/z*: 296 (M+1).

RESULTS AND DISCUSSION

Semicarbazone derivatives [2(a-p), 3(a-h), 4(a-e) and 5)] were synthesized by the condensation of semicarbazide hydrochloride with arylaldehydes/acetophenones/3-acetyl coumarins at ambient temperature under catalytic free conditions using water and methanol in 2 : 1 ratio as solvent system (Scheme 1).



Scheme 1: Catalytic free synthesis of semicarbazones

Reaction conditions: (a) Aryl aldehydes/ketones (1 mmol), H_2O:MeOH (2 : 1), Rt, 2-5 min; (b) 3-Acetyl-2*H*-chromen-2-ones (1 mmol), H_2O : MeOH (2 : 1), Rt, 2-4 min; (c) 2-Acetyl-3*H*-benzo[*f*] chromen-3-one (1 mmol), H_2O : MeOH (2 : 1), Rt, 4 min.

To optimize the reaction conditions, initially the reaction between semicarbazide hydrochloride with benzaldehyde was carried out at room temperature in different solvents (methanol, acetic acid, acetonitrile and water) and observed the maximum yield (87%) in water, to improve the yield of the product (2a) we have tried the same reaction in water with the combination of methanol in different ratios and the results were shown in Table 1. From the results it was notified that, as the ratio of methanol increases the yield of the product decreases and found maximum yield (99%) of the product (2a) with 2 : 1 ratio of water and methanol system. Same reaction was also carried out at refluxing temperature and observed no change in product yield, but requires longer reaction time (15 min).

Table 1: Optimizing the reaction conditions[a]

Entry	Solvent system	Time (min)	Yield[b] (%)
1	Methanol	20	76
2	Acetic acid	20	64
3	Acetonitrile	20	69
4	Water	20	87
5	Water : Methanol (1 : 1)	10	98
6	Water : Methanol (1 : 2)	10	96
7	Water : Methanol (1 : 3)	10	93
8	Water : Methanol (2 : 1)	3	99
9	Water : Methanol (3 : 1)	3	98

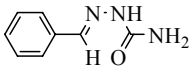
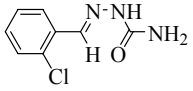
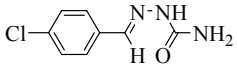
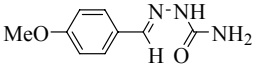
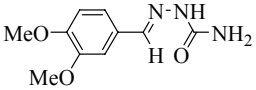
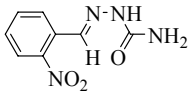
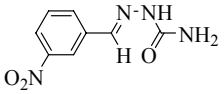
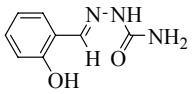
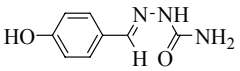
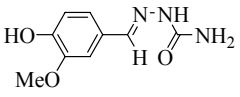
[a]Reaction conditions: Benzaldehyde (1 mmol), Semicarbazide hydrochloride (1.2 mmol), Rt stirring.

[b]Yields refers to pure isolated product (2a)

At these optimistic conditions (2 : 1 ratio of water and methanol stirring at Rt), we have synthesized various semicarbazone derivatives of aldehydes, ketones and coumarins in shorter reaction times with

excellent yields (Table 2). All the compounds were confirmed by their analytical and spectral data. The presence of peaks in the range of 1650-1685 cm^{-1} (C=O stretching) and 1555-1610 cm^{-1} (C=N stretching) from IR spetra; absence of semicarbazide (N-NH_2) protons from ^1H NMR and molecular ion peak from mass spectra confirms the formation of the product.

Table 2: Synthesis of semicabazone derivatives under catalytic-free conditions in aqueous methanol

Entry[a]	Product	Time (min)	Yield[b] (%)	M.p. (^oC)	Elemental analysis calculated (Found)		
					C	H	N
1	 **(2a)**	4	99	219-221	58.88 (58.96)	5.56 (5.72)	25.75 (25.58)
2	 **(2b)**	2	98	233-235	48.62 (48.80)	4.08 (4.33)	21.26 (21.09)
3	 **(2c)**	2	99	232-234	48.62 (48.81)	4.08 (4.37)	21.26 (21.16)
4	 **(2d)**	3	97	211-213	55.95 (56.12)	5.74 (5.57)	21.75 (21.88)
5	 **(2e)**	2	98	182-184	53.80 (53.92)	5.87 (5.74)	18.82 (18.99)
6	 **(2f)**	5	98	249-251	46.16 (46.08)	3.87 (3.99)	26.91 (26.70)
7	 **(2g)**	2	99	246-248	46.16 (46.29)	3.87 (3.96)	26.91 (26.75)
8	 **(2h)**	3	96	231-233	53.63 (53.77)	5.06 (5.30)	23.45 (23.17)
9	 **(2i)**	3	98	220-222	53.63 (53.70)	5.06 (5.22)	23.45 (23.19)
10	 **(2j)**	2	99	237-239	51.67 (51.81)	5.30 (5.42)	20.09 (19.96)

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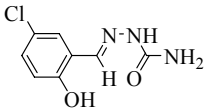
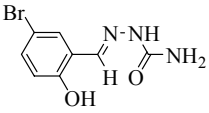
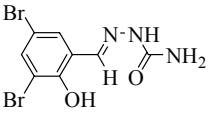
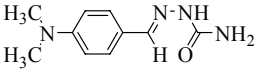
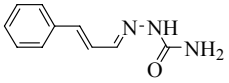
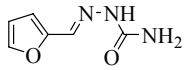
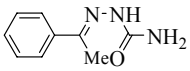
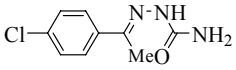
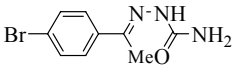
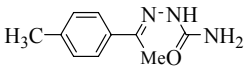
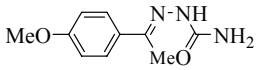
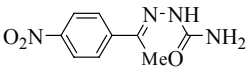
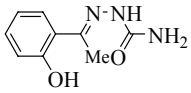
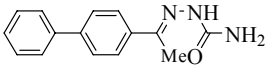
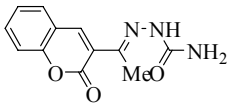
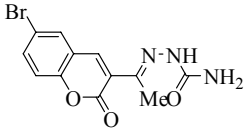
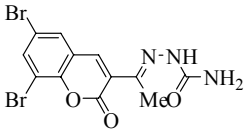
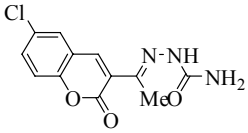
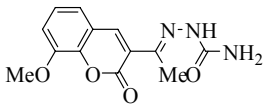
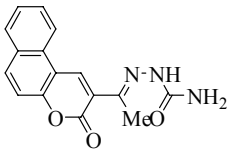
Entry[a]	Product	Time (min)	Yield[b] (%)	M.p. (°C)	Elemental analysis calculated (Found)		
					C	H	N
11	 **(2k)**	5	97	290-292	44.98 (45.20)	3.77 (3.94)	19.67 (19.45)
12	 **(2l)**	5	96	305-507	37.23 (37.49)	3.12 (3.32)	16.28 (16.05)
13	 **(2m)**	5	96	216-218	28.51 (28.74)	2.09 (2.23)	12.47 (12.19)
14	 **(2n)**	4	98	221-223	58.24 (58.53)	6.84 (6.96)	27.17 (27.04)
15	 **(2o)**	3	98	205-208	63.48 (63.54)	5.86 (5.97)	22.21 (22.03)
16	 **(2p)**	5	97	197-199	47.06 (47.32)	4.61 (4.77)	27.44 (27.17)
17	 **(3a)**	3	97	202-204	61.00 (61.27)	6.26 (6.40)	23.71 (23.53)
18	 **(3b)**	3	98	205-206	51.07 (51.42)	4.76 (4.97)	19.85 (19.55)
19	 **(3c)**	3	98	203-205	42.21 (42.53)	3.94 (4.08)	16.41 (16.17)
20	 **(3d)**	4	98	211-213	62.81 (62.99)	6.85 (6.92)	21.97 (21.66)
21	 **(3e)**	4	97	193-195	57.96 (58.14)	6.32 (6.54)	20.28 (20.06)
22	 **(3g)**	2	99	246-248	48.65 (48.81)	4.54 (4.69)	25.21 (25.04)

Cont…

Entry[a]	Product	Time (min)	Yield[b] (%)	M.p. (°C)	Elemental analysis calculated (Found)		
					C	H	N
23	 **(3g)**	5	98	221-223	55.95 (56.20)	5.74 (5.92)	21.75 (21.47)
24	 **(3h)**	4	97	169-171	71.13 (71.42)	5.97 (6.08)	16.59 (16.25)
25	 **(4a)**	2	99	217-218	58.77 (58.89)	4.52 (4.76)	17.13 (17.01)
26	 **(4b)**	3	96	222-224	44.47 (44.73)	3.11 (3.35)	12.96 (12.68)
27	 **(4c)**	4	96	225-227	35.76 (35.90)	2.25 (2.42)	10.43 (10.15)
28	 **(4d)**	4	98	205-208	51.53 (51.84)	3.60 (3.85)	15.02 (14.79)
29	 **(4e)**	4	98	213-215	56.72 (56.90)	4.76 (4.94)	15.27 (15.05)
30	 **(5)**	4	97	182-184	65.08 (65.37)	4.44 (4.63)	14.23 (14.04)

[a]Reaction conditions: Arylaldehyde/ketone/coumarin (1 mmol), Semicarbazide hydrochloride (1.2 mmol), Rt stirring. [b]Yields refers to pure isolated products.

CONCLUSION

In conclusion, we have developed a simple, efficient and eco-friendly protocol for the synthesis of semicarbazone derivatives under catalytic-free conditions using aqueous methanol. We believe that this method is superiour over the reported methods for the synthesis of highly useful intermediate semicarbazones.

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