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Short Report

Eco-Friendly, Catalyst and Solvent-Free, Synthesis of Acetanilides and *N*-Benzothiazole-2-yl-acetamides

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An expeditious and green synthesis of acetamides in a solvent-free simple way is described, without catalyst or additives, and in good yield by an instantaneous reaction of anilines or 2-aminothiazoles and acetic anhydride without external heating, and with simple purification. Sixteen substituted acetanilides and four *N*-benzothiazole-2-yl-acetamides were formed, but aliphatic amines of low molecular weight were not as effective as aromatic ones, and only cyclohexylamine and the enaminone ethyl 3-amino-2-butenoate afforded the corresponding acetamides in good yield.

Keywords: acetylation, acetamides, amides, solvente-free reaction, green chemistry

Introduction

In the modern synthetic chemistry the development of greener approaches to the functional group transformations is of continuous interest.[1] There are several ongoing efforts to develop methods which do not need solvent, additives, and without tedious purification. Even reactions carried out without heating and magnetic stirring are relevant contributions, due to the energy economy aspects.[2]

The acetamide/acetanilide are functional groups whose importance is beyond of a simple protecting group. For instance, in medicinal chemistry they play a pivotal role affording chemically stable compounds as prodrugs with improved pharmacological profile, and many *N*-acylated derivatives are in clinical use.[3] On the other hand, acetanilides have natural aptitude to act as *ortho* directing group in C–H transformations to C–C bond formation, wherein functionalized benzophenone,[4] quinone,[5] bisphenyl,[6] or styrene[7,8] derivatives can be obtained by Pd or Rh catalysis, Figure 1. Besides, the reactivity of some *ortho* functional group of acetanilides is modulated by the presence of the *N*-acetyl moiety, which is thus selectively converted to more complex compound, constituting this kind of acetanilide into important synthetic intermediates.[5,9-13]

Due to the abovementioned applications, new developments in the acetylation procedure are still desirables, and representative contributions are described, Figure 2.[14-24] Furthermore, in undergraduate courses, the parent acetanilide is extensively synthesized as classical preparation of aromatic amide.[25] Therefore, we recently developed a practical solvent-free green synthesis of such compound to experimental courses.[26] However, a search in the literature revealed that when other substituted acetanilides are needed as starting material in the context of a research project, the preparation used is very similar to that of parent acentanilide, which is almost the same of one century ago, which uses large amounts of solvents and additives such as acetic acid and sodium acetate, for instance.[5-15,19-24]

It should be pointed out that, although there are a few syntheses of acetanilides in the absence of solvent, it is always necessary the use of grinding or microwave heating in these previously described syntheses or, more recurrent, the use of catalyst such as morpholinium bisulfate, zirconyl triflate, tris(pentaflurophenyl)borate, anatase phase TiO_2 nanoparticles, or even the unconventional rice husk ash, Figure 2.[24] Despite that solvent-free catalyst's dependent approaches represent important contribution, more environmentally friendly procedures which reduce the use of chemicals and energy is still needed.

With these scenarios in mind, the solvent-free condition could be useful in the acetylation of more complex amines. In this way, we present herein a solvent-free synthesis of several acetanilides and acetamides, including heterocyclic examples, which do not involve the use of any catalyst and additive, and with practical isolation and purification

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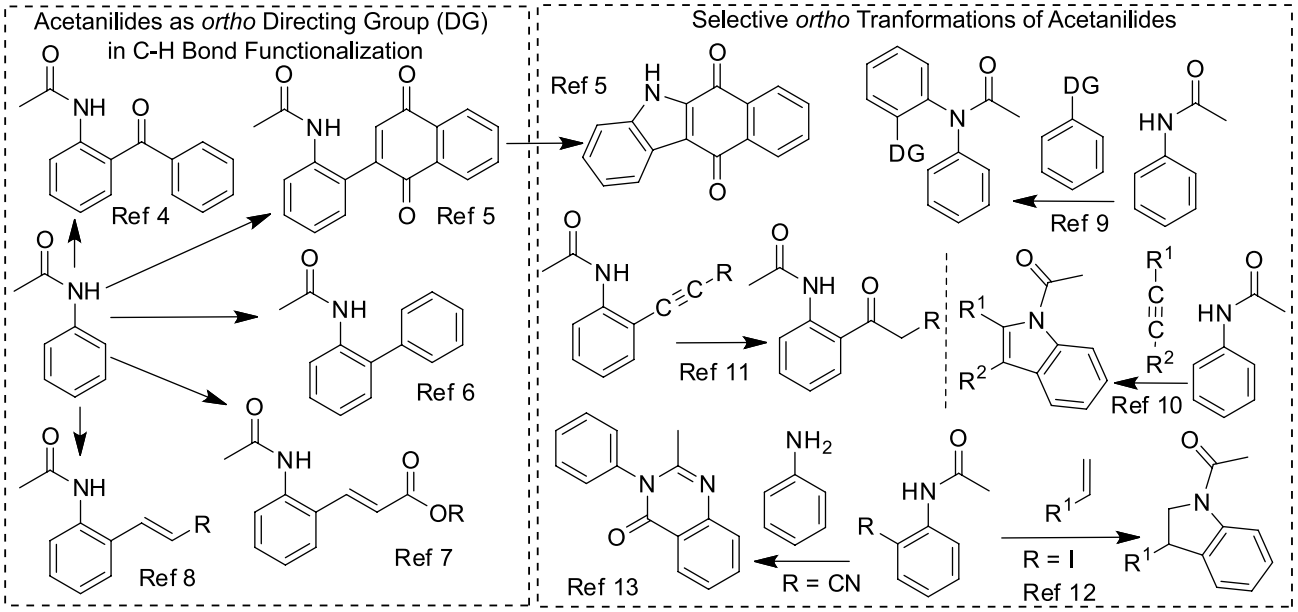


Figure 1. Representative synthetic applications of acetanilides.

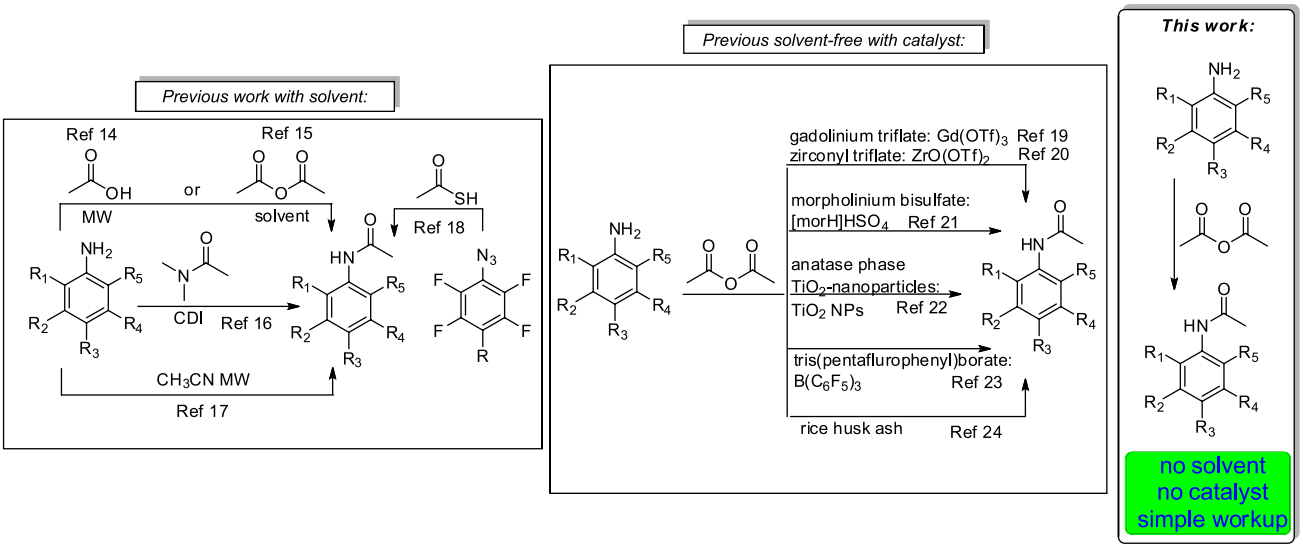


Figure 2. Selected recent syntheses of acetanilides.

steps, being a green practical alternative to the current preparations. Thus, the search for an environmental benign protocol to acetamides synthesis prompted us to try the reaction of several aromatic amines using only acetic anhydride, without any solvent or additive, Scheme 1.

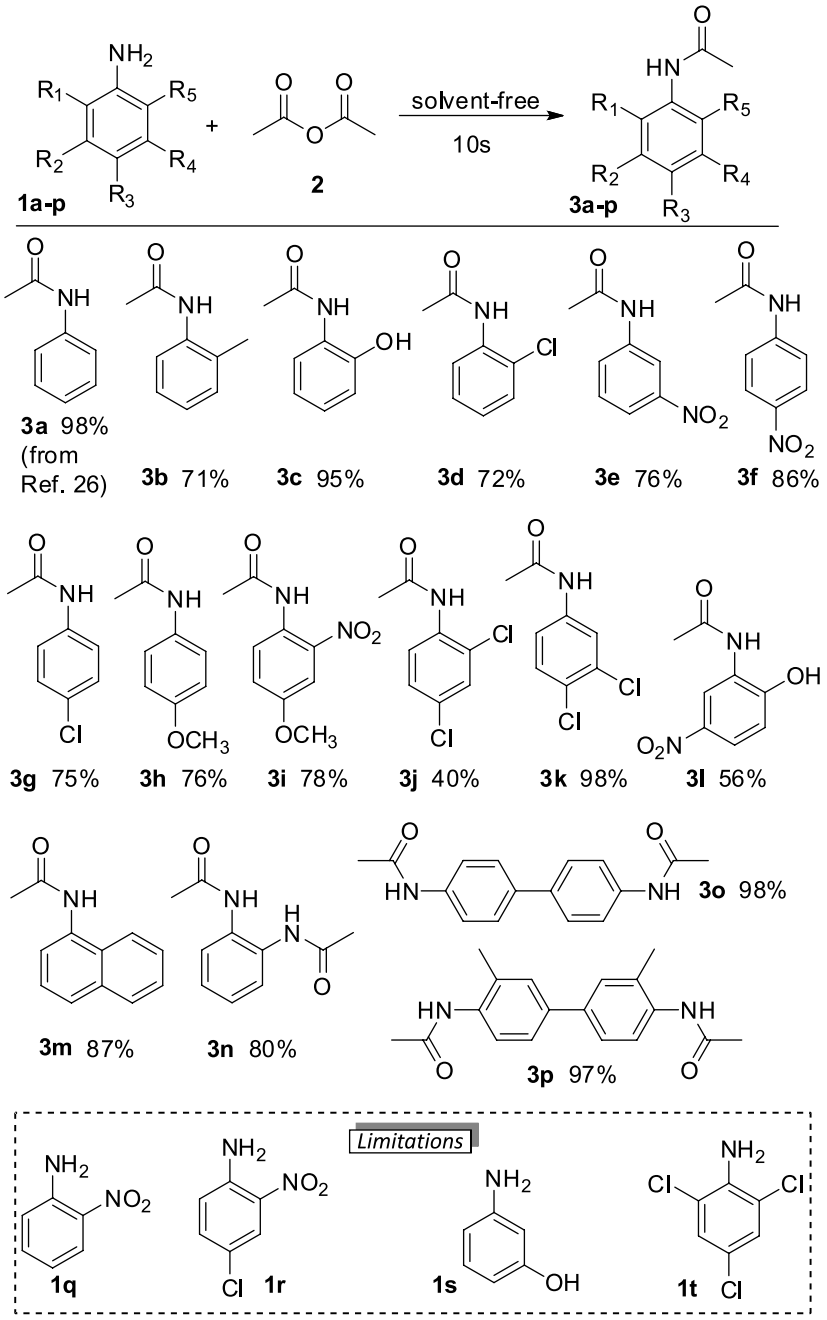
Results and Discussion

The search for environmental benign protocol to acetamides synthesis prompted us to try the reaction of several aromatic amines using only acetic anhydride, without any solvent or additive, Scheme 1.

As already mentioned, aniline **1a** afforded acetanilide **3a** in almost quantitative yield.[26] More importantly, several solid and liquid substituted aromatic amines were reactive under this catalyst and solvent-free condition, and afforded the corresponding known acetanilides[27] in an instantaneous reaction (for practical reason, the reaction time of 10 s was established), and some trends emerged from the results, Scheme 1. Thus, anilines *ortho*, *meta* and *para* substituted were tolerated (see acetanilides **3a**-**h**), but the presence of a strong electron-withdrawing group at *ortho* position precludes amide formation even under conventional

(90 °C, 24 h) or microwave heating (90 °C, 10 min), and the starting amine was recovered, as indicated for **1q** in the "Limitations" of Scheme 1. Probably, the association of the strong electron-withdrawing character of nitro group, and the steric hindered environment in the *ortho* position should preclude acetylation. However, the presence of such group was tolerated in anilines with at least one electron-releasing group at the aromatic ring (compare **3i** and **1r**). Chemioselective *N*-acetylation in the presence of OH group was observed to anilines **1c** and **1l**, albeit in modest yield to this latter. The low yield of **3l** in relation to **3c** should be due to the 1,4-relationship between hydroxyl and nitro substituents, which may increase the intensity of the intramolecular hydrogen bonding between *ortho* positioned groups $H_2N\cdots HO$, and thus decrease the nucleophilicity of the amino group. However, amine **1s** did not afford the corresponding acetanilide, being recovered. This fact is in contrast with the work of Pahari and co-workers,[17] which successfully synthesized the corresponding acetanilide of 3-hydroxy-aniline using acetonitrile as acylating reagent.

The presence of two moderated electron-withdrawing groups in the aromatic ring was possible, but yield was



Scheme 1. Scope of prepared acetanilides.

decreased when one such group is *ortho* positioned (compare **3j** and **3k**), and acetanilide was not formed with **1t**. Furthermore, naphthylamine and bisamines were very effective in this transformation, once that acetanilides **3m**-**p** were isolated in excellent yields, Scheme 1.

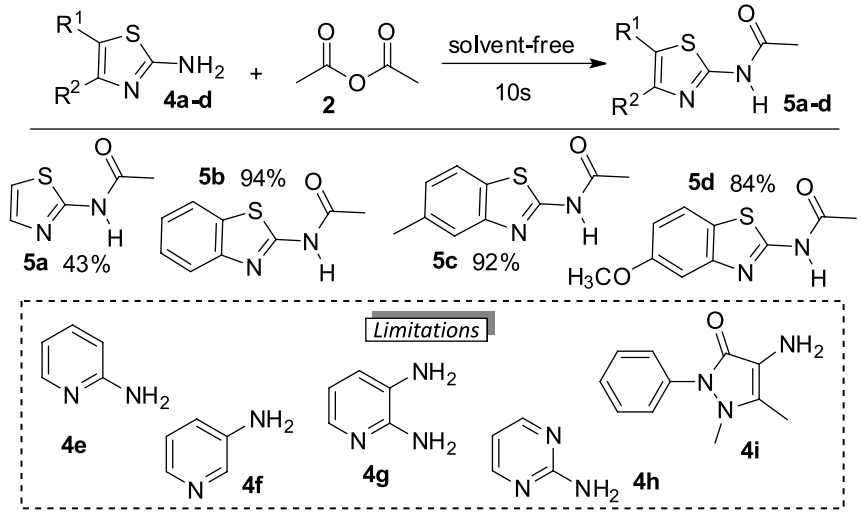
To expand the potential of developed catalyst-free and solventless acetamide synthesis, a representative set of heterocyclic amines were evaluated, Scheme 2. In this way, when 2-aminothiazole was reacted with acetic anhydride, *N*-thiazole-2-yl-acetamide **5a** had formed in same modest yield described in the literature.[14] To our delight, under the solvent-free condition, known *N*-benzothiazole-2-yl-acetamides **5b**-**c** were obtained in excellent yields.[14,28] However, with other heterocyclic amines indicated in Scheme 2, no amide formation was detected, and the amines were recovered. For 2-aminopyridine **4e**, microwave heating (90 °C, 1 min) was also inefficient.

Contrary to aromatic amines indicated in the present study, the catalyst-free and solventless condition was not effective to butylamina **6a** and ethylamine **6b**. Considering the low boiling points of amines **6a** (78 °C) and **6b** (16.6 °C) as compared to cyclohexylamine **6c** (134 °C), and the observed exothermic dissolution in acetic anhydride, amines **6a**-**b** should be volatilized under open flask reaction condition. Therefore only with **6c** the acetylation afforded **7** in 77% yield, Scheme 3.[29]

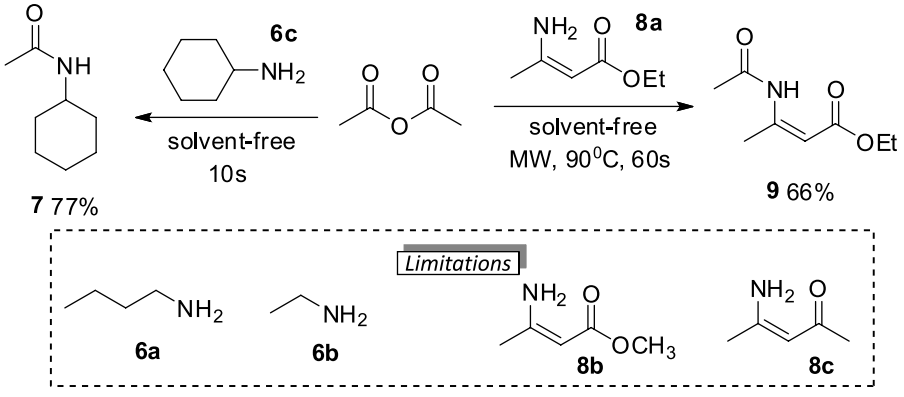
In a complementary way, due to our interest in the synthetic applications of enaminones as building block to heterocycles,[30] representative compounds **8a**-**c** were tentatively acetylated, but no reaction was observed at room temperature. Hence, microwave heating was applied, which allowed exclusive formation of *N*-acylated enaminone **9** from ethyl 3-amino-2-butenoate **8a** in yield improved when compared to that previously obtained with acid chloride.[31] However, here again, no reaction was observed to enaminones **8b**-**c**, Scheme 3.

Conclusions

We developed a fast, practical solvent-free, and eco-



Scheme 2. Heterocyclic acetamides.



Scheme 3. Acetylation of alkyl amines and enaminone.

friendly alternative protocol to access synthetically and biological important acetanilides in good yields, whereby substitution at aromatic ring was tolerated, including bisamines, and the substrate scope could be extended to *N*-benzothiazole-2-yl-acetamides in a simple way. In contrast of current methods, no additive or catalyst was necessary, being the greener approach of the investigated *N*-acetylation.

Experimental

Melting points were determined on a Microquímica MQAPF 301 hot plate apparatus and are uncorrected. Infrared spectra were recorded as KBr discs on Shimadzu IR Affinity-1 instrument. Nuclear magnetic resonance (NMR) spectra were obtained for ^{1}H at 500 MHz and for ^{13}C at 125 MHz using a Bruker Avance III 500 spectrometer. Chemical shifts are reported in ppm units downfield from reference (internal TMS or residual deuterated solvent). Microwave heating reactions were performed in a CEM Discover SP using the 10 mL Pyrex pressure vial for closed vessel reactions, under the indicated power automatically to reach and maintain the set temperature, specified in each case, with infrared (IR) temperature control and medium stirring speed using cylindrical stir bars (10 × 3 mm), default ramp time of 10 minutes. When the reaction was done in under microwave heating, this is indicated.

General procedure for the synthesis of acetamides **3a-p**, **5a-d**, and **7**

To a 10 mL round bottom flask was added 0.5 mmol of the amine and 0.1 mL of acetic anhydride. The reaction is instantaneous and exothermic, and after 10 s the solid product formed was filtered and washed with cold water. When no solid was immediately formed, 4 mL of cold water was added, and the mixture allowed standing in a refrigerator for 24 h, leading to precipitation. To all synthesized acetamides, measured physical data were in agreement to the reported values.[17-19,27,31,32]

N-(*o*-Tolyl)acetamide (**3b**)

White solid, 51.5 mg, 71% yield; m.p. 108.4-109.0 °C (Lit.[27] 108-109 °C); IR (KBr) ν / cm^{-1} 3291, 1647, 1587, 1527, 1458, 1369, 1271, 1116, 1039, 933, 854, 756, 698, 651, 607; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.19 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 7.10 (t, 1H, *J* 7.5 Hz, CH), 7.21 (t, 1H, *J* 8.0 Hz, CH), 7.71 (d, 1H, *J* 8.0 Hz, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.8, 24.2, 123.7, 125.4, 126.7, 129.7, 130.5, 135.6, 168.6.

N-(2-Hydroxyphenyl)acetamide (**3c**)

Brown solid, 98.6 mg, 95% yield; m.p. 206.5-207.4 °C (Lit.[27] 207 °C); IR (KBr) ν / cm^{-1} 3402, 3084, 1658, 1595, 1544, 1456, 1369, 1330, 1284, 1242, 1201, 1107, 1039, 842, 765, 667; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.28 (s, 3H, CH_3), 6.73 (td, 1H, *J* 8.0, 1.5 Hz, CH), 6.83 (dd, 1H, *J* 8.0, 1.5 Hz, CH), 6.93 (td, 1H, *J* 8.0, 1.5 Hz, CH), 7.44 (dd, 1H, *J* 8.0, 1.0 Hz, CH), 9.27 (brs, 1H, NH), 9.7 (brs, 1H, OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 24.1, 116.4, 119.4, 122.8, 125.1, 126.9, 148.3, 169.5.

N-(2-Chlorophenyl)acetamide (**3d**)

White solid, 60.3 mg, 72% yield; m.p. 87.9-88.1 °C (Lit.[27] 87.9-88.5 °C); IR (KBr) ν / cm^{-1} 3244, 3043, 1662, 1589, 1533, 1473, 1438, 1367, 1301, 1126, 1060, 1033, 966, 941, 848, 754, 725, 696, 648; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 3H, CH_3), 7.04 (tl, 1H, *J* 8.0 Hz, CH), 7.26 (td, 1H, *J* 8.5, 1.0 Hz, CH), 7.35 (dd, 1H, *J* 8.0, 1.0 Hz, CH), 7.71 (brs, 1H, NH), 8.32 (dl, 1H, *J* 8.0 Hz, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8, 121.8, 122.7, 124.7, 127.7, 129.0, 130.5, 134.6, 168.4.

N-(3-Nitrophenyl)acetamide (**3e**)

Yellow solid, 67.5 mg, 76% yield; m.p. 150.8-151.4 °C (Lit.[27] 152-153 °C); IR (KBr) ν / cm^{-1} 3304, 3261, 3194, 3130, 3095, 1674, 1645, 1598, 1550, 1529, 1477, 1425, 1369, 1350, 1325, 1294, 1261, 1163, 1078, 1016, 983, 887, 823, 808, 742, 711, 603; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.26 (s, 3H, CH_3), 7.52 (t, 1H, *J* 8.5 Hz, CH), 7.56 (brs, 1H, CH), 7.99-7.97 (m, 2H, CH), 8.37 (brs, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6, 114.4, 118.9, 125.4, 129.9, 138.9, 168.6.

N-(4-Nitrophenyl)acetamide (**3f**)

Yellow solid, 76.5 mg, 86% yield; m.p. 212.9-213.9 °C (Lit.[27] 212-213 °C); IR (KBr) ν / cm^{-1} 3302, 3277, 1683, 1618, 1597, 1568, 1504, 1404, 1348, 1332, 1303, 1269, 1178, 1112, 1006, 848, 750, 686, 601; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 3H, CH_3), 7.44 (brs, 1H, NH), 7.69 (d, 2H, *J* 9.0 Hz, CH), 8.21 (d, 2H, *J* 9.0 Hz, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8, 118.9, 125.1, 143.6. 168.7.

N-(4-Chlorophenyl)acetamide (**3g**)

Gray solid, 62.4 mg, 75% yield; m.p. 177.3-177.8 °C (Lit.[27] 177-178.5 °C); IR (KBr) ν / cm^{-1} 3304, 3263, 3192, 1670, 1608, 1541, 1489, 137, 1315, 1236, 1170, 1089, 1008, 821, 750, 707; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.20 (s, 3H, CH_3), 7.22 (brs, 1H, NH), 7.30 (d, 2H, *J* 8.5 Hz, CH), 7.47 (d, 2H, *J* 8.5 Hz, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6, 121.0, 129.0, 136.1, 168.2.

N-(4-Methoxyphenyl)acetamide (**3h**)

Gray solid, 61.6 mg, 76% yield; m.p. 126.2-127.3 °C (Lit.[27] 126-128 °C); IR (KBr) ν / cm^{-1} 3444, 1651, 1604, 1562, 1512, 1465, 1411, 1369, 1319; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.1 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.86 (d, 2H, *J* 8.5 Hz, CH), 7.40 (d, 2H, *J* 8.5 Hz, CH), 7.49 (brs, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.3, 55.5, 114.1, 122.0, 131.0, 156.4, 168.4.

N-(4-Methoxy-2-nitrophenyl)acetamide (**3i**)

Yellow solid, 80.4 mg, 78% yield; m.p. 117.8-118.9 °C (Lit.[27] 118 °C); IR (KBr) ν / cm^{-1} 3475, 1705, 1627, 1581, 1512, 1458, 1365, 1319, 1288, 1249, 1149, 1072, 1033, 921, 871, 844, 790, 759, 632; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.26 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.64 (s, 1H, CH), 7.22 (d, 1H, *J* 8.5 Hz, CH), 8.62 (d, 1H, *J* 8.5 Hz, CH), 10.02 (brs, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 55.9, 108.5, 123.4, 123.9, 128.5, 154.9, 168.8.

N-(2,4-Dichlorophenyl)acetamide (**3j**)

Gray solid, 40.1 mg, 40% yield; m.p. 143.6-144.7 °C (Lit.[27] 144-145 °C); IR (KBr) ν / cm^{-1} 3456, 1666, 1585, 1523, 1473, 1384, 1300, 1253, 1145, 1099, 1056, 1010, 964, 945, 860, 817, 767, 690, 663; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.2 (s, 3H, CH_3), 7.22 (dd, 1H, *J* 8.5, 2.0 Hz, CH), 7.36 (d, 1H, *J* 2.0 Hz, CH), 7.56 (brs, 1H, NH), 8.31 (d, 1H, *J* 7.5 Hz, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8, 122.4, 127.9, 128.7, 133.4, 168.2.

N-(3,4-Dichlorophenyl)acetamide (**3k**)

Brown solid, 98.4 mg, 98% yield; m.p. 122.4-123.4 °C (Lit.[27] 121.9-123.3 °C); IR (KBr) ν / cm^{-1} 3417, 1666, 1589, 1531, 1473, 1388, 1365, 1307, 1257, 1126, 1014, 871, 813, 721, 678, 609; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (s, 3H, CH_3), 7.29-7.35 (m, 2H, CH), 7.66 (brs, 1H, CH), 7.72 (brs, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.5, 119.1, 121.6, 127.5, 130.5, 132.8, 137.4, 168.7.

N-(2-Hydroxy-5-nitrophenyl)acetamide (**3l**)

Brown solid, 54.9 mg, 56% yield; m.p. 270.2-271.3 °C (Lit.[27] 271-272 °C); IR (KBr) ν / cm^{-1} 3417, 1658, 1589, 1539, 1500, 1423, 1334, 1292, 1080, 1026, 945, 894, 821, 748, 682, 640; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.12 (s, 3H, CH_3), 6.99 (d, 1H, *J* 9.0 Hz, CH), 7.86 (dd, 1H, *J* 9.0, 2.5 Hz, CH), 8.90 (d, 1H, *J* 2.5 Hz, CH), 9.41 (brs, 1H, NH), 11.50 (brs, 1H, OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 24.3, 108.7, 113.5, 113.6, 115.1, 116.9, 120.9, 127.3, 139.6, 134.2, 169.8.

N-(Naphthalen-1-yl)acetamide (**3m**)

Purple solid, 80.1 mg, 87% yield; m.p. 158.8-159.5 °C (Lit.[27] 159-160 °C); IR (KBr) ν / cm^{-1} 3429, 1654, 1546, 1504, 1427, 1342, 1280, 1018, 960, 775, 721, 605; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 3H, CH_3), 7.39-7.48 (m, 3H, CH), 7.67 (dl, 1H, *J* 8.0 Hz, CH), 7.77-7.8 (m, 4H, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.1, 121.0, 121.6, 125.6, 125.9, 126.0, 128.6, 134.1, 169.2.

N,N'-(1,2-Phenylene)diacetamide (**3n**)

Brown solid, 75.2 mg, 80% yield; m.p. 188.3-189.1 °C (Lit.[27] 188.2-188.7 °C); IR (KBr) ν / cm^{-1} 3232, 3024, 1666, 1610, 1535, 1462, 1367, 1313, 1111, 1035, 972, 765, 713, 680, 605; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.08 (s, 6H, CH_3), 7.14-7.17 (m, 2H, CH), 7.27-7.29 (m, 2H, CH), 8.44 (brs, 2H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7, 125.5, 126.1, 130.6, 169.9.

N,N'-([1,1'-Biphenyl]-4,4'-diyl)diacetamide (**3o**)

Gray solid, 131.1 mg, 98% yield; m.p. 326.2-326.7 °C (Lit.[27] 325 °C); IR (KBr) ν / cm^{-1} 3290, 1658, 1597, 1577, 1519, 1396, 1365, 1319, 1284, 1176, 1111, 1006, 817, 752, 663; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.30 (s, 6H, CH_3), 7.42 (d, 4H, *J* 8.5 Hz, CH), 7.50 (d, 4H, *J* 8.5 Hz, CH), 9.28 (brs, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.7, 115.4, 115.5, 120.2, 126.8, 127.3, 127.7.

N,N'-(3,3'-Dimethyl-[1,1'-biphenyl]-4,4'-diyl)diacetamide (**3p**)

Gray solid, 143.6 mg, 97% yield; m.p. 313.1-314.3 °C (Lit.[27] 312 °C); IR (KBr) ν / cm^{-1} 3278, 1654, 1649, 1583, 1516, 1490, 1431, 1365, 1317, 1284, 1128, 1039, 1018, 950, 867, 819, 709, 659, 613; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.06 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 7.40 (dl, 1H, *J* 8.0 Hz, CH), 7.47 (m, 2H, CH), 9.29 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.5, 23.8, 124.3, 125.6, 128.7, 132.1, 136.2, 136.7, 168.7.

N-(Thiazol-2-yl)acetamide (**5a**)

Yellow solid, 61.0 mg, 43% yield; m.p. 201.7-202.1 °C (Lit.[28] 202-203 °C), IR (KBr) ν / cm^{-1} 3448, 1689,1566, 1427, 1369, 1296, 1230, 1168, 1068, 1041, 995, 972, 875, 821, 779, 709, 659, 628; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H, CH_3), 6.99 (d, 1H, *J* 3.5 Hz, CH), 7.44 (d, 1H, *J* 3.5 Hz, CH), 12.58 (brs, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.1, 135.0, 136.1, 160.3, 168.1.

N-(Benzothiazol-2-yl)acetamide (**5b)**

White solid, 90.2 mg, 94% yield; m.p. 182.3-183.2 °C (Lit.[28] 182-183 °C), IR (KBr) ν / cm^{-1} 3448, 1693, 1604, 1546, 1446, 1369, 1269, 1076, 1049, 999, 860, 759, 725, 675, 628; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (s, 3H, CH_3), 7.33 (t, 1H, *J* 7.5 Hz, CH), 7.46 (t, 1H, *J* 7.5 Hz, CH), 7.77

(d, 1H, *J* 8.0 Hz, CH), 7.85 (d, 1H, *J* 8.0 Hz, CH), 11.44 (brs, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.5, 120.4, 121.6, 124.1, 126.4, 131.9, 147.8, 159.7, 168.8.

N-(6-Methylbenzothiazol-2-yl)acetamide (**5c**)

White solid, 94.8 mg, 92% yield; m.p. 224.3-224.7 °C (Lit.[28] 225 °C); IR (KBr) ν / cm^{-1} 3196, 1691, 1606, 1541, 1460, 1365, 1288, 1267, 1247, 1224, 1041, 993, 873, 812, 723, 657; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.26 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 7.25 (d, 1H, *J* 8.5 Hz, CH), 7.63 (s, 1H, CH), 7.64 (d, 1H, *J* 8.5 Hz, CH), 11.90 (brs, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 23.5, 119.9, 121.5, 127.9, 132.0, 134.1, 145.6, 159.3, 168.8.

N-(6-Methoxybenzothiazol-2-yl)acetamide (**5d**)

Brown solid, 93.2 mg, 84% yield; m.p. 229.1-229.7 °C (Lit.[28] 228-229 °C); IR (KBr) ν / cm^{-1} 3406, 1689, 1604, 1550, 1477, 1438, 1369, 1284, 1265, 1215, 1060, 1029, 898, 848, 813, 725, 702, 624; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (s, 3H, CH_3), 3.87(s, 3H, OCH_3), 7.04 (d, 1H, *J* 8.0 Hz, CH), 7.30 (s, 1H, CH), 7.64 (d, 1H, *J* 8.0 Hz, CH), 10.21 (brs, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.4, 55.9, 104.4, 115.3, 121.1, 133.3, 142.2, 156.9, 168.1.

N-Cyclohexylacetamide (**7**)

White solid, 54.4 mg, 77% yield; m.p. 101.5-102.3 °C (Lit.[32] 101-103 °C); IR (KBr) ν / cm^{-1} 3288, 3088, 2931, 2852, 1714, 1643, 1633, 1556, 1446, 1373, 1315, 1255, 1153, 1129, 981, 891, 736, 607, 551; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05-1.15 (m, 3H, CH_2), 1.26-1.35 (m, 2H, CH_2), 1.56-1.60 (m, 1H, CH_2), 1.65-1.69 (m, 2H, CH_2), 1.85-1.90 (m, 2H, CH_2), 1.92 (s, 3H, CH_3), 3.67-3.73 (m, 1H, CH_2), 5.89 (brs, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.5, 24.9, 25.5, 33.1, 48.2, 169.2.

Synthesis of ethyl (*Z*)-3-acetamidobut-2-enoate (**9**)

To a 10 mL Pyrex pressure vial for closed vessel for microwave heating reaction, was added 0.5 mmol of the enaminone **6a** and 0.1 mL of acetic anhydride. The mixture was subjected to heating in a CEM Discover SP reactor at 90 °C and 200 W for 1 minute, with IR temperature control and medium stirring speed using cylindrical stir bars (10 × 3 mm), default ramp time of 10 min. After this time, the mixture was cooled to room temperature and then 4 mL of distilled water was added. After cooling in the refrigerator the solid product was filtered and washed with cold water, resulting in 56.6 mg of white crystals of **9**, 66% yield; m.p. 61.8-62.2 °C (Lit[31] 63-65 °C); IR (KBr) ν / cm^{-1} 3224, 3074, 2978, 2929, 1712, 1639, 1500, 1475, 1440, 1385, 1274, 1288, 1176, 1064, 1029, 983, 839, 783, 663, 605; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.87 (d, *J* 1.0 Hz, NH), 4.14 (q, 2H, *J* 7.0 Hz, CH_2), 2.36 (d, 3H, *J* 1.0 Hz, CH_3), 2.12 (s, 3H, CH_3), 1.26 (t, *J* 7.0 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 21.8, 25.2, 59.8, 96.4, 155.0, 168.9, 169.2.

Supplementary Information

Supplementary information (IR, ^{1}H NMR and ^{13}C NMR spectra for **3a**-**q**, **5a**-**d**, and **9**) is available free of charge at http://jbcs.sbq.org.br as PDF file.

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