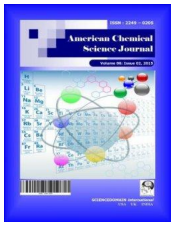

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Electronic Effect of Substituents Present on Carbonyl Compounds: Analysis of Product Formation in One-Pot Synthesis of 1, 3, 4-thiadiazole Ring

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Authors' contributions

This work was carried out in collaboration between all authors. Author SBM carried out the synthesis, characterization and wrote the first draft. Author RRK designed the scheme and the protocol for synthetic pathway and wrote the final draft. Authors GYM and MNK did the crystallographic studies and collection of the data. All authors read and approved the final manuscript.

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ABSTRACT

Functionalized N-(4-acetyl-5-substituted-4, 5-dihydro-[1, 3, 4]-thiadiazol-2-yl)-acetamides (2a-m) were synthesized by three-fold condensation of carbonyl compound, thiosemicarbazide and acetic anhydride in an one pot three component reaction. In this reaction substituents on carbonyl compounds have played a key role in yield of the product formation. Carbonyl compounds with either electron withdrawing or electron releasing substituents have formed better percentage of products than un-substituted and sterically hindered compounds.

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Keywords: Electron donating; electron withdrawing; multicomponent reaction; 1, 3, 4-thiadiazoles; electronic effect; one pot; three components; XRD; Cyclization.

1. INTRODUCTION

1, 3, 4-Thiadiazole moiety is of great importance to chemists as well as biologists as it is found in a large variety of naturally occurring compounds and also in pharmacologically potent molecules. These heterocycles have been known to exhibit broad spectrum of activities such as anti-proliferative, anti-tuberculosis, anti-inflammatory and antimicrobial [1-5]. There are several reports of synthesis of 1,3,4-thiadiazole derivatives from carbonyl compounds [6-8] but these methods involve multi-steps and vigorous reaction conditions. In multicomponent condensation reactions (MCRs) products are formed in a single step and diversity can be achieved by simply varying each component. Hence these reactions have recently been discovered to be powerful methods for the synthesis of organic compounds [9-11].

In view of the above, in this communication we are reporting the synthesis and electronic effect of substituents of carbonyl compounds on formation of functionalized 1, 3, 4-thiadiazole derivatives (2a-m) by multi component approach.

2. EXPERIMENTAL SECTION

2.1 Chemical and Analytical Methods

Melting points were determined in an open capillary and were uncorrected. Chemical names follow IUPAC nomenclature. CHN analysis was done on LECO (USA) CHNS determinator, IR spectra were recorded on Nicolet 6700 (USA) FT-IR spectrophotometer using KBr pellets. ^{1}H and C^{13} NMR spectra were recorded on a Varian (USA) FT-NMR spectrometer in DMSO-d_6/$CDCl_3$ with TMS as an internal standard. Chemical shifts are given in parts per million (ppm). Mass spectra were recorded on a GCMS Shimadzu (Japan). Single crystal X-ray diffraction study was performed on smart apex II Bruker (Germany) diffractometer. All the reagents and solvents used were of analytical grade and were purchased from S. D. Fine, Mumbai (India). TLC was performed on silica gel coated plates for monitoring the reactions.

2.2 General procedure for synthesis of N- (4-acetyl-5-substituted 4, 5-dihydro- [1.3.4] thiadiazol-2-yl-acetamide (2a-m)

A mixture of compound (1a-m) (0.005 mol), acetic anhydride (4.0 mL) and thiosemicarbazide (0.005 mol) were heated at 80-90°C for 2 hrs. The reaction mixture was cooled to room temperature and then poured into ice cold water. The precipitate obtained was filtered off, washed with water, dried and purified by recrystallization in an aqueous alcohol to get the pure crystals of the title compounds (2a-m) (Scheme 1).

2.3 Spectral Characterization Data

2.3.1 N-(4-Acetyl-5-ethyl-5-methyl-4, 5-dihydro-[1, 3, 4] thiadiazol-2-yl)acetamide (2b)

Color: Pale yellow crystals; IR (KBr): 3324 (N-H), 1644(C=O, 1624 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.93 (t, 3H, -CH_2-CH_3), 1.93 (s, 3H, CH_3-), 2.15 (s, 3H, $NCOCH_3$), 2.12 (s, 3H, $NHCOCH_3$), 2.53 (q, 2H, CH_2-CH_3), 11.67 (s, 1H, $NHCOCH_3$, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): *δ* 22.67, 22.42 ($COCH_3$), 15.10 (CH_3-CH_2-), 28.44 (CH_3-), 36.32 (CH_3-CH_2), 76.12 (C-5 of thiadiazolidine); 142.25 (C=N), 168.10($COCH_3$), 169.14 ($NHCOCH_3$). MS m/z: 229 $[M+H]^+$.Anal. Calcd. for $C_9H_{15}N_3O_2S$: C, 47.14; H, 6.59; N, 18.33. Found: C, 47.24; H, 6.54; N, 18.20%.

2.3.2 N-[4-Acetyl-5-(2-chlorophenyl)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]acetamide, (2e)

Color: Pale yellow crystals; IR (KBr): 3229 (N-H), 1650 (C=O), 1625 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.22(s, 3H, $NHCOCH_3$), 2.27 (s, 3H, $NCOCH_3$), 6.88 (s, 1H, C-5- H of thiadiazolidine)), 7.28-7.50 (m, 4H, Ar-H), 11.83 (s, 1H, $NHCOCH_3$, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): *δ* 21.74, 22.33 ($COCH_3$), 63.73 (C-5 of thiadiazolidine).125.47, 127.65, 129.81, 130.65, 137.61, 146.12 (Ar-C), 158.99 (C=N), 168.34, 169.54 ($COCH_3$). MS m/z: 298 $[M+H]^+$; Anal. Calcd. for $C_{12}H_{12}N_3ClO_2S$: C, 48.40; H, 4.06; N, 14.11. Found: C, 48.23; H, 3.98; N, 14.07%.

2.3.3 N-[4-Acetyl-5-(4-fluorophenyl)-4, 5-dihydro-[1, 3, 4]thiadiazol-2-yl]acetamide (2f):

Color: Pale yellow crystals; IR (KBr); 3233 (N-H), 1646 (C=O), 1626 (C=N); ^{1}H NMR (300 MHz,$CDCl_3$): δ 2.11 (s, 3H, NHCOC$\underline{H}_3$), 2.24 (s, 3H, NCOC$\underline{H}_3$), 6.50 (s, 1H, $\underline{C}$-5 H of thiadiazolidine), 6.85-7.57 (m, 4H, Ar-$\underline{H}$), 11.77 (s, 1H, N$\underline{H}$, D_2O exchangeable); ^{13}C NMR (300 MHz, DMSO-d_6): *δ* 21.69, 22.31 (CO$\underline{C}$H$_3$), 71.89 ($\underline{C}$-5 of thiadiazolidine).128.47, 117.75, 159.82, 136.42 (Ar-$\underline{C}$), 159.11 ($\underline{C}$=N), 168.38($\underline{C}$OCH$_3$), 169.34 (NH$\underline{C}$OCH$_3$).MS m/z: 282 $[M+H]^+$; Anal. Calcd. for $C_{12}H_{12}N_3FO_2S$: C, 51.24; H, 4.30; N, 14.94. Found: C, 51.13; H, 4.26; N, 14.87%.

2.3.4 N-(4-Acetyl-5-propyl-4, 5-dihydro-[1, 3, 4]thiadiazol-2-yl)acetamide (2g):

Color: Pale yellow crystals; IR (KBr); 3330 (N-H), 1638 (C=O), 1621 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6); δ 0.97 (t, 3H, C$\underline{H}_3$-(CH$_2$)$_2$-), 1.28-1.31 (m, 2H, CH$_3$-C$\underline{H}_2$-CH$_2$-), 1.95 (q, 2H, CH$_3$-CH$_2$- C$\underline{H}_2$-**),** 2.12 (s, 3H, NHCOC$\underline{H}_3$), 2.17 (s, 3H, NCOC$\underline{H}_3$), 6.25 (s, 1H, $\underline{C}$-5 $\underline{H}$ of thiadiazolidine), 11.52 (s, 1H, N$\underline{H}$COCH$_3$, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): *δ* 22.55, 22.35 (CO$\underline{C}$H$_3$), 22.12 (C$\underline{H}_3$-(CH$_2$)$_2$-), 26.12(CH$_3$-C$\underline{H}_2$-CH$_2$-), 43.12 (CH$_3$-CH$_2$- C$\underline{H}_2$-**),** 78.12 ($\underline{C}$-5 of thiadiazolidine); 143.15 ($\underline{C}$=N), 168.20($\underline{C}$OCH$_3$), 169.24 (NH$\underline{C}$OCH$_3$). MS m/z: 229 $[M+H]^+$; Anal. Calcd. for $C_9H_{15}N_3O_2S$: C, 47.14; H, 6.59; N, 18.33. Found: C, 47.20; H, 6.46; N, 18.30%.

2.3.5 N-(1-Acetyl-4-thia-1,2-diaza-spiro[4,4]non-2-en-3-yl)acetamide (2i)

Color: Pale yellow crystals; IR (KBr); 3298(N-H), 1652(C=O), 1628(C=N); ^{1}H NMR (300MHz, DMSO-d_6); δ 1.61 (q, 4H, 2C$\underline{H}_2$-of cyclopentyl), 2.13 (s, 3H,NCOC$\underline{H}_3$), 2.29 (s, 3H,NHCOC$\underline{H}_3$), 2.40 (t, 4H, 2C$\underline{H}_2$-of cyclopentyl), 11.81 (s, 1H, N$\underline{H}$COCH$_3$, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) *δ*: 22.55, 22.35 (CO$\underline{C}$H$_3$), 24.44, 40.00 (C$\underline{H}_2$-of cyclopentyl), 79.42 ($\underline{C}$-5 of thiadiazolidine); 142.15 ($\underline{C}$=N), 168.22 ($\underline{C}$OCH$_3$), 169.11 (NH$\underline{C}$OCH$_3$). MS m/z: 242 $[M+H]^+$; Anal. Calcd. for $C_{10}H_{15}N_3O_2S$: C, 49.77; H, 6.27; N, 17.41. Found: C, 49.62; H, 6.30; N, 17.29 %.

2.3.6 N-(1-Acetyl-4-thia-1,2-diazaspiro[4.5]dec-2-en-3-yl)acetamide (2j):

Color: Pale yellow crystals; IR (cm^{-1}): 3290 (N-H), 1657(C=O), 1620 (C=N); ^{1}H NMR (500MHz, DMSO-d_6): δ 1.19-1.93 (m, 8H, C$\underline{H}_2$- of cyclohexyl), 2.85 (t, 2H, C$\underline{H}_2$-of cyclohexyl), 2.02 (s, 3H,NCOC$\underline{H}_3$), 2.29 (s, 3H,NHCOC$\underline{H}_3$), 11.44 (s, 1H, N$\underline{H}$COCH$_3$, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) *δ*: 22.54, 22.59 (CO$\underline{C}$H$_3$), 24.42, 35.43, 40.13 ($\underline{C}$H$_2$-carbons of cyclohexyl), 83.31 ($\underline{C}$-5 of thiadiazolidine); 142.56 ($\underline{C}$=N), 168.29($\underline{C}$OCH$_3$), 169.10 (NH$\underline{C}$OCH$_3$); Mass m/z (%); 256 $[M+H]^+$;CHN Anal. Calcd. For $C_{11}H_{17}N_3O_2S$: C, 51.74; H, 6.71; N, 16.46. Found: C, 51.70; H, 6.67; N, 16.42.

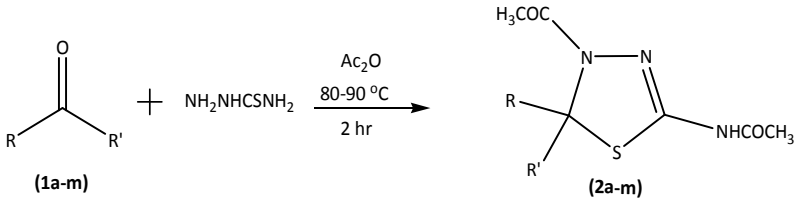
2.4 Single Crystal X-ray Diffraction Study of (2j)

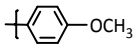
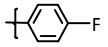
Single crystal of (N-(1-acetyl-4-thia-1,2-diaza-spiro[4,5]dec-2-en-3-yl)-acetamide (2j) was obtained by slow evaporation from its ethanol solution. Crystals suitable for X-ray diffraction studies were selected and then mounted on a Hampton Research Cryoloops using paratone-N oil for data collection diffractometer. These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44 1223 336 033, or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 931813. The asymmetric unit contains single molecule. The value of R_{int} and R_{sigma} are 0.0243 and 0.0352 respectively. The final RE value, equals 4.5%. The non-hydrogen atoms were recognized from the electron density peaks using PLATON and refined using SHELXL-97 [12]. All non-hydrogen atoms were refined anisotropic ally. The hydrogen atoms were fixed at chemically acceptable positions and were allowed to ride on the parent atom during successive refinement. 156 parameters were refined with 2271 reflections using SHELXL-97.

3. RESULTS AND DISCUSSION

3.1 Chemistry

The carbonyl compounds (1a-m) were reacted with thiosemicarbazide in acetic anhydride to get N-(4-acetyl-4,5-disubstituted-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-acetamides (2a-m) (Scheme 1) by one-pot three component approach. The carbonyl compounds (2a-d, 2g and 2h) have given better percentage of product whereas (2e and 2f) have resulted in poor amount of product formation.



	R	R'		R	R'
1a	CH_3	CH_3	1h	CH_3	Ph
1b	CH_3	C_2H_5	1i		
1c	CH_3	H	1j		
1d	H				
1e	H		1k	H	Ph
1f	H		1l	H	H
1g	H	n-butyl	1m	Ph	Ph

Scheme 1. Synthesis of 1, 3, 4-thiadiazole derivatives via three components approach

The structures of the selected compounds were confirmed by their elemental analysis, IR, ^{1}H NMR, mass spectral data. Remaining compounds (2a, 2c-d and 2h-k) are reported in the literature [8] and their formation is confirmed by comparing their physical constants with literature (Table 1). Elemental analysis and the spectral data are given in the experimental section.

The IR spectra of the title compounds showed mainly a sharp strong absorption band around 1635-1660 cm^{-1} which corresponds to amide carbonyl group with disappearance of the aldehydic/ketonic carbonyl band and appearance of medium absorption band around 1620-1630 cm^{-1} due to C=N stretching.

The ^{1}H NMR spectral analysis of the title compounds (2e, 2f and 2g) showed a characteristic singlet for one proton in the range δ 7.0-6.0 ppm due to 1,3,4-thiadiazolidine ring proton (C-5-H) this is a strong evidence to prove the cyclization of thiosemicarbazones. The other protons on substituents and remaining protons appeared in their respective regions for the title compounds. Mass spectral analysis has shown molecular ion peak and other fragment peaks at their respective positions.

The cyclization is further strongly supported by single crystal XRD study of the compound (2j). ORTEP of the molecules is shown in (Fig. 1) and crystal packing in (Fig. 2). The torsion angles about C6-N1-C7-C8, C4-C5-C6-N1, C7-N1-C7-C8 and C6-S1-C9-N3 being -179º and -178º show peri-planner conformation respectively.

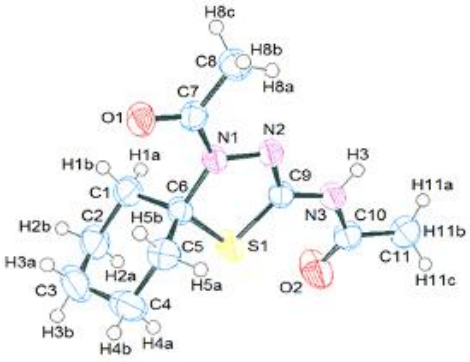


Fig. 1. ORTEP diagram of 2j.

The molecule exhibits intra and inter-molecular hydrogen bonds of the type C-H...O, C-H…S, C-H…N and N-H…O. The crystal shows five intermolecular hydrogen bonds [C(1)···H(1B)···O(1) = 3.0334 Å, C(2)···H(2A)···S(1) = 3.2239 Å, C(4)···H(4A)···S(1) = 3.2166 Å, C(5)···H(5B)···O(1) = 3.0666 Å and C(8)···H(8A)···N(2) = 2.7036 Å] corresponding to bond angles 120º, 104º, 105º, 119º, 112º and two weak intermolecular

hydrogen bonds [N(3)····H(3)····O(1) = 2.8097 Å and C(11)····H(11A)····O(1) = 3.2192 Å] having bond angles 158º, 147º, with the symmetry codes -1/4+y, 1/4-x, 1/4-z.

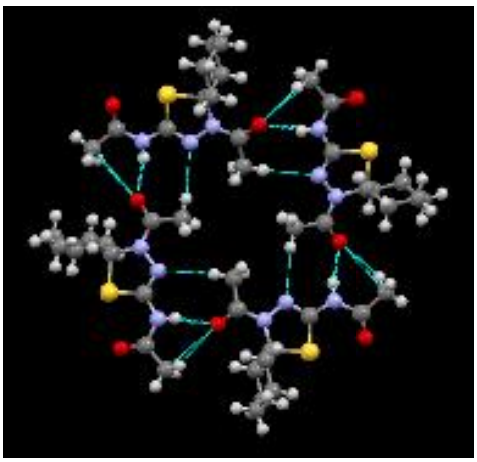


Fig. 2. Packing of the molecules of 2j along b-axis

3.2 Electronic Effect of Substituents

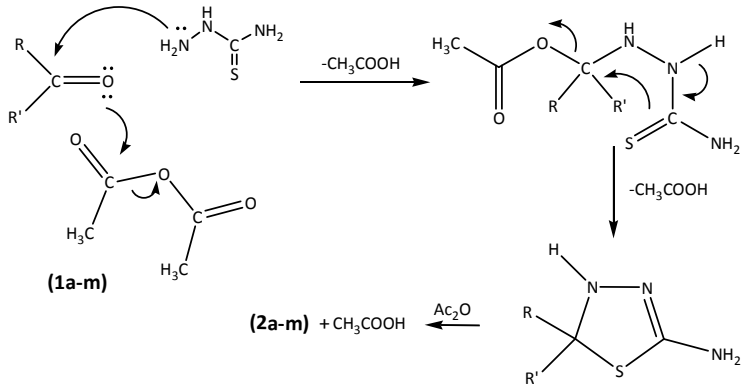
During this reaction, we have made an interesting observation that aldehydes and ketones containing electron withdrawing (2e and 2f) or electron releasing substituents (2a-d, 2g-j) have been more efficiently converted into the title compounds. However, the unsubstituted and compounds with bulky substituents (2k-m) have resulted in a trace amount of the products.

Electron withdrawing groups attached to carbonyl group will favor the nucleophilic attack *via* nitrogen of thiosemicarbazide due to the increased electrophilic character of carbonyl carbon. On the contrary, if electron donating groups are present nevertheless to our surprise the reaction still gave better yield. This might be because of the electron donating effect of the groups which decrease the electrophilic nature of the carbonyl carbon but promote the interaction of lone pair of electrons on the oxygen of carbonyl group with carbonyl carbon of acetic anhydride in turn resulting into enhancement of electrophilic character of carbon of carbonyl compound as evidenced by the yields of the product. The effect of these electron donating and electron withdrawing groups is confirmed by carrying out the reaction of paraformaldehyde with thiosemicarbazide which gave only 3% yield for 1,3,4-thiadiazole derivative (2l).

The compound (2 m) with bulky substituents will experience stearic repulsion in multicomponent approach [13] and hence has resulted in very poor product formation.

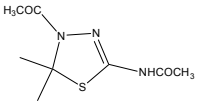
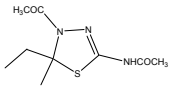
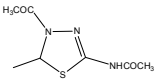
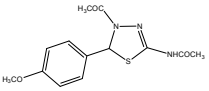
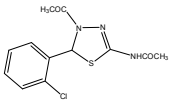
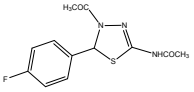
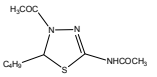
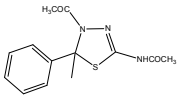
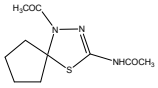
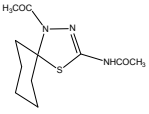
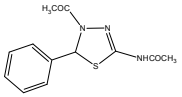
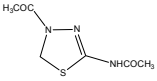
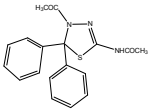
3.3 Possible Mechanism for the Reaction

Mechanism may involve the simultaneous nucleophilic attack by the thiosemicarbazide on the carbonyl carbon and simultaneous electrophilic attack by the acetic anhydride on carbonyl oxygen (Scheme 2) followed by cyclization to give the title compounds (2a-m). As it involves simultaneous electrophilic and nucleophilic attack on the carbonyl compound hence the reaction is favored by presence of either the electron donating or withdrawing substituents on carbonyl compounds (2a-j) (Table 1).



Scheme 2. Proposed mechanism for the formation of products (2a-m)

Table 1. One-pot synthesis of N-(4-acetyl-5-substituted-4,5-dihydro- [1,3,4]thiadiazol-2-yl)-acetamides (2a-m)

Entry no.	Carbonyl compound (1a-m)	Product		Yield %	mp ºC
1	Acetone	2a		76	194-196[a]
2	Ethylmethylketone	2b		78	200-202
3	Acetaldehyde	2c		72	162-164[b]
4	*p*-Anisaldehyde	2d		78	168-169[c]
5	*o*-Chlorobenzaldehyde	2e		70	205-206
6	*p*-Fluorobenzaldehyde	2f		80	215-217
7	n-Butanal	2g		72	212-215
8	Acetophenone	2h		74	216-217[d]
9	Cyclopentanone	2i		78	198-200
10	Cyclohexanone	2j		75	225-227
11	Benzaldehyde	2k		05	224-225[e]
12	Formaldehyde	2l		03	237-238
13	Benzophenone	2m		03	230-233

[a] Lit. [8] mp 195-196°C. [b] Lit. [8] mp 164- 165°C; [c] Lit. [8] mp: 168-169°C; [d] Lit. [8] mp: 216-217 °C; [e] Lit. [8] mp : 222-223°C

4. CONCLUSION

In summary, we have presented here a one-pot methodology for efficient preparation of functionalized 1, 3, 4-thiadiazole derivatives starting from carbonyl compounds. Analysis of the electronic effect of substituents on carbonyl carbon of reactant indicates that to get better

yield of products, the reactants should have either electron donating or withdrawing groups. These functionalized thiadiazoles may be versatile scaffolds for the synthesis of heterocycles of potent biological activities. This protocol minimizes the reaction time since it is a one pot three component approach.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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