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ORIGINAL PAPER

Utility of bis(methylthio)methylene malononitrile as a synthon in the synthesis of new poly-functionalized cyanoiminopyrimidines

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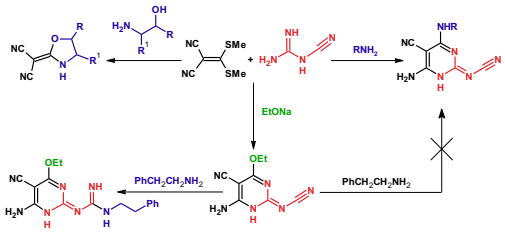
Abstract A new series of 4-(alkyl/arylamino)-6-amino-5-cyano-2-cyanoimino-1*H*-pyrimidine was obtained via one-pot three-component reaction of bis(methylthio)methylene malononitrile, primary amines, and cyanoguanidine using sodium ethoxide as basic catalyst. The same new products were prepared by classical route via reaction of (alkyl/arylamino)(methylthio)methylene malononitrile with cyanoguanidine in presence of sodium ethoxide. In absence of amines, bis(methylthio)methylene malononitrile reacts directly with cyanoguanidine in presence of sodium ethoxide to give 4-ethoxy-2-cyanoimino-1*H*-pyrimidine. On the other hand, multicomponents reaction of bis(methylthio)methylene malononitrile with cyanoguanidine and binucleophilic *β*-hydroxyamines and/or *ortho*-phenylenediamine gave perspective 4-methyl- and/or 5-methyl-1,3-oxazolidin-2-ylidenemalononitrile and 1,3-dihydro-2*H*-benzimidazol-2-ylidenemalononitrile, which are inactive compounds toward reaction with cyanoguanidine to give the expected 4-(alkyl/arylamino)-2-cyanoimino-1*H*-pyrimidines.

Graphical abstract



Keywords Bis(methylthio)methylene malononitrile · Amines · Cyanoguanidine · Cyanoiminopyrimidine · Multicomponent reaction · Cycloadditions

Introduction

Bis(methylthio)methylene malononitrile is an attractive synthon extensively utilized as reactant or reaction intermediate, where the dimethylthio and/or the dicyano groups in its structure are suitably situated to enable reactions with various binucleophilic reagents to form a diverse of heterocyclic compounds [1–9]. Literature survey showed that the pyrimidine scaffold has been identified as a central structure element in a number of biological active compounds and has broad application in drug development for the treatment of bacterial infection [10], cancer [11], tuberculosis [12], leukemia [13], malaria parasite infection [14], HIV-1 infection [15], leishmaniasis [16], and inflammations [17]. We here envisioned that the multicomponent reaction of bis(methylthio)methylene malononitrile, primary aliphatic/aromatic amines, and cyanoguanidine would be utilized in pyrimidine syntheses.

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Results and discussion

Herein, we reported a new method for the synthesis of poly-functionalized 4-(alkyl/arylamino)-2-cyanoimino-1*H*-pyrimidine (4-alkyl/arylamino-CIPMs). The target 4-(alkyl/arylamino)-6-amino-5-cyano-2-cyanoimino-1*H*-pyrimidines **5a–5g** were prepared via one-pot multicomponent reaction of bis(methylthio)methylene malononitrile (**1**), primary aliphatic/aromatic amines **2a–2g** namely: aniline, 4-chloro-, 2-methyl-, 3-methyl-, 4-methyl-aniline, 2-aminopropane, and *β*-phenylethylamine, respectively, and cyanoguanidine (**3**) in the presence of sodium ethoxide as basic catalyst (method A). The same products **5a–5g** were also prepared through two-component reaction of (alkyl/arylamino)(methylthio)methylene malononitrile **4a–4g** with cyanoguanidine in presence of sodium ethoxide (method B). The reaction mechanism for the formation of product **5** was assumed to proceed via nucleophilic substitution of the first methylthio group by primary amine, in absence of catalyst [18] to give the (un)separated products **4a–4g**, followed by another nucleophilic substitution of the second methylthio group by amino group of cyanoguanidine, in the presence of strong base (sodium ethoxide) to give intermediate **I**, which underwent intramolecular cyclization through nucleophilic addition of NH_2 group on C≡N group (Scheme 1).

On the other hand, one-pot multicomponents reaction of bis(methylthio)methylene malononitrile with cyanoguanidine in sodium ethoxide, then followed by addition of primary aliphatic/aromatic amines **2a–2g** afforded on hot the corresponding 6-amino-5-cyano-2-cyanoimino-4-ethoxy-1*H*-pyrimidine (4-ethoxy-CIPM, **6**) instead of **5a–5g**. The inactivity of product **6** to react with primary amines may be attributed to its precipitation through the reaction. However, reaction of 4-ethoxy-CIPM with *β*-phenylethylamine took place by refluxing them in DMF to give product **7** instead of expected product **5g** (Scheme 1).

The chemical structures of the new pyrimidines **5a–5g**, **6**, and **7** were proved by ^{1}H, ^{13}C NMR, and IR spectroscopy and elemental analysis. The IR spectra of **5a–5g** and **6** showed formation of cyanoimino =N– C≡N group, in which an absorption band of cyano group is given at 2180–2194 cm^{-1} [19]. For example the IR spectrum of **5c** showed characteristic absorption bands at 3229, 3137 cm^{-1} for NH_2 and NH groups, 3055 cm^{-1} for the aromatic C–H, 2927 cm^{-1} for the aliphatic C–H, 2215, 2189 cm^{-1} for two C≡N groups. Its ^{1}H NMR spectrum showed the presence of singlet signal at 10.18 ppm characteristic of NH, multiplet signal at 7.30–7.26 ppm due to aromatic protons, three singlet signals at 4.08, 2.63, 2.25 ppm characteristic of NH, NH_2, and methyl groups, respectively. The ^{13}C NMR spectrum of **5c** showed twelve signals at 172.2, 137.1, 135.4, 135.0, 134.6, 131.2, 128.8, 128.0, 127.4, 127.2, 117.0, 59.6 ppm, which are assigned to carbons of aromatic and two nitrile groups, while CH_3 is characterized by signal at 17.9 ppm.

IR spectrum of **6** showed characteristic absorption bands at 3376, 3327, 3197 cm^{-1} for NH_2 and NH groups, 2993, 2940 cm^{-1} for the aliphatic C–H, 2226, 2187 cm^{-1} for two C≡N groups. The ^{1}H NMR spectrum of **6** showed the presence of two broad singlet signals at 11.51 and 7.71 ppm, which are characteristic of NH and NH_2, respectively, quartet and triplet signals at 4.42 and 1.32 ppm with coupling constant $J = 7.0$ Hz attributed to methylene and methyl of ethoxy group, respectively. Its ^{13}C NMR spectrum showed six signals at 171.5, 163.6, 159.9, 114.2, 112.3, 66.7 ppm, which are assigned to carbons of aromatic and two nitrile groups, while two sp^3 carbons of ethoxy group are characterized by two signals at 64.1 and 14.6 ppm. The NOESY spectrum of **6** showed a correlation peak between a proton of NH at 11.51 ppm and two protons of the NH_2 group at 7.71 ppm, which confirmed the cyanoimino form of product **6**.

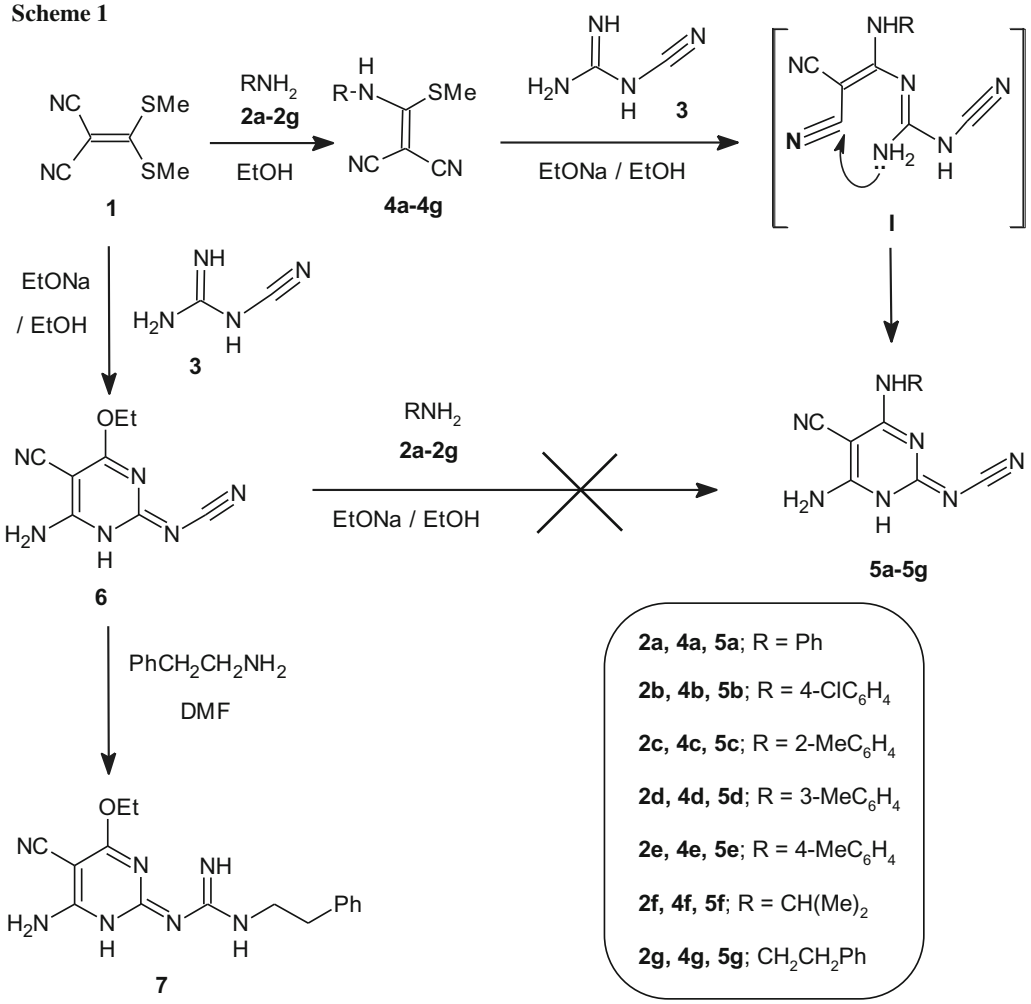
One-pot multicomponents reaction of bis(methylthio)-methylene malononitrile (**1**), cyanoguanidine (**3**), and bifunctional nucleophiles like *β*-hydroxyamines and *ortho*-phenylenediamine afforded oxazolines **8a**, **8b** and 1,3-dihydro-2*H*-benzoimidazole **9** [20], respectively, instead of expected products **4h–4j** or **5h–5j** (Scheme 2).

The chemical structure of products **8** and **9** was fully characterized using ^{1}H, ^{13}C NMR, and IR spectroscopy and elemental analysis. IR spectrum of **8b** showed characteristic absorption bands at 3259 cm^{-1} for NH group, 2991, 2904 cm^{-1} for C–H aliphatic, 2216, 2194 cm^{-1} for cyano groups. Its ^{1}H NMR spectrum showed the presence of broad singlet signal at 9.94 ppm for NH; multiplet signal at 5.17–5.10 ppm for CH, two triplet signals at 3.88 and 3.37 ppm with coupling constant $J = 8.8$ and 8.4 Hz, respectively, due to CH_2 protons, and doublet signal at 1.43 ppm with coupling constant $J = 4.5$ Hz, which is characteristic of methyl group. The ^{13}C NMR spectrum of **8b** showed three signals at 172.4, 116.2, and 81.5, which are assigned to olefin and cyano groups; in addition to three signals at 50.3, 31.7, and 19.6 ppm attributed to CH, CH_2, and CH_3 carbons, respectively.

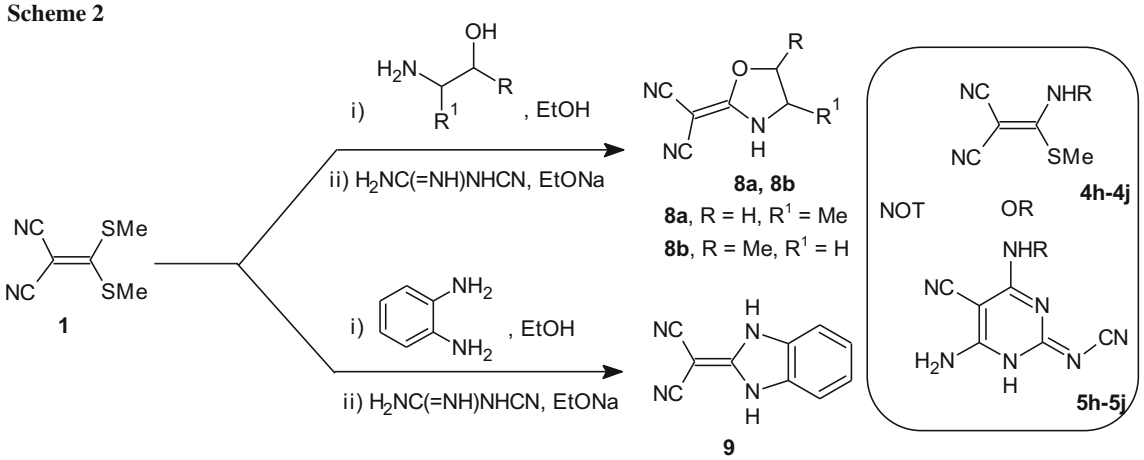
Conclusion

In conclusion, we have demonstrated that a new series of 4-(alkyl/arylamino)-6-amino-5-cyano-2-cyanoimino-1*H*-pyrimidines **5a–5g** can be synthesized via one-pot three-component reaction of bis(methylthio)methylene malononitrile with primary amines and cyanoguanidine using sodium ethoxide as basic catalyst.

Scheme 1



Scheme 2



Experimental

Melting points were detected with a Kofler melting points apparatus. Infrared spectra were recorded with a FT-IR-ALPHBROKER-Platinum-ATR spectrometer. ^{1}H NMR and ^{13}C NMR spectra for all compounds were recorded in DMSO-d_6 on a Bruker Bio Spin AG spectrometer at 400 MHz and 100 MHz, respectively. Elemental analyses were obtained on a Perkin-Elmer CHN-analyzer model.

General procedure for the synthesis of compounds 5a–5g

Method A (three components)
Equimolar amounts (3 mmol) of bis(methylthio)methylene malononitrile (**1**) and primary amine **2** namely: aniline, 4-chloro-, 2-methy-, 3-methy-, 4-methy-aniline, 2-aminopropane or β-phenylethylamine in 40 cm^3 ethanol were stirred with reflux for about 8 h, then 3 mmol of cyanoguanidine (**3**) in freshly prepared sodium ethoxide solution (4 mmol of sodium in 20 cm^3 absolute ethanol) was added and the reaction mixture was refluxed for about 5 h. After completion of reaction (monitored with TLC), the reaction mixture was cooled to RT and poured in ice-cold water and neutralized to pH 7.0 with diluted HCl. The formed precipitate was collected by filtration, washed several times with distilled water, dried, and recrystallized from ethanol.

Method B (two components)
Equimolar amounts (3 mmol) of (alkyl/arylamino)(methylthio)methylene malononitile **4a**–**4g** and cyanoguanidine (**3**) were added to a freshly prepared sodium ethoxide solution (4 mmol of sodium in 60 cm^3 of absolute ethanol). The resulting mixture was heated under reflux for about 5 h. After completion of reaction (monitored with TLC), the reaction mixture was cooled to RT and poured in ice-cold water and neutralized to pH 7.0 with diluted HCl. The formed precipitate was collected by filtration, washed several times with distilled water, dried, and recrystallized from ethanol.

6-Amino-4-anilino-2-cyanoimino-1,2-dihydropyrimidine-5-carbonitrile (**5a**, $C_{12}H_9N_7$)
Yield: method A 69%, method B 74%; m.p.: 228–229 °C; FT-IR: $\bar{\nu} = 3240$, 3116, 3067, 3012, 2210, 2183, 1598 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 10.52$ (s, 1H, NH), 7.44–739 (m, 2H, CH_{phenyl}), 7.31–7.27 (m, 3H, CH_{phenyl}), 4.06 (s, 2H, NH_2), 2.53 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 172.0$, 136.6, 129.6, 128.6, 127.2, 124.8, 124.4, 121.5, 119.5, 62.6 ppm.

6-Amino-4-[(4-chlorophenyl)amino]-2-cyanoimino-1,2-dihydropyrimidine-5-carbonitrile (**5b**, $C_{12}H_8ClN_7$)
Yield: method A 62%, method B 69%; m.p.: 252–254 °C; FT-IR: $\bar{\nu} = 3219$, 3123, 3069, 3010, 2208, 2194, 1588 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 10.55$ (s, 1H, NH), 7.47 (d, $J = 7.2$ Hz, 2H, CH_{arom}), 7.33 (d, $J = 7.2$ Hz, 2H, CH_{arom}), 4.08 (s, 1H, NH), 2.56 (s, 2H, NH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 172.2$, 137.9, 135.6, 131.2, 129.6, 128.3, 126.6, 126.1, 121.0, 62.6 ppm.

6-Amino-2-cyanoimino-1,2-dihydro-4-[(2-methylphenyl)amino]pyrimidine-5-carbonitrile (**5c**, $C_{13}H_{11}N_7$)
Yield: method A 62%, method B 67%; m.p.: 237–239 °C; FT-IR: $\bar{\nu} = 3229$, 3137, 3055, 3003, 2927, 2215, 2189, 1586 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 10.18$ (s, 1H, NH), 7.30–7.26 (m, 4H, CH_{arom}), 4.08 (s, 1H, NH), 2.63 (s, 2H, NH_2), 2.25 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 172.2$, 137.1, 135.4, 135.0, 134.6, 131.2, 128.8, 128.0, 127.4, 127.2, 117.0, 59.6, 17.9 ppm.

6-Amino-2-cyanoimino-1,2-dihydro-4-[(3-methylphenyl)amino]pyrimidine-5-carbonitrile (**5d**, $C_{13}H_{11}N_7$)
Yield: method A 69%, method B 70%; m.p.: 234–235 °C; FT-IR: $\bar{\nu} = 3299$, 3148, 3089, 3010, 2960, 2206, 2193, 1600 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 10.45$ (s, 1H, NH), 7.29 (s, 1H, CH_{arom}), 7.09 (m, 3H, CHarom), 4.05 (s, 2H, NH_2), 2.52 (s, 1H, NH), 2.33 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 171.9$, 139.1, 136.5, 129.4, 127.9, 125.2, 124.7, 121.8, 121.4, 120.1, 116.7, 62.6, 21.3 ppm.

6-Amino-2-cyanoimino-1,2-dihydro-4-[(4-methylphenyl)amino]pyrimidine-5-carbonitrile (**5e**, $C_{13}H_{11}N_7$)
Yield: method A 64%, method B 67%; m.p.: 242–244 °C; FT-IR: $\bar{\nu} = 3215$, 3119, 3054, 3003, 2951, 2209, 2188, 1587 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 10.43$ (s, 1H, NH), 7.22 (d, $J = 6.8$ Hz, 2H, CH_{arom}), 7.16 (d, $J = 7.6$ Hz, 2H, CH_{arom}), 4.05 (s, 3H, NH_2 + NH), 2.32 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 171.9$, 136.7, 133.9, 130.1, 129.0, 124.9, 124.5, 123.4, 119.6, 60.3, 21.0 ppm.

6-Amino-2-cyanoimino-1,2-dihydro-4-(2-propylamino)pyrimidine-5-carbonitrile (**5f**, $C_9H_{11}N_7$)
Yield: method A 58%, method B 62%; m.p.: 218–219 °C; FT-IR: $\bar{\nu} = 3269$, 3187, 3096, 3073, 2972, 2935, 2208, 2191, 1567 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 8.52$ (s, 1H, NH), 4.01 (m, 4H, CH + NH_2 + NH), 1.21 (d, $J = 5.8$ Hz, 6H, $2CH_3$) ppm; ^{13}C NMR

(100 MHz, DMSO-d_6): $\delta = 171.5$, 163.0, 124.2, 117.4, 117.2, 60.2, 46.4, 22.8 ppm.

6-Amino-2-cyanoimino-1,2-dihydro-4-[(2-phenylethyl)amino]pyrimidine-5-carbonitrile (**5g**, $C_{14}H_{13}N_7$)

Yield: method A 61%, method B 64%; m.p.: 241–242 °C; FT-IR: $\bar{\nu} = 3281$, 3127, 3077, 3025, 2953, 2933, 2208, 2180, 1591 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 8.74$ (s, 1H, NH), 7.35–7.19 (m, 5H, CH_{phenyl}), 3.88 (s, 3H, NH_2 + NH), 3.57 (q, $J = 7.2$ Hz, 2H, CH_2), 2.88 (t, $J = 7.2$ Hz, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 172.4$, 138.5, 129.2, 129.0, 128.9, 128.8, 126.9, 126.5, 116.9, 59.9, 44.7, 35.5 ppm.

6-Amino-2-cyanoimino-1,2-dihydro-4-ethoxypyrimidine-5-carbonitrile (**6**, $C_8H_8N_6O$)

A mixture of bis(methylthio)methylene malononitrile (1, 0.51 g, 3 mmol) and cyanoguanidine (3, 0.25 g, 3 mmol) in freshly prepared sodium ethoxide solution (4 mmol of sodium in 50 cm^3 absolute ethanol) was refluxed for about 5 h. After completion of the reaction, the formed precipitate was filtered on hot and recrystallized from DMF. Yield: 77%; m.p.: >300 °C; FT-IR: $\bar{\nu} = 3376$, 3327, 3197, 2993, 2940, 2226, 2187, 1593 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 11.51$ (br. s, 1H, NH), 7.71 (br. s, 2H, NH_2), 4.42 (q, $J = 7.0$ Hz, 2H, CH_2), 1.32 (t, $J = 7.0$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 171.5$, 163.6, 159.9, 114.2, 112.3, 66.7, 64.1, 14.6 ppm.

1-[6-Amino-5-cyano-4-ethoxypyrimidin-2(1H)-ylidene]-3-(2-phenylethyl)guanidine (**7**, $C_{16}H_{19}N_7O$)

A mixture of 6-amino-5-cyano-2-cyanoimino-4-ethoxy-1*H*-pyrimidine (6, 0.61 g, 3 mmol) and *β*-phenylethylamine (0.38 cm^3, 3 mmol) in 40 cm^3 DMF was refluxed for 5 h. After completion of reaction (monitored with TLC), the reaction mixture was concentrated and cooled to RT, the resulted precipitate was collected by filtration and recrystallized from DMF. Yield: 68%; m.p.: 273–275 °C; FT-IR: $\bar{\nu} = 3381$, 3332, 3225, 3197, 3017, 2978, 2949, 2208, 1621 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 8.68$ (br. s, 1H, NH), 7.96 (br. s, 2H, 2NH), 7.35–7.29 (m, 5H, $CH_{arom.}$), 6.64 (br. s, 2H, NH_2), 4.30 (q, $J = 7.1$ Hz, 2H, OCH_2), 3.58 (t, $J = 7.3$ Hz, 2H, CH_2), 2.92 (t, $J = 7.3$ Hz, 2H, CH_2), 1.31 (t, $J = 7.1$ Hz, 3H, CH_3) ppm.

General procedure for the synthesis of compounds 8a, 8b and 9

Equimolar amounts (3 mmol) of bis(methylthio)methylene malononitrile (**1**) and bidentate amine namely: 2-aminopropan-1-ol, 1-aminopropan-2-ol or *o*-phenylenediamine in 40 cm^3 ethanol were stirred with reflux for about 8 h, then 3 mmol of cyanoguanidine (**3**) in freshly prepared sodium ethoxide solution (4 mmol of sodium in 20 cm^3 absolute ethanol) was added and the reaction mixture was refluxed for about 5 h. After completion of reaction (monitored with TLC), the reaction mixture was cooled to RT and poured in ice-cold water and neutralized to pH ~7.0 with diluted HCl. The formed precipitate was collected by filtration, washed several times with distilled water, dried, and recrystallized from dioxane.

(4-Methyl-1,3-oxazolidin-2-ylidene)malononitrile (**8a**, $C_7H_7N_3O$)

Yield 81%; m.p.: 128–130 °C; FT-IR: $\bar{\nu} = 3230$, 3173, 2981, 2940, 2217, 2195, 1601 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 9.97$ (br. s, 1H, NH), 4.77 (m, 1H, CH), 4.25 (m, 2H, CH_2), 1.26 (d, $J = 5.8$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 172.4$, 116.2, 115.8, 77.3, 52.9, 31.8, 19.4 ppm.

(5-Methyl-1,3-oxazolidin-2-ylidene)malononitrile (**8b**, $C_7H_7N_3O$)

Yield 84%; m.p.: 140–142 °C; FT-IR: $\bar{\nu} = 3259$, 2991, 2904, 2216, 2194, 1602 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 9.94$ (br. s, 1H, NH), 5.17–5.10 (m, 1H, CH), 3.88 (t, $J = 8.8$ Hz, 1H, CH_2), 3.37 (t, $J = 8.4$ Hz, 1H, CH_2), 1.43 (d, $J = 4.5$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 172.4$, 116.2, 81.5, 50.3, 31.7, 19.6 ppm.

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