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Synthesis of novel heterocyclic 2-(2-ylidene) malononitrile derivatives

Hamid Beyzaei*, Reza Aryan, Masoomeh Gomroki

Department of Chemistry, Faculty of Science, University of Zabol, Zabol 9861335856, (IRAN)

E-mail : hbeyzaei@yahoo.com

ABSTRACT

Novel 2-(imidazolidin or tetrahydropyrimidin-2-ylidene) malononitrile derivatives (3a-f) have been synthesized in good yields from thecyclocondensation of 2[bis (methylthio) methylene] malononitrile (1) and diaminoalkanes (2a-f). The chemical structures of novel compounds were confirmed by ^{1}H NMR, ^{13}C NMR, elemental analysis and FT IR spectrometry.

KEYWORDS

Imidazolidine;
Tetrahydropyrimidine;
Cyclic 1,3-diamine;
Cyclocondensation;
Diaminoalkane.

INTRODUCTION

Imidazolidines (tetrahydroimidazol derivatives) are cyclic aminals of pharmacological interest due to the bioactivity shown by some members, which is closely related to the substitution patterns. For example, N,N'-dibenzyl-2-arylimidazolidines showed antibacterialand antiamebic activity[1]. Fungicide, bactericide, and antiviral activities had also been reported for N,N'-bisaminoalkylimidazolidines andN,N'-dihydroxyphenylimidazolidines[2]. Some bisimidazolidines (bis (3-arylimidazolidinyl-1) methanes) displayedinteresting bactericidal activity[3]. On the other hand, due to the hydrophobic nature of imidazolidines they can be used to increase the bioavailability of biologically active precursors. Thus, they had been employed as carriers of ethylenediamines[4] or carbonyl compounds[5]. They are also used as model of the coenzyme N,N-methylenetetrahydrofolic acid, which participates in single carbon transfer at the oxidation level of formaldehyde[6]. Recently, a series of imidazolidines were studied as anti-*Trypanosoma cruzi* agents and some of the derivatives were found to have high and selective activity against the proliferative stages of the parasite[7].

The Chemistry of pyrimidines and derivatives have been studied since past century due to their close pharmacological association with diverse pharmacological properties. The corresponding six-membered heterocyclic analogs vis., tetrahydropyrimidines, is still to be explored. It has been recognized that tetrahydropyrimidines are important intermediates in the catabolism of pyrimidines and their derivatives are assumed to play an important role in the nucleic acid synthesis[8]. Tetrahydropyrimidines are one of the fundamental heterocycles, which have been the subject of intense research for their outstanding biological properties and wide range of applications to pharmaceutical compounds and synthetic intermediates[9]. Pyrimidine derivatives possessing anti-inflammatory and analgesic activities have been reported in the literature[10]. In addition above mentioned activities, these derivatives also

have antitumor[11], antimicrobial[12], antibacterial[13], antifungal[14], anti-infective[15], anti-tuberculosis[16] and anticancer[17] activities.

Previously, reaction of two diaminoalkanes with 2-[bis (methylthio) methylene]malononitrile (1) has been described[18,19]. The application of these compounds in pharmaceutical field and in connection with our interest in the synthesis of new imidazolidines and tetrahydropyrimidines[20] as potential precursors for the synthesis of heterocyclic compounds of biologically importance have encouraged us in this research to study the reaction of compound (1) and other diaminoalkanes (2a-f) in order to synthesize the new 2-(imidazolidin or tetrahydropyrimidin-2-ylidene) malononitriles (3a-f). These synthesized compounds are characterized by NMR, IR spectral data, and elemental analysis.

EXPERIMENTAL

General

All chemicals and solvents were purchased from Merck and TCI chemical companies. All yields refer to isolated products. Melting points were recorded on a Kruss type KSP1N melting point meter and are uncorrected. The IR spectra of products were determined using KBr disks with Bruker Tensor-27 FT-IR spectrometer and only major absorptions are listed. The ^{1}H and ^{13}C NMR spectra of DMSO-d_6 solutions were recorded on a Bruker FT-NMR Ultra Shield-400 spectrometer (400 and 100 MHz, respectively) with residual protons of the solvent as internal standard (2.50 ppm for ^{1}H and 39.48 ppm for ^{13}C). Elemental analyses were performed on a Thermo Finnigan Flash EA microanalyzer. Monitoring of the progress of reactions and the purity of the products were effected by TLC on alufoil plates pre-coated with silica gel (60, Merck), eluent was $CHCl_3$-CH_3OH, 9:1, visualization with I_2 vapor. Compound (1) was obtained according to the published method[21].

General procedure for the synthesis of2-(imidazolidin or tetrahydropyrimidin-2-ylidene) malononitriles (3a-f)

A suspension of [bis (methylthio) methylene]malononitrile (1) (1.7 g, 10 mmol) and diaminoalkanes (2a-f) (10 mmol) in ethanol (96%) (10 ml) was stirred at room temperature for10-30 min. The reaction mixture was poured on ice and the precipitate was filtered, and washed with cold ethanol, the residual products are recrystallized from methanol to give (3a-f).

2-(5,5-Dimethyltetrahydropyrimidin-2(1*H*)-ylidene) malononitrile (3a)

IRνcm^{-1}: 3257 (NH), 2168 (Ca”N), 1616 (C=C).^{1}H NMR 5Øÿ Þppm: 0.92 (s, 6H, CH_3), 2.88 (d, 4H, J = 2.3 Hz, CH_2), 7.75 (b, 2H, NH).^{13}C NMR 5Øÿ Þppm: 23.4 (CH_3), 26.4 (-C $(CH_3)_2$), 29.0 (Na”C-C=C-), 49.7 (CH_2), 118.7 (Ca”N), 158.6 (Na”C-C=C-). Analysis calculated for $C_9H_{12}N_4$: C,61.34; H, 6.86; N, 31.80. Found: C, 61.40; H, 6.91;N, 31.69.

2-(4-Ethyltetrahydropyrimidin-2(1*H*)-ylidene) malononitrile (3b)

IR νcm^{-1}: 3288 (NH), 2172 (Ca”N), 1573 (C=C).^{1}H NMR 5Øÿ Þppm: 0.84 (t, 3H, J = 7.4 Hz, CH_3), 1.39, 1.83 (m, 1H, m, 1H, -NHCH$_2$CH$_2$-), 1.62 (m, 2H, -CH$_2$CH$_3$), 3.19 (m, 2H, -NHCH$_2$-), 3.26 (m, 1H, -CHEt),7.58, 7.75 (b, 1H, b, 1H, NH).^{13}C NMR 5Øÿ Þppm: 9.4 (CH_3), 23.6 (-CH$_2$CH$_3$), 27.0 (-NHCH$_2$CH$_2$-), 27.7 (Na”C-C=C-), 36.6 (-NHCH$_2$-), 50.0 (-CHEt), 118.8 (Ca”N), 159.2 (Na”C-C=C-). Analysis calculated for $C_9H_{12}N_4$: C, 61.34; H, 6.86; N, 31.80. Found: C, 61.38; H, 6.79; N, 31.83.

2-(5-Hydroxytetrahydropyrimidin-2(1*H*)-ylidene) malononitrile (3c)

IR νcm^{-1}: 3313 (NH, OH), 2172 (Ca”N), 1616 (C=C). ^{1}H NMR 5Øÿ Þppm: 3.06, 3.22 (d, 2H, J = 12.5 Hz, d, 2H, J = 12.5 Hz,-NHCH$_2$-), 3.97 (s, 1H, -CHOH), 5.28 (b, 1H, OH), 7.61 (b, 2H, NH). ^{13}C NMR 5Øÿ Þppm: 29.2 (Na”C-C=C-), 44.9 (-NHCH$_2$-), 58.2 (-CHOH), 118.8 (Ca”N), 159.0(Na”C-C=C-). Analysis calculated for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13; O, 9.75. Found: C, 51.18; H, 4.87; N, 34.19; O, 9.76.

2-(4,4-Dimethylimidazolidin-2-ylidene) malononitrile (3d)

IR νcm^{-1}: 3300 (NH), 2170 (Ca”N), 1589 (C=C).

^{1}H NMR 5ØÿÞppm: 1.77 (t, 6H, *J* = 5.3 Hz, CH_3), 3.32 (s, 2H, -NHC$\underline{H}_2$-), 7.70 (b, 2H, NH). ^{13}C NMR 5ØÿÞppm: 19.6 (CH_3), 28.3 (Na"C-$\underline{C}$=C-), 50.6 (-$NHCH_2$-), 59.0 (-$\underline{C}(CH_3)_2$), 118.7 (Ca"N), 159.4 (Na"C-C=$\underline{C}$-). Analysis calculated for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.55. Found: C, 59.18; H, 6.30; N, 34.52.

2-(4-Methylimidazolidin-2-ylidene) malononitrile (3e)

IR *v*cm^{-1}: 3260 (NH), 2186 (Ca"N), 1601 (C=C). ^{1}H NMR 5ØÿÞppm: 1.17 (d, 3H, *J* = 6.2 Hz, CH_3), 3.11, 3.67 (t, 1H, *J* = 9.8 Hz, t, 1H, *J* = 9.8 Hz, -NHC$\underline{H}_2$-), 3.98 (m, 1H, -C$\underline{H}CH_3$),8.16, 8.38 (b, 1H, b, 1H, NH). ^{13}C NMR 5ØÿÞppm: 20.2 (CH_3), 27.5 (Na"C-$\underline{C}$=C-), 50.5 (-$NHCH_2$-), 52.0 (-$\underline{C}HCH_3$), 117.8 (Ca"N), 165.4 (Na"C-C=$\underline{C}$-). Analysis calculated for $C_7H_8N_4$: C, 56.74; H, 5.44; N, 37.82. Found: C, 56.66; H, 5.48; N, 37.86.

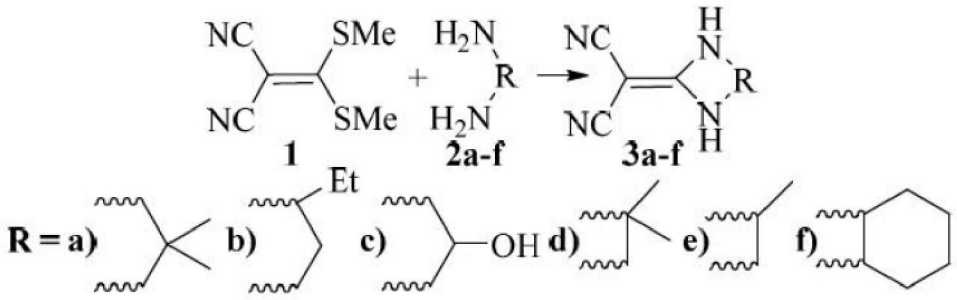
2-(Octahydro-2*H*-benzo[*d*]imidazol-2-ylidene) malononitrile (3f)

IR *v*cm^{-1}: 3253 (NH), 2197 (Ca"N), 1600 (C=C). ^{1}H NMR 5ØÿÞppm: 1.25-1.38 (m, 4H, -$CHCH_2C\underline{H}_2$-), 1.71, 2.01 (d, 2H, *J* = 8.6 Hz, d, *J* = 10.7 Hz, 2H, -$CHC\underline{H}_2CH_2$-), 3.03 (m, 2H, -NHC$\underline{H}$-),8.44 (b, 2H, NH). ^{13}C NMR 5ØÿÞppm: 19.5, 23.3 (-$CHCH_2\underline{C}H_2$-), 26.3, 28.4 (-$CH\underline{C}H_2CH_2$-), 54.6, 63.0 (-NHCH-),30.0 (Na"C-$\underline{C}$=C-), 117.2 (Ca"N), 168.6 (Na"C-C=$\underline{C}$-). Analysis calculated for $C_{10}H_{12}N_4$: C, 63.81; H, 6.42; N, 29.77. Found: C, 63.78; H, 6.51; N, 29.71.

RESULTS AND DISCUSSION

2-(imidazolidin or tetrahydropyrimidin-2-ylidene) malononitriles (3a-f) were preparedin asimple and fastprocedure (10-30 min) from two successive Michaelsubstitution reaction 2-[bis (methylthio) methylene]malononitrile (1) and diaminoalkanes (2a-f) in ethanol as a solvent at room temperature (Scheme 1). The yields of the products obtained were relatively high (81-95%) and depicted in TABLE 1.

The structural assignments of compounds (3a-f) were based on their analytical and spectral data. The ^{1}HNMRspectra of compounds (3a–e) showed signals due to methylene and –CH– groups adjacent to the –NH– groups within 5ØÿÞ = 2.88–3.67 and 3.03-3.98 ppm, respectively and broad signals due to–NH– groups within 5ØÿÞ = 7.58–8.44 ppm. The^{13}CNMR spectra of the products exhibited signals within 5ØÿÞ = 27.5–30.0, 117.2–118.8, 158.6–168.8 ppm attributed to the Na"C–$\underline{C}$=C–,–Ca"N, Na"C–C=$\underline{C}$– carbons respectively, signals appeared within 5ØÿÞ = 44.9-50.6 belonged to methylene groups adjacent to the –NH– groups of compounds (3a-e). The FT-IR spectra of (3a-f) in KBr disk showed the absorption bands within *v*= 3253–3313 cm^{-1} corresponding to –NH–



Scheme 1 : Total synthesis of heterocyclic 1,3-diamines 3a-f

TABLE 1 : Results of reaction compound 1 and diaminoalkanes 2a-f in ethanol at room temperature

Entry	Products	Diaminoalkane	Time (min)	Yield (%)	m.p. (^{o}C)
1	3a	2,2-Dimethyl-l,3-propanediamine	30	95	308-310
2	3b	1,3-Diaminopentane	15	89	188-190
3	3c	1,3-Diamino-2-propanol	30	86	278-280
4	3d	1,2-Diamino-2-methylpropane	10	81	328-329
5	3e	1,2-Diaminopropane	10	87	246-247
6	3f	1,2-Diaminocyclohexane	25	92	330-331

groups, within $\acute{\imath}$ = 2168–2197 cm^{-1} belonging to nitrile groups and within $\acute{\imath}$ = 1573–1616 cm^{-1} attributed to the –C=C– exocyclic. All this evidence plus microanalytical data strongly support the formation of all products.

Interestingly, hydroxyl group of 1,3-diamino-2-propanol doesn't react with methylthio groups of compound 1. This is probably due to the higher nucleophilicity of –NH– groups againsthydroxyl group.

CONCLUSIONS

In summary, several new imidazolidines and tetrahydropyrimidines have been synthesized from the cyclocondensation of 2-[bis (methylthio) methylene]malononitrile with several various diaminoalkanes, Which constitute potential precursors for the synthesis of various biological and pharmaceutical compounds.

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