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THE INVESTIGATION OF REACTION OF VARIOUS THIOPHENE BASED KNOEVENAGEL ADDUCTS WITH ACETOACETANILIDE

F.N. Naghiyev, A.M. Maharramov, A.R. Asgarova, A.G. Rahimova,
M.A. Akhundova, I.G. Mamedov

Baku State University
23, Z.Khalilov str., AZ-1148 Baku, Azerbaijan; e-mail: farid.orgchemist@gmail.com

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The reaction of Michael addition interaction of 3-phenyl-2-(thiophene-2-carbonyl)acrylonitrile, 2-(thiophene-2-carbonyl)-3-(p-tolyl)acrylonitrile, 3-(4-methoxyphenyl)-2-(thiophene-2-carbonyl)acrylonitril, as well as 3-pyridinyl-2-(thiophene-2-carbonyl)acrylonitrile with acetoacetanilide made it possible to produce substituted hexanones and 3,4-dihydro-2H-pyrane derivatives. Structures of synthesized compounds were acknowledged by NMR and X-Ray structural analysis.

Keywords: *thiophene, acrylonitrile, acetoacetanilide, pyran, NMR*

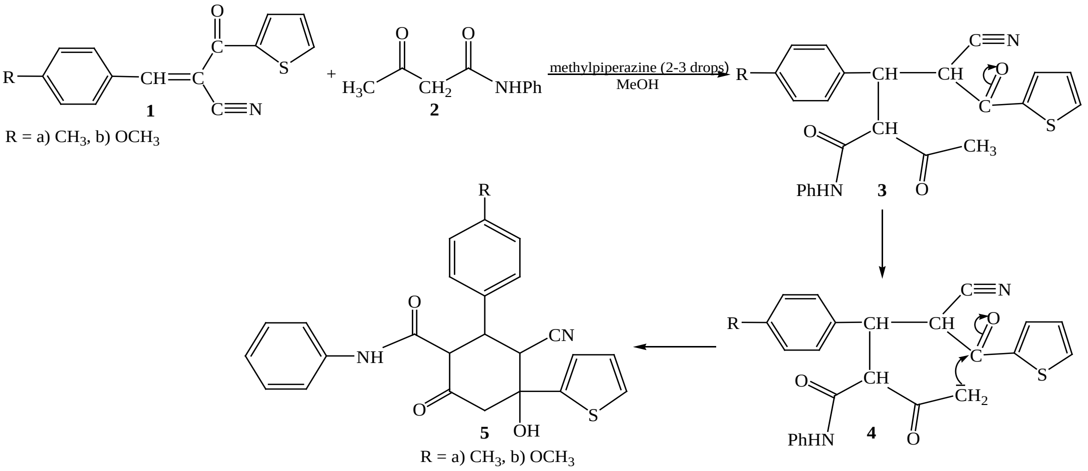
INTRODUCTION

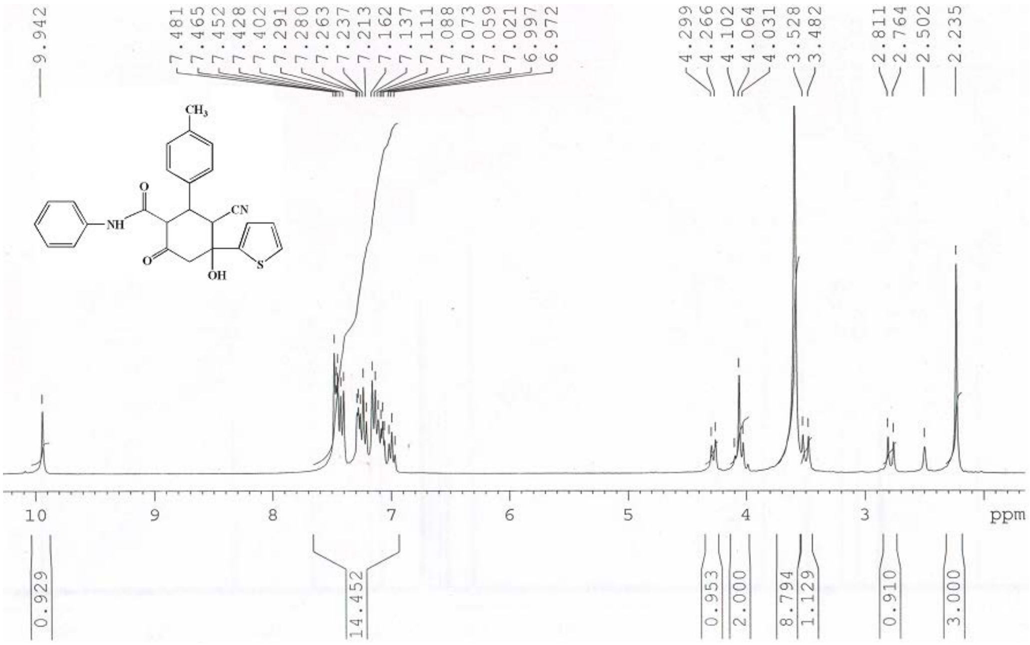
Pyranes and cyclic ketones are biologically active compounds to make up a structural part of natural compounds [1-2]. New [4+2] annulations were carried out in the presence of triphenylphosphine catalyst and high yield synthesized functionalized dihydropyranes [3]. A similar reaction of α-valin derived phosphine was used as catalyst in another work [4]. Also, new cyclation was carried out for α,β-unsaturated ketones through the use of DABCO-catalyst and synthesized diastereomeric dihydropyrane derivatives [5]. A cascade reaction of malononitrile and α-substituted calcone allowed to synthesize chiral multi-substituted amino-4H-pyrane derivatives. Alkoloids were checked up as catalyst in pyrane synthesis reactions [6].

The reaction of isatilidenmalononitriles with malononitriles and 2-tiophenmethylamine (or furfuril amine) one-pot three component condensation was carried out for the first time to obtain appropriate spiropiridines [7].

RESULTS AND DISCUSSION

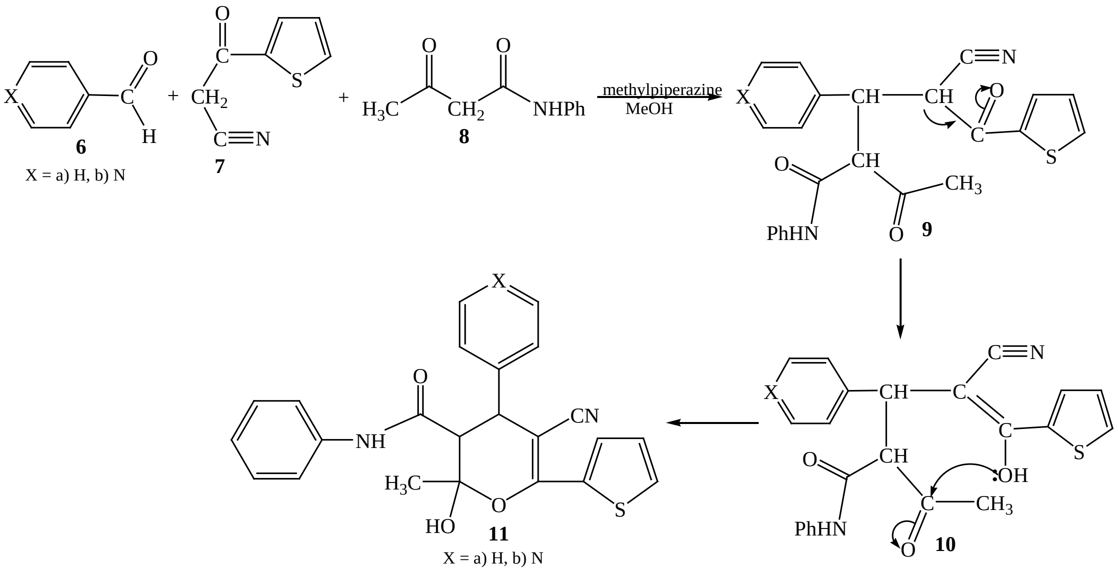
We carried out an experiment through the use of the Michael addition reaction for 2-(thiophene-2-carbonyl)-3-(p-tolyl)acrylonitrile and 3-(4-methoxyphenyl)-2-(thiophene-2-carbonyl)acrylonitrile with acetoacetanilide at room temperature in methanol media using of 2-3 drops of methylpiperazine to obtain corresponding hexanone-substituted derivatives. As follows from the reaction mechanism, at the first stage the Michael addition of methylene active compound to double bond takes place and from the obtained Michael adduct (**3**) forms CH_2-anion by action of base. At the last stage this anion atacks a carbonyl group of anion to synthesize an appropriate reaction products(**5**).

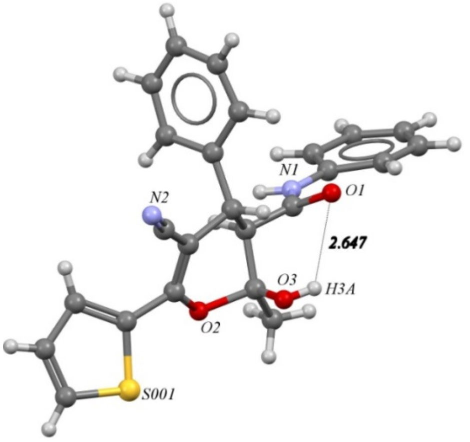




^{1}H NMR spectra of 3-cyano-4-hydroxy-6-oxo-N-phenyl-4-(thiophen-2-yl)-2-(p-tolyl)cyclohexane-1-carboxamide (**5a**)

Subsequently by means of the Michael addition reaction of Knoevenagel adduct obtained as a result of interaction between pyridine aldehyde and 2-thenoylacetonitrile, with acetoacetanilide in ethanol-water media through the use of 2-3 drops of methylpiperazine to obtain appropriate 3,4-dihydro-2*H*-pyrane derivatives.





X-Ray structure of 5-cyano-2-hydroxy-2-methyl-N,4-diphenyl-6-(thiophen-2-yl)-3,4-dihydro-2H-pyran-3-carboxamide (**11a**)

EXPERIMENTAL PART

It should be noted that all used reagents were bought from Merc and Fluca and used without cleaning. The melting points of compounds were measured at STUART SPM30. Purity of synthesized compounds were checked by TLC, and structures acknowledged on "Bruker 300" NMR apparatus (300 and 75 MHz).

3-Cyano-4-hydroxy-6-oxo-N-phenyl-4-(thiophen-2-yl)-2-(p-tolyl)cyclohexane-1-carboxamide (5a): Mixture of 2-(thiophene-2-carbonyl)-3-(p-tolyl)acrylonitrile (2.9 mmol) and acetoacetanilide (3 mmol) dissolved in 35 ml of methanol was stirrered for 5-7 minutes and a 2-3 drop methylpiperazine was added, so the stirring was continued. The reaction progress was tracked by TLC (EtOAc/n-hexane, 2:1) and the mixture kept quietly for 24-48 hours. Through evaporating of solvent it became possible to precipitate crystals. Note that crystals were separated by filter paper and recrystalliized from ethanol (95%) - water mixture, yield 0.89 g, 71.60%. mp. 210°C.

^{1}H NMR (300 MHz, DMSO-*d*6), δ, m.h.: 2.23 (s, 3H, CH_3); 2.79 (d, 1H, CH, $^3J_{H\text{-}H}$ = 14.1); 3.50 (d, 1H, CH, $^3J_{H\text{-}H}$ = 13.8); 4.06 (s, 2H, CH_2); 4.28 (d, 1H, CH, $^3J_{H\text{-}H}$ = 9.9); 6.97-7.48 (m, 12H, 9Ar-H+3$CH_{thiophenyl}$); 9.94 (s, 1H, NH). ^{13}C NMR spektr (DMSO-*d*6), δ, m.h.: 21.14 (CH_3-Ar), 44.26 (CH), 47.40 (CH), 54.07 (CH_2), 62.64 (CH), 75.29 ($C_{quat.}$), 119.02 (CN), 119.49 (2CH_{arom}), 123.87 ($CH_{thiophenyl}$), 124.45 (CH_{arom}), 125.71 ($CH_{thiophenyl}$), 127.63 ($CH_{thiophenyl}$), 128.75 (2CH_{arom}), 129.14 (2CH_{arom}),129.54 (2CH_{arom}), 137.06 (C_{ar}), 137.17 (C_{ar}), 139.14 (C_{ar}), 150.57 (C_{thioph}), 165.85 ($\underline{C}$ONH), 203.12 (C=O).

Found, %: 69.70 C; 5.07 H. $C_{25}H_{22}N_2O_3S$. Calculated, %: 69.77 C; 5.12 H.

3-Cyano-4-hydroxy-2-(4-methoxy- phenyl)-6-oxo-N-phenyl-4-(thiophen-2-yl)- cyclohexane-1-carboxamide (5b): it was synthesized in the same condition (yield 1.1 g, 85.61%). mp.208°C.

^{1}H NMR (300 MHz, DMSO-*d*6), δ, m.h.: 2.77 (d, 1H, CH, $^3J_{H\text{-}H}$ = 14.1); 3.48 (d, 1H, CH, $^3J_{H\text{-}H}$ = 15.3); 3.69 (s, 3H, CH_3O); 4.03 (s, 2H, CH_2); 4.27 (d, 1H, CH, $^3J_{H\text{-}H}$ = 9.6); 6.89-7.47 (m, 12H, 9Ar-H+3$CH_{thiophenyl}$); 9.93 (s, 1H, NH). ^{13}C NMR spektr (DMSO-*d*6), δ, m.h.: 43.88 (CH), 47.51 (CH), 54.06 (CH_2), 55.37 (CH_3O), 62.79 (CH), 75.22 ($C_{quat.}$), 114.23 (2CH_{arom}), 119.07 (CN), 119.52 (2CH_{arom}), 123.87 ($CH_{thiophenyl}$), 124.42 (CH_{arom}), 125.70 ($CH_{thiophenyl}$), 127.62 ($CH_{thiophenyl}$), 129.14 (2CH_{arom}), 129.98 (2CH_{arom}), 131.96 (C_{ar}), 139.13 (C_{ar}), 150.59 (C_{thioph}), 158.90 (O-C_{ar}), 165.90 ($\underline{C}$ONH), 203.14 (C=O).

Found, %: 67.50 C; 4.45 H. $C_{25}H_{20}N_2O_4S$. Calculated, %: 67.57 C; 4.50 H.

5-Cyano-2-hydroxy-2-methyl-N,4-diphenyl-6-(thiophen-2-yl)-3,4-dihydro-2H-pyran-3-carboxamide (11a):

Mixture of 3-phenyl-2-(thiophene-2-carbonyl)acrylonitrile (2.9 mmol) and acetoacetanilide (3 mmol) dissolved in 35 ml of methanol was stirrered for 5-7 minutes and a 2-3 drop methylpiperazine was added, so the stirring was continued. Reaction progress was tracked by TLC (EtOAc/n-hexane, 2:1), and the mixture was kept quietly for 24-48 hours. By evaporating of solvent crystals were precipitated. Crystals were separated by filter paper and recrystalliized from ethanol (95%) - water mixture. yield 0.9 g, 75%. mp.174°C.

^{1}H NMR (300 MHz, DMSO-*d*6), δ, m.h.: 1.72 (s, 3H, CH_3); 3.07 (d, 1H, CH, $^3J_{H\text{-}H}$ = 11.7); 4.38 (d, 1H, CH, $^3J_{H\text{-}H}$ = 11.7); 7.00-7.89 (m, 13H, 10Ar-H+3$CH_{thiophenyl}$); 9.86 (s, 1H, NH). ^{13}C NMR spektr (DMSO-*d*6), δ, m.h.: 26.38 (CH_3), 40.62 (CH), 55.87 (CH), 86.25 (=$C_{quat.}$), 99.73 (O-$C_{quat.}$), 119.58 (CN), 119.66 (2CH_{arom}), 124.15 (CH_{arom}), 128.03 (CH_{arom}), 128.47 ($CH_{thiophenyl}$), 128.60 (CH_{arom}), 128.87 (2CH_{arom}), 129.05 (3CH_{arom}), 129.78 ($CH_{thiophenyl}$), 130.63 ($CH_{thiophenyl}$), 135.99 (C_{ar}), 138.87 (C_{thioph}), 140.12 (C_{ar}), 166.77 ($\underline{C}$ONH), 167.63 (O-$C_{quat.}$=).

Found, %: 69.17 C; 4.76 H. $C_{24}H_{20}N_2O_3S$. Calculated, %: 69.23 C; 4.81 H.

5-Cyano-2-hydroxy-2-methyl-N-phenyl-4-(pyridin-4-yl)-6-(thiophen-2-yl)-3,4-dihydro-2H-pyran-3-carboxamide (11b):

Mixture 4-pyridinecarboxaldehyde or (2.9 mmol) and 2-thenoylacetonitrile (3 mmol) dissolved in 50 ml of ethanol-water (4:1) was stirrered 5 minutes, reaction mixture was kept quietly for 36 hours. Then acetoacetanilide (3 mmol) was added to reaction mixture, stirred for 5 minutes and after 2-3 drop methylpiperazine was added and stirring was continued. Reaction progress was tracked by TLC (EtOAc/n-hexane, 2:1). Reaction mixture was kept quietly for 36 hours. Through evaporating of solvent it became possible to precipitate crystals. Crystals were separated by filter paper and recrystalliized from ethanol (95%) - water mixture. yield 0.97 g, 79.51%. mp.165°C.

^{1}H NMR (300 MHz, DMSO-*d*6), δ, m.h.: ^{13}C NMR spektr (DMSO-*d*6), δ, m.h.: 1.70 (s, 3H, CH_3); 3.05 (d, 1H, CH, $^3J_{H\text{-}H}$ = 11.4); 4.39 (d, 1H, CH, $^3J_{H\text{-}H}$ = 11.4); 7.03-8.56 (m, 12H, 9Ar-H+3$CH_{thiophenyl}$); 9.88 (s, 1H, NH). ^{13}C NMR spektr (DMSO-*d*6), δ, m.h.: 26.31 (CH_3), 40.21 (CH), 55.04 (CH), 84.45 (=$C_{quat.}$), 99.72 (O-$C_{quat.}$), 119.71 (CN), 120.02 (2CH_{arom}), 124.29 (CH_{arom}), 124.44 (CH_{arom}), 128.52 ($CH_{thiophenyl}$), 129.21 (3CH_{arom}), 130.11 ($CH_{thiophenyl}$), 130.97 ($CH_{thiophenyl}$), 135.67 (C_{ar}), 138.68 (C_{thioph}), 149.17 (C_{ar}), 150.38 (2CH_{arom}), 166.68 ($\underline{C}$ONH), 167.23 (O-$C_{quat.}$=).

Found, %: 66.12 C; 4.51 H. $C_{23}H_{19}N_3O_3S$. Calculated, %: 66.19 C; 4.56 H.

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TİOFEN ƏSASLI BƏZİ KNOEVENAGEL ADDUKTLARININ ASETOASETANİLİDLƏ REAKSİYASININ TƏDQİQİ

F.N. Nağıyev, A.M.Məhərramov, A.R. Əsgərova, A.G. Rəhimova,
M.A. Axundova, I.G. Mamedov

Bakı Dövlət Universiteti
AZ 1148 Bakı, Z.Xəlilov küç., 23; e-mail: farid.orgchemist@gmail.com

3-Fenil-2-(tiofen-2-karbonil)akrilonitril, 2-(tiofen-2-karbonil)-3-(p-tolil)akrilonitril və 3-(4-metoksifenil)-2-(tiofen-2-karbonil)akrilonitril, eləcə də 3-piridinil-2-(tiofen-2-karbonil)akrilonitrilin asetoasetanilid ilə Mixael birləşmə reaksiyasiyasından əvəzlənmiş heksanon və 3,4-dihidro-2H-piran törəmələrinin alınması müəyyən edirilmişdir. Sintez edilən birləşmələin quruluşu NMR və RQA analiz metodlarının köməyilə təsdiq olunmuşdur.

Açar sözlər: *tiofen, akrilonitril, asetoasetanilid, piran, NMR*

ИССЛЕДОВАНИЕ РЕАКЦИИ ВЗАИМОДЕЙСТВИЯ НЕКОТОРЫХ АДДУКТОВ КНЕВЕНАГЕЛЯ НА ОСНОВЕ ТИОФЕНА С АЦЕТОАЦЕТАНИЛИДОМ

Ф.Н. Нагиев, А.М. Магеррамов, А.Р. Аскерова, А.Г. Рагимова,
М.А. Ахундова, И.Г. Мамедов

Бакинский государственный университет
AZ 1148 Баку, ул. З.Халилова, 23; e-mail: farid.orgchemist@gmail.com

Путем реакции присоединения по Михаэлю взаимодействием 3-фенил-2-(тиофен-2-карбонил) акрилонитрила, 2-(тиофен-2-карбонил)-3-(п-толил)акрилонитрила и 3-(4-метоксифенил)-2-(тиофен-2-карбонил)акрилонитрила, а также 3-пиридинил-2-(тиофен-2-карбонил)акрилонитрила с ацетоацетанилидом были получены соответствующие замещенные гексаноны и 3,4-дигидро-2H-пиран-производные. Структуры синтезированных соединений были подтверждены методами ЯМР и рентгеноструктурного анализа.

Ключевые слова: *тиофен, акрилонитрил, ацетоацетанилид, пиран, ЯМР*