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Electrochemically induced chain transformation of salicylaldehydes and alkyl cyanoacetates into substituted 4*H*-chromenes

Michail N. Elinson,* Alexander S. Dorofeev, Sergey K. Feducovich, Sergey V. Gorbunov, Ruslan F. Nasybullin, Nikita O. Stepanov and Gennady I. Nikishin

N. D. Zelinsky Institute of Organic Chemistry, Leninsky prospect 47, 119991 Moscow, Russia

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Abstract—Electrolysis of salicylaldehydes and alkyl cyanoacetates in ethanol in an undivided cell in the presence of sodium bromide results in the formation of substituted alkyl 2-amino-4-(1-cyano-2-alkoxy-2-oxoethyl)-4*H*-chromene-3-carboxylates in 85–95% yields.

The chromene (or benzopyran) moiety often appears as an important structural component in both biologically active and natural compounds. Chromene fragments occur in alkaloids, flavonoids, tocopherols and anthocyanins.[1] Moreover, functionally substituted chromenes have played increasing roles in synthetic approaches to promising compounds in the field of biomedicinal chemistry.[2] The current interest in 4*H*-chromene derivatives bearing a nitrile functionality arises from their potential application in the treatment of human inflammatory TNFα-mediated diseases, such as rheumatoid and psoriatic arthritis, and of cancer therapy. Thus, the corresponding (4*H*-chromen-4-yl)malononitriles were found to inhibit mitogen-activated protein kinase-activated protein kinase 2 (MK-2) and suppress the expression of the TNFα in U937 cells.[3] In the case of cancer therapy, substituted alkyl (4*H*-chromen-4-yl)cyanoacetates are a new class of small molecules that exhibit a binding activity for the surface pocket of cancer implicated Bcl-2 protein and induce apoptosis or programmed cell death in tumor cells.[4]

The condensation of salicylaldehyde derivatives with active methylene compounds in the presence of ammonium acetate, pyridine, or piperidine usually leads to coumarins,[5] or coumarin imines, which can be hydrolyzed to coumarins.[5c]

Nevertheless, synthetic approaches to the corresponding 4*H*-chromen-4-yl derivatives are known and employ the reaction of salicylaldehydes with alkyl cyanoacetates catalyzed by ammonium acetate,[6] aluminum oxide,[7] molecular sieves 3 Å[8] or by potassium exchanged layered zirconium phosphate under solvent-free conditions.[9] The catalysis with ammonium acetate requires careful temperature control (5–10) °C to ensure product selectivity and the yields of the desired product are in the range of 40–80%.[6] The application of solid phase catalysis using aluminum oxide[7] or the molecular sieves 3 Å[8] is more convenient and results in the formation of the corresponding 4*H*-chromene derivatives in 50–85% yields. The best yields (70–95%) of the corresponding substituted 4*H*-chromenes were reported for the reaction of salicylaldehydes with alkyl cyanoacetates using potassium exchanged layered zirconium phosphate catalyst under the solvent-free conditions, but this method requires long reaction times (2–15 h) and a 60 °C reaction temperature.[9]

Due to the extensive research on the electrochemistry of organic compounds over the last three decades, electrosynthesis has become a useful method in modern organic chemistry.[10] Additionally, electrochemical processes are beneficial from the viewpoint of environmentally benign organic synthesis as electricity is the most ecologically

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* Corresponding author. Tel.: +7 495 938 35 42; fax: +7 495 137 38 42; e-mail: elinson@ioc.ac.ru

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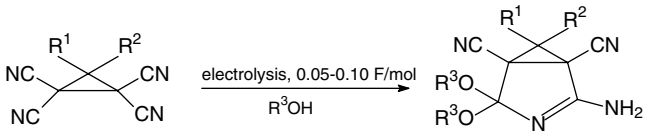
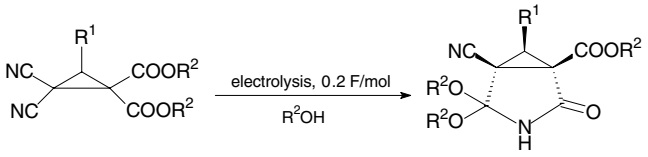


Scheme 1.



Scheme 2.

Table 1. Electrocatalytic transformation of salicylaldehyde **1a** and methyl cyanoacetate **2a** into 4*H*-chromene **3a**[a,b,14]

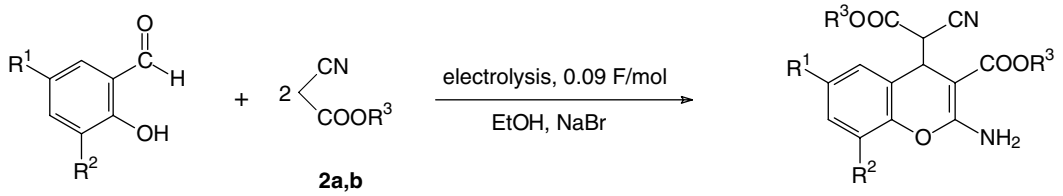
I (mA)	Time (min)	Electricity passed (F/mol)	Yield (%)[c]
250	30	0.47	68
125	30	0.23	75
50	30	0.09	95
20	30	0.04	79

[a] 10 mmol of salicylaldehyde **1a**, 20 mmol of methyl cyanoacetate, 1 mmol of NaBr, 20 ml of EtOH, Fe-cathode (5 cm^2), C-anode (5 cm^2), 20 °C.
[b] Melting point **3a**: 121–123 °C, lit. melting point 120–122 °C.[7] The ratio of diastereoisomers was 2:1 (according to NMR data in DMSO-d_6).
[c] Isolated yields.

Table 2. Electrocatalytic transformation of substituted salicylaldehydes **1a–e** and alkyl cyanoacetates **2a,b** into 4*H*-chromenes **3b–j**[a,14]

Aldehyde	Alkyl cyanoacetate	4*H*-Chromene	Yield, %[b]	Ratio of isomers[c]	Mp °C found	Mp °C reported
1a	**2b**	**3b**	91	2:1	141–143	142–143[6]
1b	**2a**	**3c**	93	3:2	126–127	—
1b	**2b**	**3d**	88	2:1	107–108	104–105[6]
1c	**2a**	**3e**	85	3:2	155–156	156[9]
1c	**2b**	**3f**	87	5:2	134–135	—
1d	**2a**	**3g**	84	2:1	156–157	150–153[7]
1d	**2b**	**3h**	89	2:1	125–126	126–127[6]
1e	**2a**	**3i**	85	7:2	150–152	—
1e	**2b**	**3j**	83	2:1	127–128	—

[a] 10 mmol of salicylaldehyde, 20 mmol of alkyl cyanoacetate, 1 mmol of NaBr, 20 ml of EtOH, Fe-cathode (5 cm^2), C-anode, (5 cm^2), 20 °C.
[b] Isolated yields.
[c] According to ^{1}H NMR data in DMSO-d_6.



1a-e

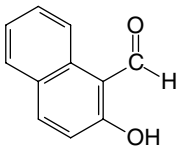
a R^1 = R^2 = H
b R^1 = Br, R^2 = H
c R^1 = NO_2, R^2 = H
d R^1 = H, R^2 = MeO

2a,b

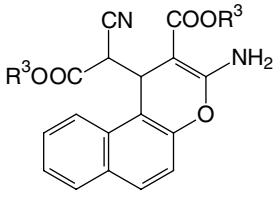
a R^3 = Me
b R^3 = Et

3a-j

a R^1 = R^2 = H, R^3 = Me; **b** R^1 = R^2 = H, R^3 = Et;
c R^1 = Br, R^2 = H, R^3 = Me; **d** R^1 = Br, R^2 = H, R^3 = Et;
e R^1 = NO_2, R^2 = H, R^3 = Me; **f** R^1 = NO_2, R^2 = H, R^3 = Et;
g R^1 = H, R^2 = MeO, R^3 = Me; **h** R^1 = H, R^2 = MeO, R^3 = Et;



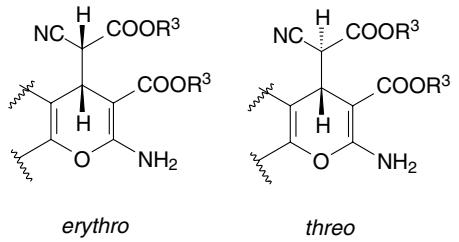
1e



3i,j

i R^3 = Me, **j** R^3 = Et

Scheme 3.



Scheme 4.

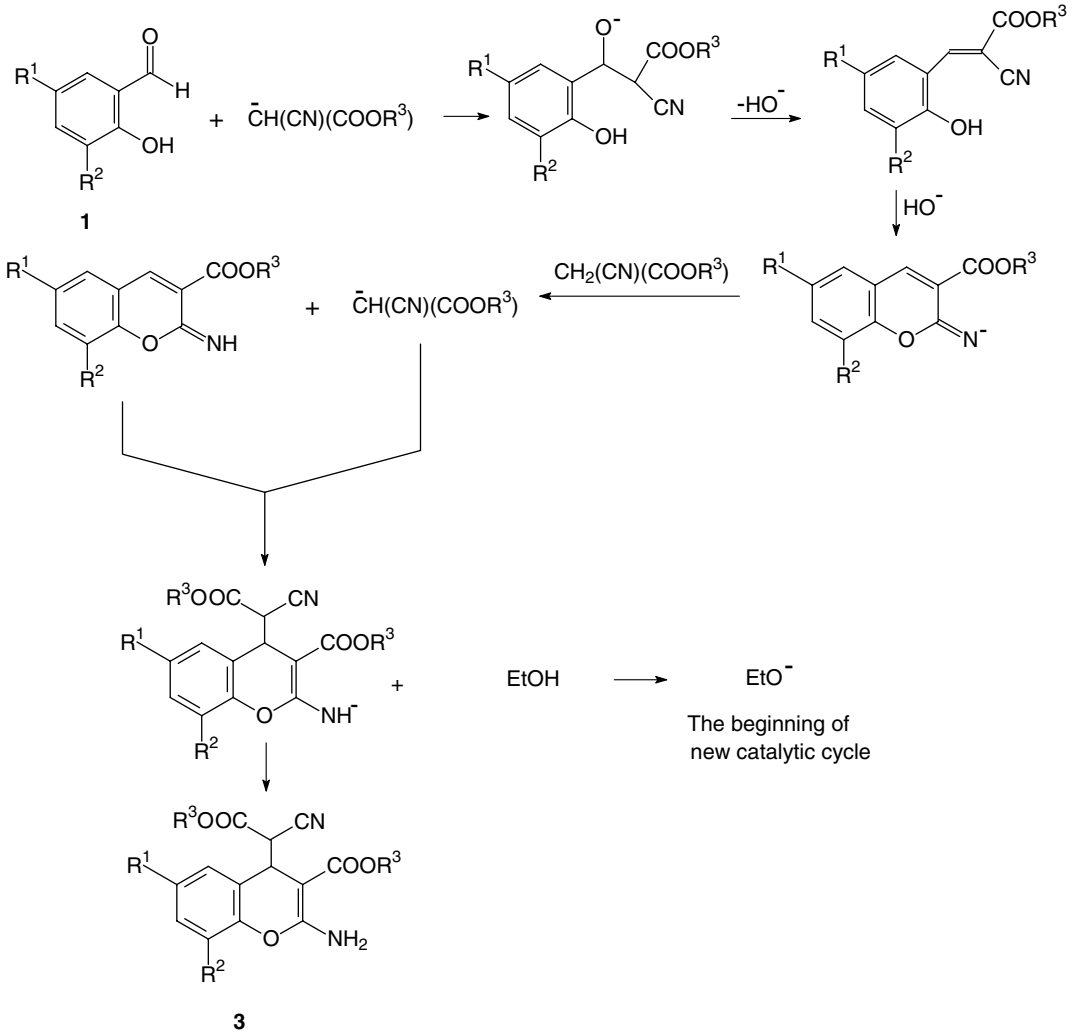
pure oxidative and reductive agent. Despite the significant synthetic potential and ecological advantages, the practical use of electrochemical procedures has often been limited on account of technical complexity and generally long processing times.

In the course of our studies on the electrochemical oxidation of organic compounds in the presence of alkali metal halides,[11] we have developed a new type of electrochemical transformation, namely, the electrocatalytic chain transformation of organic compounds in an undivided cell. The first example of this process involved the electrocatalytic chain cyclization of tetracyanocyclopropanes in an undivided cell, by the action of alkoxide anions generated at the cathode, into substituted 2-amino-4,4-dialkoxy-1,5-dicyano-3-azabicyclo[3.1.0]hex-2-enes[12] (Scheme 1).

Recently, we reported a similar stereoselective electrocatalytic chain transformation of 3-substituted 2,2-dicyanocyclopropane-1,1-dicarboxylates into $(1R,5R,6R)^*$-6-substituted-4,4-dialkoxy-5-cyano-2-oxo-3-azabicyclo-[3.1.0]hexane-1-carboxylates[13] (Scheme 2).

We now report the use of the electrocatalytic chain procedure for the preparation of 4*H*-chromenes **3a**–**j** under mild conditions by the combined electrolysis of salicylaldehydes **1a**–**e** and alkyl cyanoacetates **2a**,**b** in ethanol in an undivided cell (Tables 1 and 2; Scheme 3).

First, to evaluate the synthetic potential of the procedure and to optimize the electrolysis conditions, the electrocatalytic transformation of salicylaldehyde **1a** and 2 equiv of methyl cyanoacetate **2a** into 4*H*-chromene **3a** was studied (Table 1).



Scheme 5.

Under the optimal conditions found ($I = 50$ mA, current density = 10 mA/cm^2, 0.09 F/mol electricity passed, time = 30 min) the electrolyses of substituted salicylaldehydes **1a**–**e** and alkyl cyanoacetates **2a**,**b** were carried out in EtOH. The results are summarized in Table 2.

^{1}H and ^{13}C NMR data showed that the 4*H*-chromenes **3a**–**j** thus obtained were mixtures of two diastereoisomers. From a thermodynamic point of view, the more abundant isomer should have an *erythro* configuration (Scheme 4).

Taking into consideration the above results and the data on the chain electrocatalytic transformation of tetracyanocyclopropanes[12] and the electrocatalytic cyclization of 3-substituted 2,2-dicyanocyclopropane-1, 1-dicarboxylates,[13] the following mechanism for the electrocatalytic chain transformation of salicylaldehydes **1a**–**e** and alkyl cyanoacetates **2a**,**b** into 4*H*-chromenes **3a**–**j** is proposed (Scheme 5).

$$\text{cathode:}\quad 2\text{EtOH} + 2\text{e} \rightarrow 2\text{EtO}^- + \text{H}_2$$

in solution:

$$\text{CH}_2(\text{CN})(\text{COOR}^3) + \text{EtO}^- \rightarrow \bar{\text{C}}\text{H}(\text{CN})(\text{COOR}^3) + \text{EtOH}$$

The ethoxide anion generated from the ethanol at the cathode reacts with the alkyl cyanoacetate. Next, Knoevenagel condensation of the alkyl cyanoacetate anion and salicylaldehyde takes place with the elimination of a hydroxide anion,[15] followed by the cyclization and addition of the second alkyl cyanoacetate anion, which gives the 4*H*-chromene **3** with regeneration of the ethoxide anion in the last stage; the ethoxide anion continues the catalytic chain process by interaction with the next molecule of alkyl cyanoacetate. Theoretically, the generation of a single ethoxide anion at the cathode is sufficient for the full conversion of all the salicyaldehyde and alkyl cyanoacetate into the corresponding 4*H*-chromene.

Thus, a simple electrocatalytic system can produce, under mild conditions, a direct transformation of salicylaldehydes **1** and alkyl cyanoacetates **2** into 4*H*-chromenes **3** in high yields. This electrocatalytic chain process is an efficient and convenient method for the synthesis of substituted cyano-functionalized 4*H*-chromenes. The procedure utilizes inexpensive reagents, simple equipment and an undivided cell, it is easily carried out and the work-up is not complicated.

Acknowledgements

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14. *General electrolysis procedure.* A solution of salicylaldehyde (10 mmol), alkyl cyanoacetate (20 mmol), and

sodium bromide (1 mmol) in ethanol (20 ml) was electrolyzed in an undivided cell equipped with a magnetic stirrer, a graphite anode and an iron cathode at an ambient temperature under a constant current density 10 mA/cm^2 ($I = 50$ mA, electrodes square 5 cm^2) until the catalytic quantity of electricity equal to 0.09 F/mol was passed. The solution was then evaporated and the solid product was crystallized directly from the reaction mixture with 3 ml of cold ethanol–water solution (9:1). Further filtration gave a pure crystalline product.

All compounds (**3a**–**j**) gave expected NMR (DMSO-d_6) and IR spectra. For new compounds satisfactory elemental analyses were obtained.

Methyl 2-amino-6-bromo-4-(1-cyano-2-methoxy-2-oxoethyl)-4H-chromene-3-carboxylate **3c**: IR (KBr, cm^{-1}): ν 3428, 3312, 2956, 2252, 1744, 1688, 1524, 1436, 1232, 1024. Anal. Calcd for $C_{15}H_{13}BrN_2O_5$: C, 47.26; H, 3.44; Br, 20.96; N, 7.35. Found: C, 47.13; H, 3.53; Br, 20.81; N, 7.19.

Major diastereoisomer: ^{1}H NMR (250 MHz, DMSO-d_6): $\delta = 3.65$ (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.40 (d, $J = 3.6$ Hz, 1H, CH), 4.52 (d, $J = 3.6$ Hz, 1H, CH), 7.08 (d, $J = 8.7$ Hz, 1H, Ar), 7.18 (s, 1H, Ar), 7.57 (d, $J = 8.7$ Hz, 1H, Ar), 7.91 (s, 2H, NH_2); ^{13}C NMR (62.5 MHz, DMSO-d_6): $\delta = 36.0$, 46.8, 50.9, 53.1, 70.7, 115.9, 116.2, 118.4, 124.2, 130.6, 132.2, 149.4, 162.2, 165.6, 167.5. Minor diastereoisomer: ^{1}H NMR (250 MHz, DMSO-d_6): $\delta = 3.57$ (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 4.26 (d, $J = 3.0$ Hz, 1H, CH), 4.55 (d, $J = 3.0$ Hz, 1H, CH), 7.05 (d, $J = 8.5$ Hz, 1H, Ar), 7.52 (d, $J = 8.5$ Hz, 1H, Ar), 7.62 (s, 1H, Ar), 7.89 (s, 2H, NH_2); ^{13}C NMR (62.5 MHz, DMSO-d_6): $\delta = 36.3$, 47.0, 50.8, 53.0, 69.9, 116.0, 116.1, 118.1, 122.9, 131.4, 132.0, 149.3, 162.5, 165.4, 167.7.

Ethyl 2-amino-4-(1-cyano-2-ethoxy-2-oxoethyl)-6-nitro-4H-chromene-3-carboxylate **3f**: IR (KBr, cm^{-1}): ν 3428, 3316, 2992, 2260, 1740, 1692, 1520, 1472, 1228, 1040. Anal. Calcd for $C_{17}H_{17}N_3O_7$: C, 54.40; H, 4.57; N, 11.20. Found: C, 54.26; H, 4.62; N, 11.07.

Major diastereoisomer: ^{1}H NMR (250 MHz, DMSO-d_6): $\delta = 1.23$ (t, $J = 7.3$ Hz, 3H, CH_3), 1.28 (t, $J = 7.3$ Hz, 3H, CH_3), 4.05–4.27 (m, 4H, $2OCH_2$), 4.47 (d, $J = 3.7$ Hz, 1H, CH), 4.75 (d, $J = 3.7$ Hz, 1H, CH), 7.39 (d, $J = 9.1$ Hz, 1H, Ar), 7.93 (s, 2H, NH_2), 8.02 (s, 1H, Ar), 8.28 (d, $J = 9.1$ Hz, 1H, Ar); ^{13}C NMR (62.5 MHz, DMSO-d_6): $\delta = 13.8$, 14.2, 36.0, 46.9, 59.5, 62.5, 70.7, 116.0, 117.6, 121.8, 124.2, 125.3, 143.4, 154.6, 161.5, 165.0, 166.9.

Minor diastereoisomer: ^{1}H NMR (250 MHz, DMSO-d_6): $\delta = 1.07$ (t, $J = 7.3$ Hz, 3H, CH_3), 1.16 (t, $J = 7.3$ Hz, 3 H, CH_3), 4.05–4.27 (m, 4H, $2OCH_2$), 4.33 (d, $J = 3.0$ Hz, 1H, CH), 4.74 (d, $J = 3.0$ Hz, 1H, CH), 7.34 (d, $J = 8.55$ Hz, 1H, Ar), 7.91 (s, 2H, NH_2), 8.26 (d, $J = 8.5$ Hz, 1H, Ar), 8.41 (s, 1H, Ar); ^{13}C NMR (62.5 MHz, DMSO-d_6): $\delta = 13.6$, 14.3, 35.8, 45.9, 59.4, 62.2, 70.5, 116.3, 117.3, 122.8, 124.9, 125.1, 143.6, 154.5, 161.6, 164.8, 167.2.

Methyl 3-amino-1-(1-cyano-2-methoxy-2-oxoethyl)-1H-benzo[f]chromene-2-carboxylate **3i**: IR (KBr, cm^{-1}): ν 3468, 3316, 2956, 2252, 1744, 1684, 1520, 1444, 1220, 1080. Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.61; H, 4.53; N, 7.81.

Major diastereoisomer: ^{1}H NMR (250 MHz, DMSO-d_6): $\delta = 3.64$ (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.23 (d, $J = 2.0$ Hz, 1H, CH), 5.20 (d, $J = 2.0$ Hz, 1H, CH), 7.35 (d, $J = 9.2$ Hz, 1H, Ar), 7.52–8.08 (m, 7H, Ar, NH_2); ^{13}C NMR (62.5 MHz, DMSO-d_6): $\delta = 33.7$, 46.8, 50.9, 53.2, 70.3, 114.5, 116.0, 116.6, 121.5, 125.4, 128.2, 129.3, 130.1, 130.3, 130.9, 148.0, 162.9, 165.9, 168.0. Minor diastereoisomer: ^{1}H NMR (250 MHz, DMSO-d_6): $\delta = 3.47$ (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.31 (d, $J = 3.7$ Hz, 1H, CH), 5.24 (d, $J = 3.7$ Hz, 1H, CH), 7.52–8.08 (m, 8 H, Ar, NH_2); ^{13}C NMR (62.5 MHz, DMSO-d_6): $\delta = 33.2$, 46.1, 50.8, 52.9, 72.3, 114.0, 116.4, 116.7, 122.1, 125.2, 127.4, 128.9, 130.2, 130.4, 130.6, 148.8, 162.8, 165.7, 167.7.

Ethyl 3-amino-1-(1-cyano-2-ethoxy-2-oxoethyl)-1H-benzo[f]chromene-2-carboxylate **3j**: IR (KBr, cm^{-1}): ν 3456, 3328, 2976, 2256, 1740, 1676, 1516, 1464, 1228, 1076. Anal. Calcd. for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36. Found: C, 66.19; H, 5.37; N, 7.18.

Major diasteroisomer: ^{1}H NMR (250 MHz, DMSO-d_6): $\delta = 1.26$ (t, $J = 7.3$ Hz, 3H, CH_3), 1.29 (t, $J = 7.3$ Hz, 3H, CH_3), 3.85–4.28 (m, 5H, $2OCH_2$, CH), 5.22 (d, $J = 1.8$ Hz, 1H, CH), 7.34 (d, $J = 9.2$ Hz, 1H, Ar), 7.50–8.10 (m, 7H, Ar, NH_2); ^{13}C NMR (62.5 MHz, DMSO-d_6): $\delta = 13.9$, 14.4, 33.5, 46.7, 59.2, 62.1, 71.0, 114.8, 116.1, 116.6, 121.6, 125.3, 128.1, 128.9, 129.1, 130.1, 130.9, 147.9, 162.8, 165.3, 167.6. Minor diasteroisomer: ^{1}H NMR (250 MHz, DMSO-d_6): $\delta = 0.99$ (t, $J = 7.3$ Hz, 3H, CH_3), 1.34 (t, $J = 7.3$ Hz, 3H, CH_3), 3.85–4.28 (m, 5H, $2OCH_2$, CH), 5.25 (d, $J = 3.7$ Hz, 1H, CH), 7.50–8.10 (m, 8H, Ar, NH_2); ^{13}C NMR (62.5 MHz, DMSO-d_6): $\delta = 13.3$, 14.3, 33.2, 46.2, 59.3, 62.0, 72.3, 114.1, 116.5, 116.7, 122.1, 125.1, 127.3, 128.8, 129.3, 130.0, 130.6, 148.7, 162.6, 165.2, 167.4.

15. Patai, S.; Israeli, Y. *J. Chem. Soc.* **1960**, 2025–2030.