SYNTHESIS OF 2-AMINO-4-ARYL-3-CYANO-6-METHYL-5-ETHOXYCARBONYL-4*H*-PYRANS

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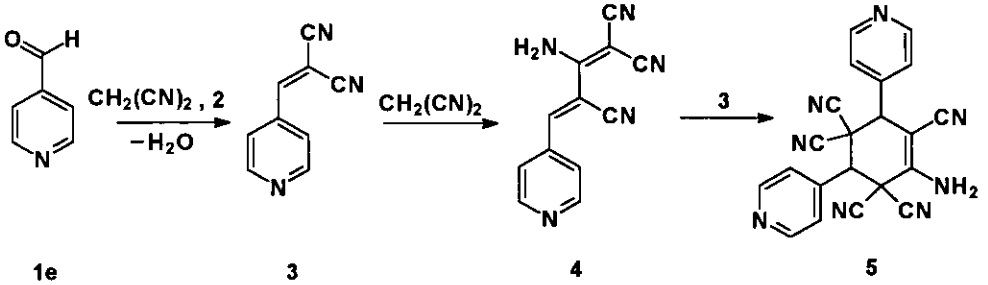
Abstract - A one-step electrochemical synthesis of the title compounds has been devised. The starting materials are aromatic and heteroaromatic aldehydes, malononitrile and ethyl acetoacetate. The overall reaction is catalyzed by electrogenerated base (EGB) formed at a platinum cathode in acetonitrile.

Substituted 2-amino-4*H*-pyrans are significant in a number of practical applications. Some have been shown to exhibit biological activity[1,2] and they also serve as convenient starting materials for the synthesis of esoteric condensed heterocycles.[3-7] Synthesis of substituted 2-amino-4*H*-pyrans is usually a two-step process that is carried out in the presence of a base as catalyst (piperidine, morpholine or metal alkoxides) in refluxing ethanol or other solvents. The first step is the formation and isolation of an α,β-unsaturated nitrile that is subsequently reacted with a 1,3-dicarbonyl compound to form the 2-amino-4*H*-pyran.[4,6-10] However, this method does not always succeed. When 4-pyridinecarboxaldehyde (**1e**) and malononitrile (**2**) were used in the first step of the above process, substituted cyclohexene (**5**) was obtained instead of the expected unsaturated nitrile (**3**).[11] Formation of **5** was observed no matter what ratio of aldehyde to malononitrile was used, the highest yields being observed with a ratio of 1.5:1. This outcome can be explained by the Knoevenagel reaction of **1e** with **2** to form the desired **3** which undergoes rapid nucleophilic addition of malononitrile (**2**) to 3 followed by a Diels-Alder reaction of **4** and **3** producing the observed product (**5**). In the present work it will be shown that a one-step electrochemical synthetic procedure can produce the desired substituted 2-amino-4*H*-pyran (**7e**) in excellent yield by reaction of 4-pyridinecarboxaldehyde, malononitrile and ethyl acetoacetate.



The electrochemical generation of reactive anions has proven to be quite useful in synthetic chemistry.[12] The anions can be formed by direct reduction at the cathode, for example by reduction of an element-hydrogen bond (E-H) to give the anion E^- and 1/2 H_2 or by reduction of a disulfide to form two thiolate anions. Another approach is to add a probase to the electrolysis solution. The probase is reduced at the cathode forming a radical anion, anion or dianion (electrogenerated base, EGB) that is very basic and is able to deprotonate the substrate making the desired anion. In previous work in the Delaware group, both approaches have been used. For the catalyzed addition of thiols to levoglucosenone,[13,14] the thiolate was generated by direct reduction of the thiol, whereas, addition of nitroalkanes to levoglucosenone[13] and other Michael acceptors[15-17] was catalyzed by the EGB superoxide, formed by reduction of dioxygen at the cathode.

Base-catalyzed condensation of aldehydes with various nitro compounds have also been achieved using superoxide as EGB.[18-20] These successes prompted us to investigate the EGB-catalyzed condensation of aldehydes with other active methylene groups, malononitrile in particular. We discovered that it is possible to electrolyze solutions containing simultaneously all three reactants (aldehyde, malononitrile, and ethyl acetoacetate) and produce the desired substituted 2-amino-4*H*-pyran. To our knowledge, such a one-step combined condensation/addition/cyclization reaction is unprecedented in electrochemical synthesis.

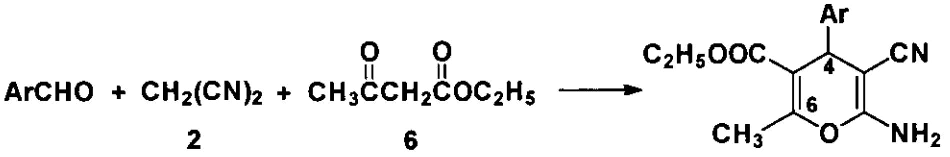
The new synthesis of substituted 2-amino-4*H*-pyrans (7) begins with an equimolar mixture of aldehydes (**1**), malononitrile (**2**) and ethyl acetoacetate (**6**). The reagents that have been selected here were simply chosen as examples of what may possibly be developed as a fairly general approach to substituted pyrans.

The electrolyses were carried out in a divided cell with a platinum cathode with an equimolar mixture (0.01 mol) of **1**, **2** and **6** in the cathode compartment. The solvent was acetonitrile and 0.10 M Bu_4NBr was used as the electrolyte. Only a catalytic amount of electricity was needed to complete the transformation. The amount of electricity is expressed as the number of Faradays of charge passed per mole of reactant, F/mol. When F/mol is unity or larger, the electrolysis requires a stoichiometric amount of electricity whereas when F/mol << 1, a catalytic reaction is indicated. For **1a-e**, F/mol ranged from 0.07 to 0.11. The results are summarized in Table 1. The regioselectivity of the reaction is very high and the product yield (isolated) of 75-88% for 7**a-e** is very good.

Table 1. Electrochemical synthesis, MS, and ^{1}H NMR spectra of 2-amino-4*H*-pyrans (**7a-f**).

Compound	mp (°C)	Yield (%)	Faraday/mol[a]	MS (m/z, (%, ion))	Chemical shifts in the ^{1}H NMR spectra of 7a-f (δ values in DMSO-d_6, ppm)					
					$C\underline{H}_3CH_2$ (t)	$C\underline{H}_3C^6$ (s)	$CH_3C\underline{H}_2$ (q)	C^4H (s)	NH_2 (s)	Ar
7a	180-182	75	0.111	285 (5, M^++1) 284 (32, M^+) 207 (100, M^+-Ar)	1.01 J=7.3 Hz	2.30	3.95 J=7.3 Hz	4.27	6.90	7.11-7.33 (m, 5H)
7b	171-173	88	0.076	320 (7, M^++2) 318 (21, M^+) 207 (100, M^+-Ar)	1.02 J=7.3 Hz	2.30	3.96 J=7.3 Hz	4.29	6.98	7.14 (d, 2H, J=8.3 Hz) 7.36 (d, 2H, J=8.3 Hz)
7c	183-185	87	0.077	330 (2, M^++1) 329 (10, M^+) 207 (100, M^+-Ar)	1.01 J=7 Hz	2.33	3.94 J=7 Hz	4.51	7.10	7.60-7.66 (m, 2H) 7.97 (s, 1H) 8.08-8.13 (m, 1H)
7d	194-196	80	0.079	291 (18, M^++1) 290 (100, M^+) 207 (25, M^+-Ar)	1.13 J=6.8 Hz	2.27	4.08 J=6.8 Hz	4.63	7.06	6.84 (s, 1H) 6.92 (t, 1H, J=3.7 Hz) 7.37 (d, 1H, J=3.7 Hz)
7e	162-163	87	0.074	286 (4, M^++1) 285 (23, M^+) 207 (100, M^+-Ar)	1.00 J=6.8 Hz	2.33	3.95 J=6.8 Hz	4.30	7.06	7.16 (d, 2H, J=2.5 Hz) 8.48 (d, 2H, J=2.5 Hz)
7f	255-257 decomp	57	0.125	490 (4, M^+) 207 (100, M^+-Ar)	0.97 J=7 Hz	2.28	3.95 J=7 Hz	4.24	6.87	7.38 (s, 4H)

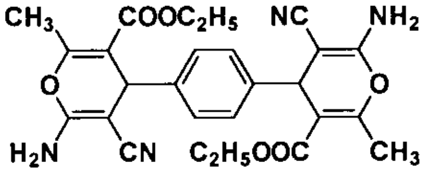
[a] Per mol of aldehyde



7a-e

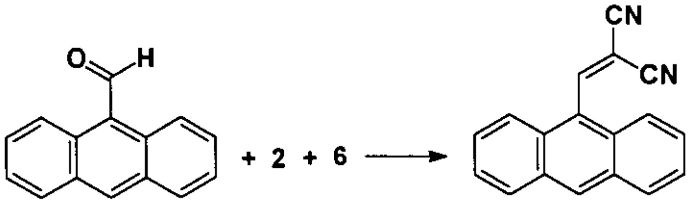
1a = C_6H_5
1b = 4-Cl-C_6H_4
1c = 3-O_2N-C_6H_4
1d = 2-Thienyl
1e = 4-Pyridyl

Terephthalaldehyde (1,4-benzenedicarboxaldehyde, **1f**) produced the bis(2-amino-4*H*-pyran) derivative **7f**, though in lower yield (57%). Only one diastereomer of **7f** was detected by NMR but its stereochemistry was not established.



7f

Electrolysis of 9-anthracenecarboxaldehyde with **2** and **6** gave only the product (**8**) of the first step of the desired sequence of reactions. Steric and electronic deactivation of the –CH=C(CN)$_2$ fragment by the anthracene ring probably prevents subsequent transformation of **8**. Ferrocenecarboxaldehyde yielded a tarry product.



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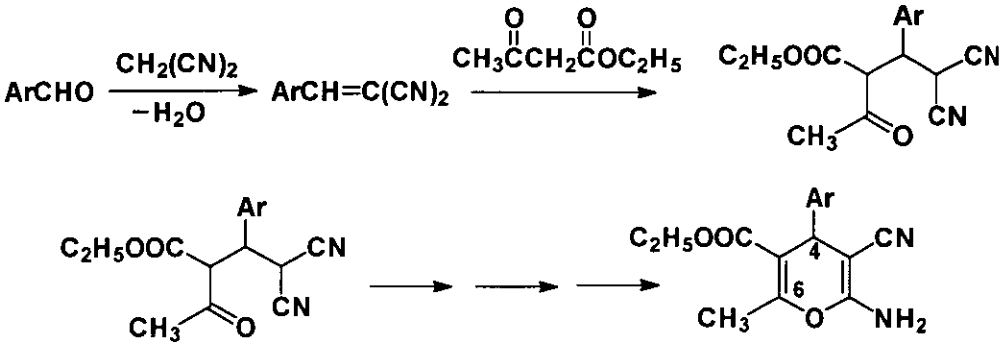
The structures of known compounds (**7a-c**) were confirmed by ^{1}H NMR and MS and by comparison of melting points with literature data. In addition to NMR and MS, FT-IR and chemical analysis were employed to establish the structures of novel compounds (**7d-f**) (Table 1). In addition to the characteristic chemical shifts of the functional groups, the ^{1}H NMR spectra of **7a-f** show the presence of C^{4}H and NH$_2$ protons as singlets in the range δ = 4.24-4.63 and 6.87-7.10 ppm, respectively, as required for 2-amino-4*H*-pyran derivatives.

The formation of **7a-f** can be rationalized by the following reaction sequence: Knoevenagel condensation, Michael addition and Thorpe-Ziegler cyclization. Thus, a regioselective one-step electrochemical method of synthesis of substituted 2-amino-4*H*-pyrans has been developed, which does not require the preliminary preparation of unsaturated nitriles.



7a-e

EXPERIMENTAL

All materials were of standard commercial origin and were used as received. A Kepco model OPS 100-5power supply in conjunction with an Electrosynthesis 640 digital coulometer was used to conduct the electrolyses. ^{1}H NMR were obtained in DMSO- d_6 on a Brüker 250 MHz spectrometer. IR spectra were recorded using KBr pellets on a Nicolet 510 FT-IR spectrometer. MS were recorded on a ZAB-2SE spectrometer. A Büchi 510 melting point apparatus was used and the melting points are uncorrected.

Standard Procedure. The cell for the electrolysis was an 80-mL glass beaker with a polyethylene cover into which were fitted the anode compartment which was surrounded by a cylindrically-shaped platinum gauze cathode (*ca.* 20 cm^2). The anode compartment was a polyethylene tube about 2 cm in diameter into which the magnesium anode (6-mm diameter rod) was fitted through a pierced septum. About 30 holes (5 mm) were drilled through the side of the tube that was wrapped with three layers of tracing paper to serve as separator between the anode and cathode compartments.

The catholyte was 40 mL of 0.10 M Bu_4NBr in acetonitrile containing 0.01 mol each of **1**, **2** and **6** (for **7f** the amount of **2** and **6** was 0.02 mol). The anode compartment held about 20 mL of electrolyte. The electrolyses were carried out under controlled current conditions (*ca.* 10-20 mA) in vigorously stirred solutions. No provision was made to supply air (for the generation of superoxide) to the reaction. Sufficient oxygen was present in the initially air-saturated catholyte to effect the transformation. After passing the specified amount of charge (Table 1), the solvent was removed from the catholyte with a rotary evaporator. The residue was taken up in ethanol (*ca.* 20 mL) and the product was precipitated by addition of 5-10 mL of water. The precipitate was filtered off and washed with ethanol to give **7a-f**. No purification was required.

For **7f** only, the electrolyzed solution was allowed to stand overnight to allow the reaction to reach completion before workup.

Derivatives (**7a-c**) have been described in the literature.[21]

Analytical data for other compounds.

7d: mp 194-196 °C; IR (cm^{-1}): 3395 (s), 3329 (s), 3264 (m), 3225 (m), 3203 (m), 2994 (w), 2980 (w), 2968 (w), 2911 (w), 2193 (s), 1693 (s), 1676 (s), 1649 (m), 1611 (m), 1413 (m), 1382 (m), 1371 (s), 1330 (s), 1262 (s), 1207 (m), 1178 (m), 1115 (m), 1066 (s), 1040 (m), 1016 (m), 874 (w), 858 (m), 833 (w), 795 (m), 767 (w), 701 (s), 630 (w), 507 (m). High-resolution MS: M^+ 290.0721 (obs); 290.0725 (calc). Anal. Calcd for $C_{14}H_{14}N_2O_3S$: C, 57.92; H, 4.86; N, 9.65; S, 11.04. Found: C, 57.81; H, 4.79; N, 9.70; S, 10.86.

7e: mp 162-163 °C; IR (cm^{-1}): 3382 (s), 3328 (s), 3267 (m), 3222 (s), 3199 (m), 3069 (w), 2970 (w), 2925 (w), 2190 (s), 1697 (s), 1680 (s), 1650 (m), 1609 (m), 1597 (m), 1418 (m), 1383 (m), 1371 (m), 1333 (s), 1266 (s), 1212 (m), 1179 (m), 1123 (m), 1065 (s), 1017 (m), 861 (m), 841 (w), 818 (w), 789 (w), 765 (m), 739 (w), 691 (w), 634 (w), 543 (w), 523 (m). High –resolution MS: 285.1122 (obs); 285.1113 (calc). Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.97; H, 5.64; N, 14.51.

7f: mp 225-227 °C (decomp); IR (cm^{-1}): 3397 (s), 3339 (s), 3272 (s), 3226 (s), 2987 (w), 2936 (w), 2915 (w), 2191 (s), 1691 (s), 1678 (s), 1648 (m), 1605 (m), 1415 (w), 1372 (s), 1333 (s), 1264 (s), 1211 (m), 1178 (m), 1119 (m), 1063 (s), 1019 (m), 955 (w), 867 (w), 816 (w), 759 (w), 644 (w), 512 (w). High-resolution MS: 490.1871 (obs); 490.1852 (calc). Anal. Calcd for $C_{26}H_{26}N_4O_6$: C, 63.66; H, 5.34; N, 11.42. Found: C, 63.31; H, 5.22; N, 11.73.

ACKNOWLEDGMENT

This research was supported by the National Science Foundation through grant CHE-9704211.

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Received, 6th January, 1999