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Synthesis of (*E*)-3-(2-carboxy-2-pyridyl-vinyl)-4,6-dichloro-1*H*-indole-2-carboxylic acids, glycine-site NMDA receptor antagonists, utilizing the Knoevenagel condensation reaction

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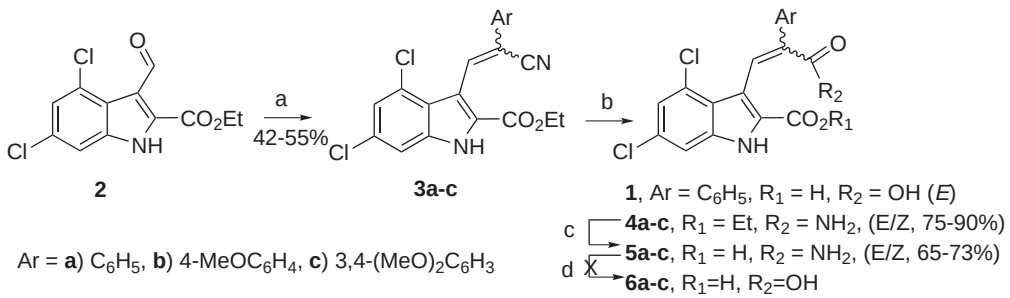
Abstract—The Knoevenagel condensation of arylacetonitriles with ethyl 4,6-dichloro-3-formyl-1*H*-indole-2-carboxylate (**2**), followed by hydrolysis, provides a convenient entry into a series of analogs of MDL 105,519, **1**, a selective glycine site *N*-methyl-D-aspartate (NMDA) receptor antagonist. Surprisingly, the hydrolysis of the indole arylpropenenitriles terminates at the formation of the corresponding carboxamide and does not proceed further to the desired dicarboxylic acid. However, when the aryl substituent is pyridine, hydrolysis proceeds via an azepinoindole unique to this series, which upon further hydrolysis converts smoothly to the desired dicarboxylic acid analog.

Development of a selective glycine-site NMDA antagonist could offer a novel mechanism of neuroprotection and cell death prevention, precluding the effects of stroke and head trauma.[1] MDL 105,519, (*E*)-3-(2-carboxy-2-phenyl-vinyl)-4,6-dichloro-1*H*-indole-2-carboxylic acid (**1**), was identified as a potent glycine antagonist that has affinity for the glycine-site of the NMDA receptor (IC_{50} versus [^{3}H]glycine of 24 nM) and brain penetration (demonstrated by anticonvulsant activity; ED_{50} versus audiogenic seizures of 11 mg/kg i.p. and 29 mg/kg i.v. versus maximal electroshock in the rat).[2] In order to optimize in vivo potency, duration of action, and binding affinity, a series of aryl indole amide carboxylic acids and dicarboxylic acid analogs of **1** (Scheme 1) was synthesized using the Knoevenagel reaction.

Under classical Knoevenagel condensation conditions,[3] arylacetic esters react with aldehydes and ketones in the presence of a catalytic amount of base to afford arylpropenoic esters. When indole aldehyde **2**[4] was reacted with arylacetic esters under these conditions, none of the desired condensation product was observed, possibly due to the conjugation effect of the indole nitrogen resulting in decreased electrophilicity of the aldehyde carbonyl. Upon further investigation it was discovered



Scheme 1. (a) Arylacetonitrile, cat. piperidine, EtOH, Δ. (b) H_2SO_4/HOAc, Δ. (c) LiOH, THF/H_2O. (d) 6N NaOH, THF, Δ.

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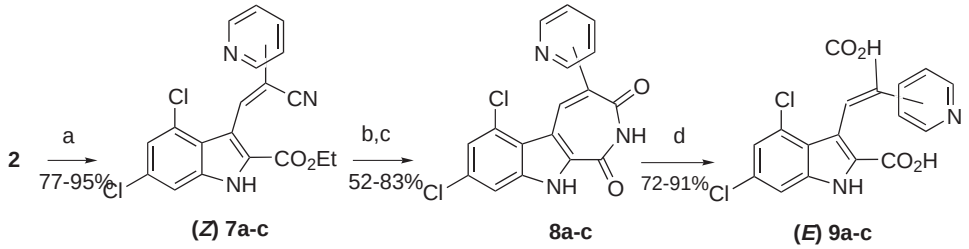

Scheme 2. (a) Pyridylacetonitrile, cat. piperidine, EtOH, Δ. (b) H_2SO_4/HOAc, Δ. (c) LiOH, THF/H_2O. (d) 6N NaOH, THF, Δ.

that the reaction of arylacetonitriles with indole aldehyde **2** afforded the corresponding arylpropenenitriles (Scheme 1). In a typical experiment, indole aldehyde **2** (1.43 g, 5.0 mmol), the arylacetonitrile (1.0 equiv., 5.0 mmol) and piperidine (four drops) were refluxed for 16 h in EtOH (95%, 30 mL). After cooling to rt, the reaction was diluted with Et_2O and the resulting solid was filtered, washed with Et_2O, and dried under vacuum. Chromatography afforded ethyl 4,6-dichloro-3-(2-cyano-2-aryl-vinyl)-1*H*-indole-2-carboxylates (**3a**–**c**) in moderate yield, as *E*/*Z* mixtures (Scheme 1).[5] Acid hydrolysis of propenenitrile esters **3a**–**c** under the indicated conditions afforded propenamide esters **4a**–**c**, which upon subsequent alkaline hydrolysis gave the propenamide acids **5a**–**c** (Scheme 1). The propenamide acids **5a**–**c** are very stable, and attempts to further hydrolyze them to the desired dicarboxylic acid analogs **6a**–**c** were either unsuccessful or required harsh conditions.[6] Under analogous conditions, a different course of events was observed in the case of the pyridyl analogs **7a**–**c**, which are obtained exclusively as *Z* isomers from the Knoevenagel reaction (Scheme 2).[7] Unique to the pyridyl series is the formation of azepinoindole[8] intermediates **8a**–**c**. As a representative example, azepinoindole **8a** is characterized by two sharp singlets at δ 13.43 (indole NH) and δ 12.10 (azepinedione NH) in the ^{1}H NMR spectrum (400 MHz, DMSO-d_6), and two carbonyl resonances at δ 163.5 and δ 157.8 (proximal to indole) in the ^{13}C NMR spectrum.[9] Treatment of azepinoindoles **8a**–**c** with 6N NaOH and heating for 16 h provided the desired *E*-pyridyl indole dicarboxylic acids, **9a**–**c**, in good to moderate yields.

It appears that formation of an azepinoindole intermediate is a prerequisite for successful hydrolysis to the desired indole dicarboxylic acids under reasonably mild conditions. While indole propenenitriles **3a**–**c** contain a proportion of the *Z* isomer required for cyclization to the corresponding azepinoindole intermediate,[8] and while *E*/*Z* equilibration of **3a**–**c** under the hydrolysis conditions appears conceivable, azepinoindole formation from **3a**–**c** was not observed under similar reaction conditions. Attempts were made to increase the proportion of the *Z* isomer of **3a**–**c**, based on the observation that the *E*/*Z* distribution is dependent on the number of equivalents of base used and the reaction temperature.[10] Unfortunately, increased temperature and addition of pyridine to the reaction mixture failed to result in exclusive formation of the *Z* isomer of propenenitriles **3a**–**c**, and subsequent formation of the respective azepinoindole intermediate necessary for complete conversion to the desired dicarboxylic acids **6a**–**c**. It is envisaged that the intramolecular presence of a pyridine ring facilitates not only the exclusive formation of the *Z* indole propenenitrile intermediates **7a**–**c**, but also their subsequent cyclization to provide the azepinoindole intermediates **8a**–**c** observed in only the pyridyl series.

In conclusion, the one-step preparation of arylpropenenitriles **3a**–**c** and **7a**–**c** provided a convenient entry into a class of compounds related to MDL 105,519, **1**. Conditions were developed for the synthesis of the propenamide carboxylic acids **5a**–**c** via this route, in three short steps (Scheme 1). In addition, the 2-, 3- and 4-substituted pyridine analogs of MDL 105,519, **9a**–**c**, were synthesized in three steps in good to moderate yields (Scheme 2). Analog **9b** was found to have an affinity for the glycine-site of the NMDA receptor of 126 nM (IC_{50} versus [^{3}H]glycine).

References

1. Choi, D. W.; Rothman, S. M. *Annu. Rev. Neurosci.* **1990**, *13*, 171–182.
2. (a) Baron, B. M.; Harrison, B. L.; Kehne, J. H.; et al. *Eur. J. Pharmacol.* **1997**, *323*, 181–192; (b) [3H]MDL 105,519 is commercially available (Amersham Pharmacia Biotech) as a high-affinity radioligand for the NMDA receptor-associated glycine recognition site, see: Baron, B. M.; et al. *J. Pharmacol. Exp. Ther.* **1996**, *279*, 62–68.
3. For a review of the Knoevenagel reaction, see: Jones, G. *Org. React.* **1967**, *15*, 204–599.
4. Aldehyde **2** was readily obtained in high yield by the reaction of 2-ethoxycarbonyl-4,6-dichloroindole[11] with $POCl_3$ and DMF in dichloroethane at 90°C.
5. Depending on the aryl substituent, the Knoevenagel condensation can be sluggish and may proceed in low yield with starting material being recovered. While substituted phenyl and pyridylacetonitriles reacted to give acceptable yields of the condensation product, thiophene and furan acetonitriles did not react.
6. 3-(2-Carbamoyl-2-phenylvinyl)-4,6-dichloro-1*H*-indole-2-carboxylic acid ethyl ester **4a** can be hydrolyzed to MDL 105,519, **1**, using 9 M H_2SO_4 in refluxing dioxane for 16 h, as described in: Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361–9362.

7. Compound **7a**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.93 brs, 8.83 s, 8.71 ddd (J=5, 2, 1 Hz), 7.97 dd (J=8, 7.5 Hz), 7.82 ddd (J=8, 1, 1 Hz), 7.56 d (J=2 Hz), 7.47 ddd (J=7.5, 5, 1 Hz), 7.34 d (J=2 Hz), 4.33 q (2H; J=7 Hz), 1.23 t (3H; J=7 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.3 s, 150.3 s, 149.9 d, 138.5 d, 137.9 d, 137.3 s, 129.6 s, 127.2 s, 127.0 s, 124.1 d, 122.1 s, 122.0 d, 120.4 d, 117.7 s, 116.8 s, 114.2 s, 111.8 d, 61.3 t, 13.9 q; assignment of trisubstituted olefin geometry in **7a**–**c** was based on NOE data (strong NOE between olefinic proton and proximal protons of *syn*-vicinal pyridyl residue versus weak or absent NOE in case of analogs with *anti*-vicinal aromatic residue) and/or the size of vicinal proton–carbon coupling constants involving the olefinic proton (e.g. large *trans*-coupling of 12.5–14 Hz to nitrile carbon versus smaller *cis*-couplings of 6.5–8 Hz observed for *syn*-vicinally situated carbons).
8. Pigulla, J.; Röder, E. *Arch. Pharm.* **1978**, *311*, 822–827.
9. Azepinoindole **8a**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.43 s, 12.10 s, 8.83 d (J=5 Hz), 8.80 s, 8.30 dd (J=8, 8 Hz), 7.76 dd (J=8, 5 Hz), 7.58 d (J=1.5 Hz), 7.46 d (J=1.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.5 s, 157.8 s, 153.7 s, 145.1 d, 141.7 d, 138.1 s, 133.9 s, 133.2 s, 130.8 s, 127.1 s, 126.6 d, 124.5 d, 123.7 d, 120.8 s, 113.4 s, 112.3 d; the structural assignment, and the positional assignment of NH protons and carbonyl carbons, are based on long-range proton–carbon shift correlation data.
10. Micheli, F.; DiFabio, R.; et al. *Arch. Pharm. Med. Chem.* **1999**, 271–278.
11. For preparation of 2-ethoxycarbonyl-4,6-dichloroindole, see: Salituro, F. G.; et al. *J. Med. Chem.* **1990**, *33*, 2946–2948.