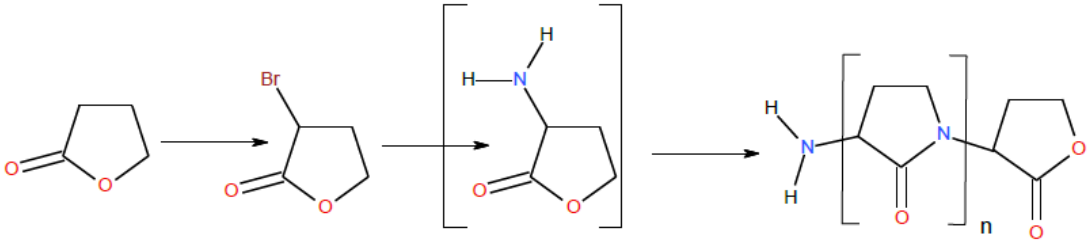
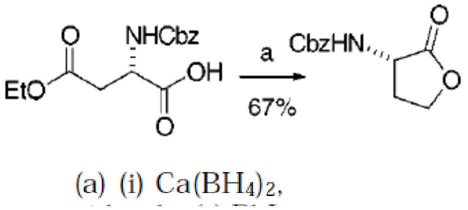
2,5-DiketoPiperazine Polymers

By: Robert B. Login   rloginconsulting.com

Looking for a new idea to keep me busy during the pandemic, I asked myself why aminolactones don't spontaneous form polyamides? Since I have had a long time interest in pyrrolidones, I visualized the following:



Scheme 1: This seems so obvious then why is it not in the literature?

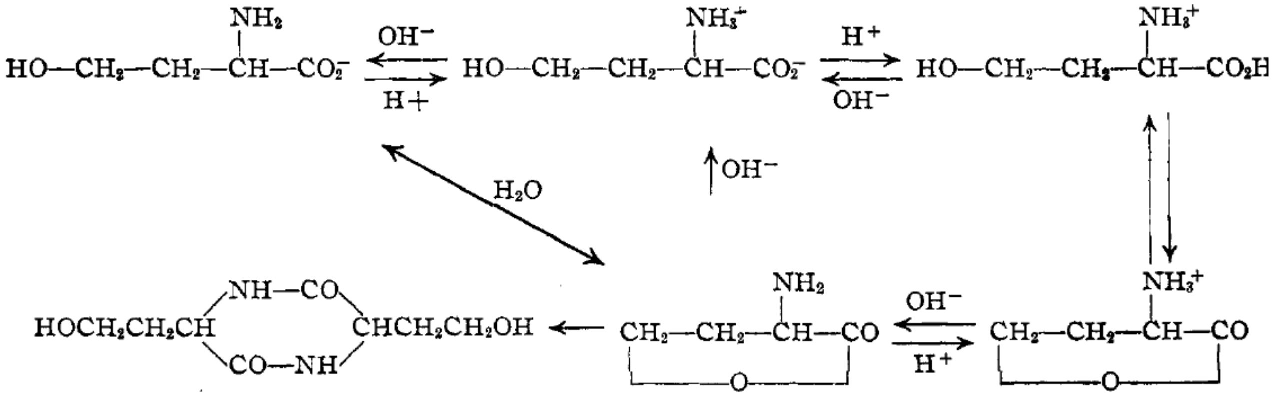


Seki, M., Shimizu, T., & Matsumoto, K. (2000). Stereo-selective Synthesis of β-Benzyl-α-alkyl-β-amino Acids from l-Aspartic Acid1.*The Journal of organic chemistry*, *65*(5), 1298-1304.

Stacy, D. M., Le Quement, S. T., Hansen, C. L., Clausen, J. W., Tolker-Nielsen, T., Brummond, J. W., ... & Blackwell, H. E. (2013). Synthesis and biological evaluation of triazole-containing N-acyl homoserine lactones as quorum sensing modulators. *Organic & biomolecular chemistry*, *11*(6), 938-954.

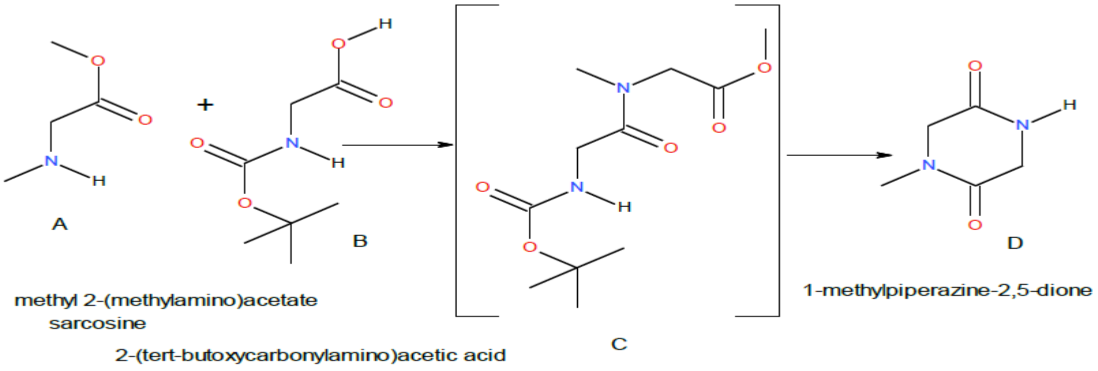
Its easy enough to make the starting amine from inexpensive aspartic acid.

The reason is that the polymerization is not how the reaction proceeds.

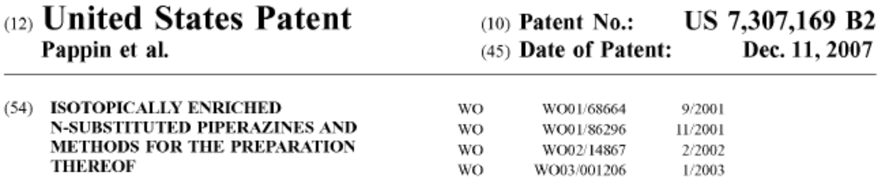


Armstrong, M. D. (1949). The relationship between homoserine and its lactone. *Journal of the American Chemical Society*, *71*(10), 3399-3402.

You can see that instead of the polymer, the diketopiperazine is the product. I looked at its structure and was struck by new possibilities that occurred to me.



Scheme 2: There are many references to amino acid dimers.


(12) **United States Patent**
Pappin et al.

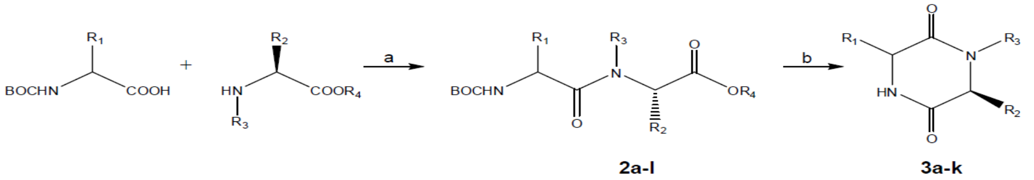
(10) **Patent No.:** **US 7,307,169 B2**
(45) **Date of Patent:** **Dec. 11, 2007**

(54) **ISOTOPICALLY ENRICHED N-SUBSTITUTED PIPERAZINES AND METHODS FOR THE PREPARATION THEREOF**

WO	WO01/68664	9/2001
WO	WO01/86296	11/2001
WO	WO02/14867	2/2002
WO	WO03/001206	1/2003

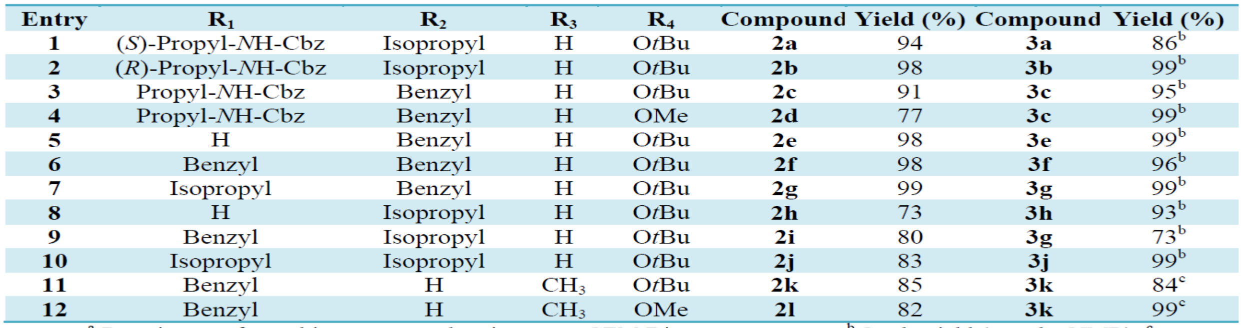
Azuse, I., Tamura, M., Kinomura, K., Okai, H., Kouge, K., Hamatsu, F., & Koizumi, T. (1989). Peptide Synthesis in Aqueous Solution. IV. Preparation and Properties of [p-(Benzyloxycarbonyloxy) phenyl] dimethylsulfonium Methyl Sulfate (Z-ODSP),[p-(t-Butoxycarbonyloxy) phenyl] dimethylsulfonium Methyl Sulfate (Boc-ODSP) and [p-(9-Fluorenylmethyloxycarbonyloxy) phenyl] dimethylsulfonium Methyl Sulfate (Fmoc-ODSP) as Water-Soluble N-Acylating Reagents. *Bulletin of the Chemical Society of Japan*, *62*(10), 3103-3108.

Table 2. Coupling of amino acids and ring closure under microwave irradiation.[a]



2a-l **3a-k**

(a) EDAC, HOBt, DMAP, TEA/CH_2Cl_2, 5 °C, then overnight at rt; (b) H_2O (1 mL), MW (250 °C, 250 W and 150 psi) for 10 min.



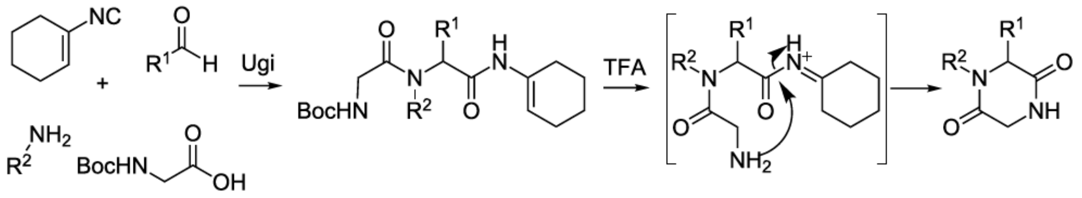
Entry	R_1	R_2	R_3	R_4	Compound	Yield (%)	Compound	Yield (%)
1	(*S*)-Propyl-*N*H-Cbz	Isopropyl	H	O*t*Bu	**2a**	94	**3a**	86[b]
2	(*R*)-Propyl-*N*H-Cbz	Isopropyl	H	O*t*Bu	**2b**	98	**3b**	99[b]
3	Propyl-*N*H-Cbz	Benzyl	H	O*t*Bu	**2c**	91	**3c**	95[b]
4	Propyl-*N*H-Cbz	Benzyl	H	OMe	**2d**	77	**3c**	99[b]
5	H	Benzyl	H	O*t*Bu	**2e**	98	**3e**	99[b]
6	Benzyl	Benzyl	H	O*t*Bu	**2f**	98	**3f**	96[b]
7	Isopropyl	Benzyl	H	O*t*Bu	**2g**	99	**3g**	99[b]
8	H	Isopropyl	H	O*t*Bu	**2h**	73	**3h**	93[b]
9	Benzyl	Isopropyl	H	O*t*Bu	**2i**	80	**3g**	73[b]
10	Isopropyl	Isopropyl	H	O*t*Bu	**2j**	83	**3j**	99[b]
11	Benzyl	H	CH_3	O*t*Bu	**2k**	85	**3k**	84[c]
12	Benzyl	H	CH_3	OMe	**2l**	82	**3k**	99[c]

[a] Reactions performed in a monomode microwave CEM Discover apparatus; [b] Crude yield (pure by NMR); [c] Isolated yield after chromatography .

Pérez-Picaso, L., Escalante, J., Olivo, H. F., & Rios, M. Y. (2009). Efficient microwave assisted syntheses of 2, 5-diketopiperazines in aqueous media. *Molecules*, *14*(8), 2836-2849.

The above microwave synthesis results in excellent yields.

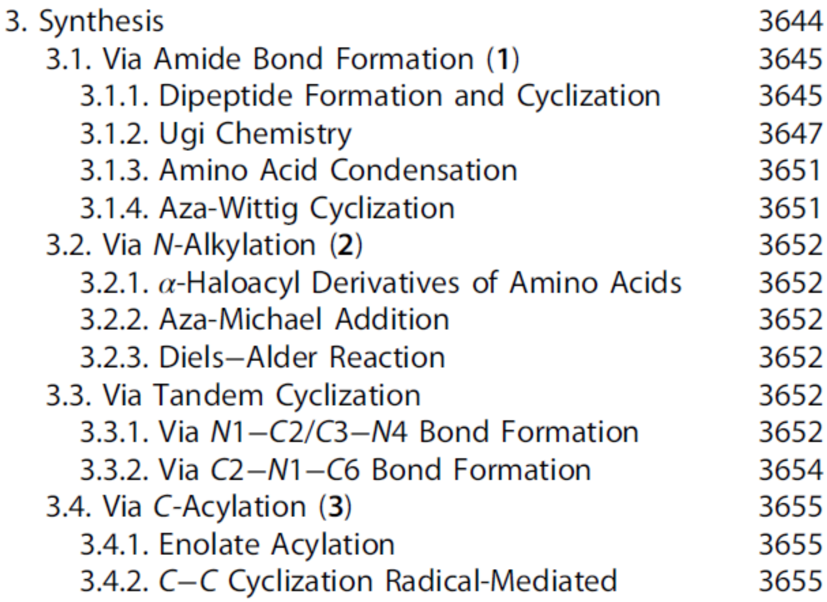
Ling, Y., Ye, X., Ji, H., Zhang, Y., Lai, Y., Peng, S., & Tian, J. (2010). Synthesis and evaluation of nitric oxide-releasing derivatives of farnesylthiosalicylic acid as anti-tumor agents. *Bioorganic & Medicinal Chemistry*, *18*(10), 3448-3456.



Scheme 5: Ugi reaction that involves the condensation of Armstrong's convertible isocyanide.

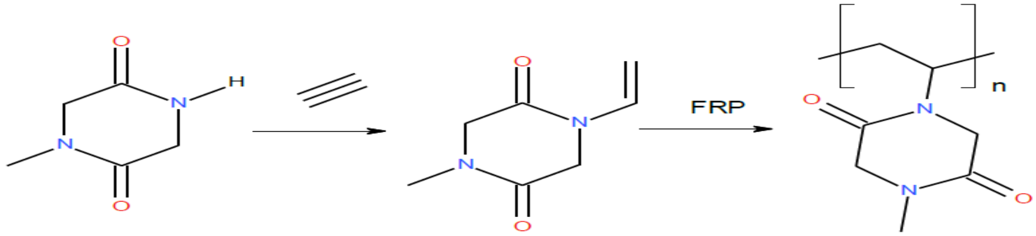
Koopmanschap, G., Ruijter, E., & Orru, R. V. (2014). Isocyanide-based multicomponent reactions towards cyclic constrained peptidomimetics. *Beilstein Journal of Organic Chemistry*, *10*(1), 544-598.

You can also buy these Boc amino acids from Sigma/Aldrich and others.



Borthwick, A. D. (2012). 2, 5-Diketopiperazines: synthesis, reactions, medicinal chemistry, and bioactive natural products. *Chemical reviews*, *112*(7), 3641-3716.

The above is just a section of the index concerning synthesis but the review is a complete review of all aspects of this chemistry as of 2012! Its amazing that this review was the work of one person!

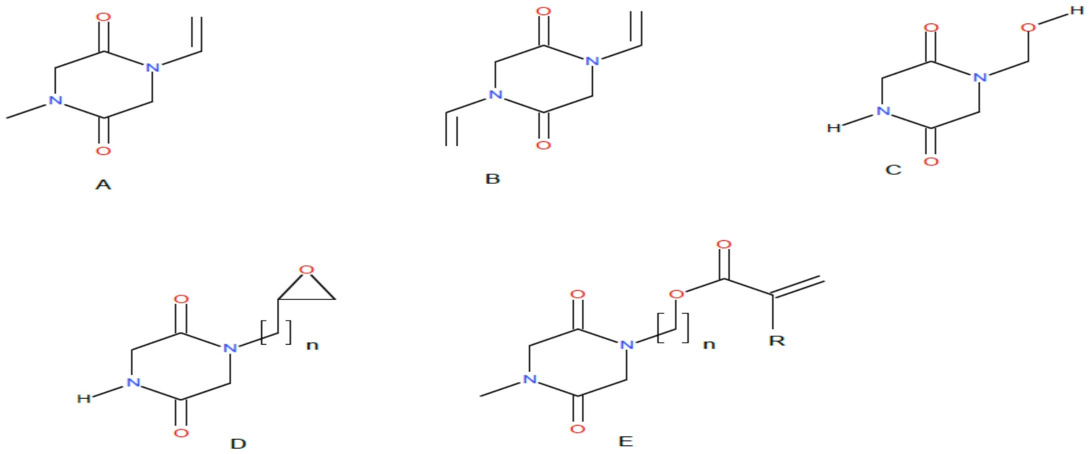


Scheme 3: Example of the free-radical polymerization. This can be viewed as a version of both polyvinylpyrrolidone and n-methyl pyrrolidone combined. See my reference

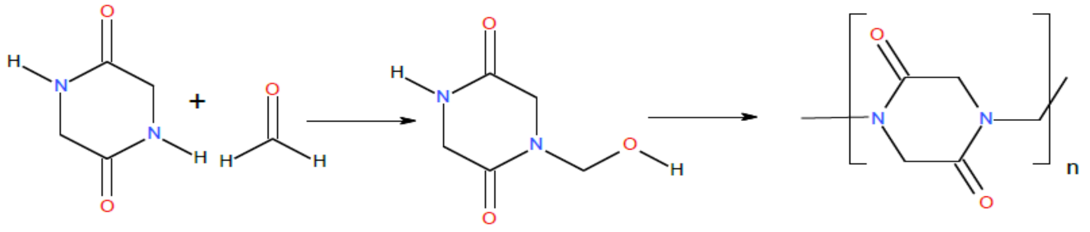
concerning PVP and related chemistry concerning vinylation.
N-Vinylamide Polymers
RB Login- Kirk-Othmer Encyclopedia of Polymer Science and Technology, 2002

As you can see the n-methyl pyrrolidone resembling group, sticks out of the polymer backbone. NMP itself is referred to as a super solvent. Might this polymer exhibit unique solubility and solvency? Just like PVP the other lactam faces the polymer back bone. Might it not have related complexing ability? If this is true then this polymer would dissolve many medicinal actives and deliver them to surfaces like skin. Where it could result in transdermal delivery. Not only that but in a polymer structure, the chances are that toxicity would be very low.

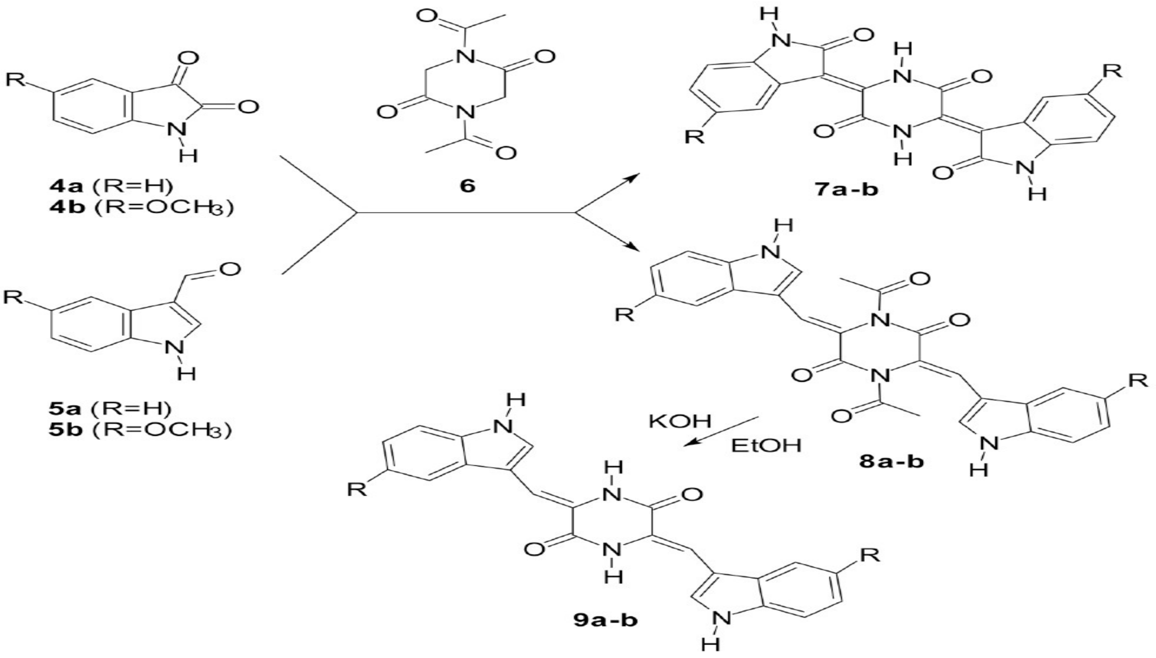
I thought of additional ideas:



Scheme 4: Additional monomer ideas. We have discussed A but the divinyl derivative B would be a valuable cross-linker that could be employed to prepare water "soluble" gels with vinylpyrrolidone or with A above as two examples. Monomers D & E are obvious and their functional group polymerization is well known. C however might be less obvious?

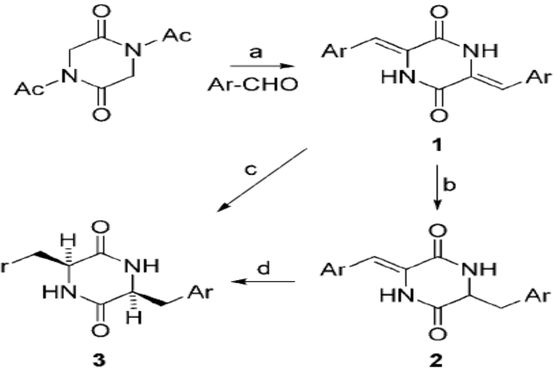


Scheme 5: Formaldehyde can react with amides to form condensation polymers. The reaction of formaldehyde with amides is called Hydroxymethylation.
Hachemi, M. (2015). Reaction in water under microwave: rapid and convenient synthesis of N-hydroxymethylimides and N-hydroxymethyl lactams. *Algerian Journal of Environmental Science and Technology*, *1*(1).



Andreani, A., Burnelli, S., Granaiola, M., Leoni, A., Locatelli, A., Morigi, R., ... & Kunkel, M. W. (2008). Antitumor activity of bis-indole derivatives. *Journal of medicinal chemistry*, *51*(15), 4563-4570.

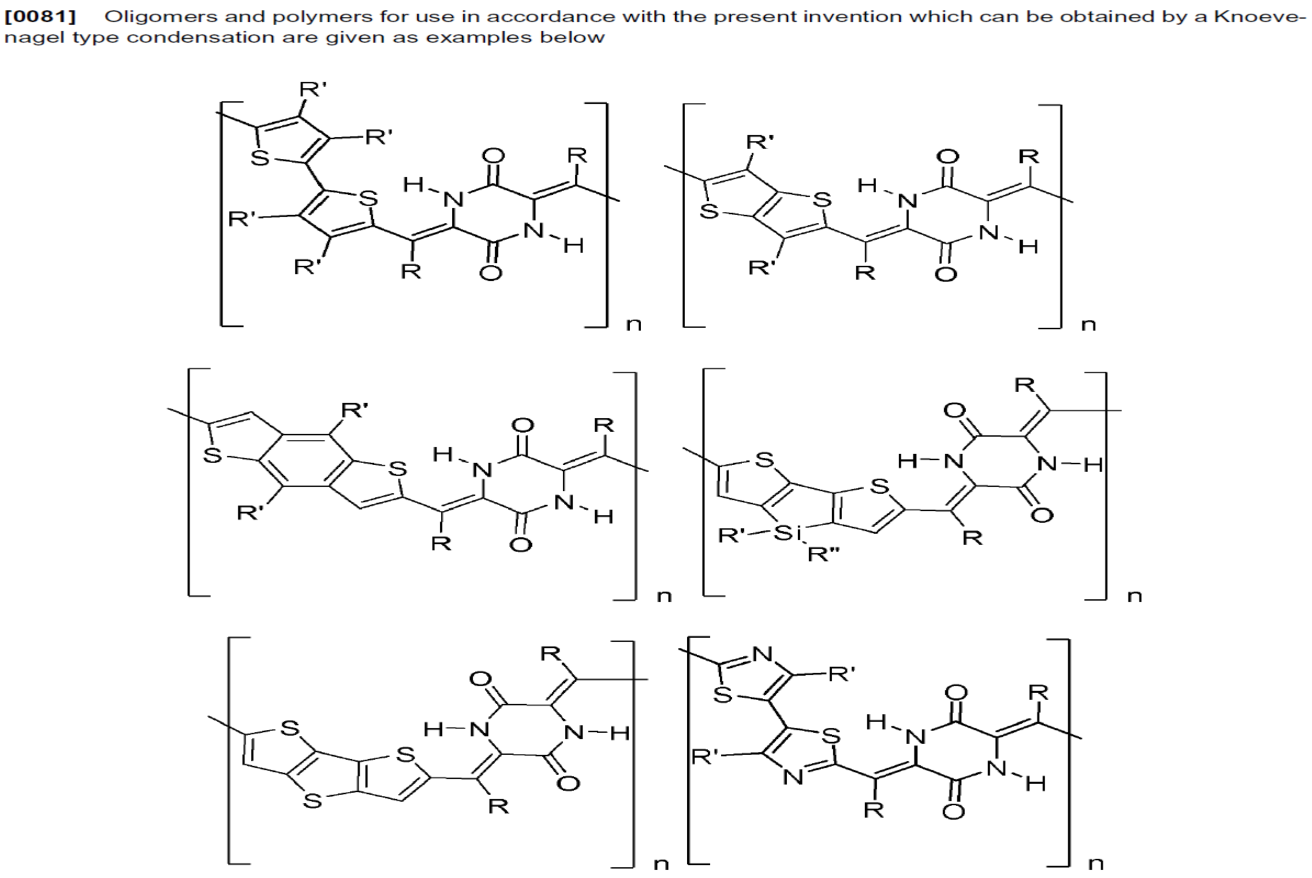
This reference led me to think that this chemistry with the proper di-aldehydes would generate polymers.



Scheme 1. *Reagents and conditions*: a) Et_3N, DMF, RT, 14 h or Et_3N, DMF, 150 °C, 12-48 h; b) Zn, AcOH, reflux, 1–48 h; c) H_2 (30 psi), 30% Pd-C, CH_3OH, RT, 24 h; d) Zn, AcOH, reflux, 24 h.

Bolognesi, M. L., Ai Tran, H. N., Staderini, M., Monaco, A., López-Cobeñas, A., Bongarzone, S., ... & Legname, G. (2010). Discovery of a class of diketopiperazines as antiprion compounds. *ChemMedChem*, *5*(8), 1324-1334.

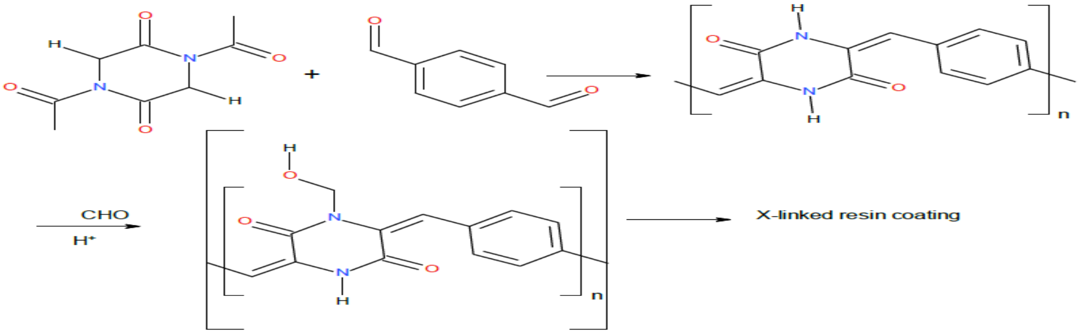
Here if the aromatic aldehyde was difunctional, polymerization would be expected, as revealed in the following patent.



[0081] Oligomers and polymers for use in accordance with the present invention which can be obtained by a Knoevenagel type condensation are given as examples below

This is claimed in EP2887413A1 **Use of compounds comprising a piperazine structural element in organic electronic devices and compounds and polymers comprising a piperazine structural element (2013).**

Besides the above, no other polymer references have been found therefore new ideas should be proposed.



Scheme 6: Employing the reactions and reagents from the above references, I'm proposing that the above polymer could be cross-linked with hydroxymethylation onto various surfaces such as plastics and glass. If the same idea is employed with dialdehyde precursors of value because of their electrical conductivity, then this hydroxymethylation cured glass or plastic coating would be very valuable for solar cells for example.

Asking Google Scholar for Aromatic Diadehydes resulted in over 15,000 hits so I'm not going to try to cover all the aromatic types! However please go to my web page rloginconsulting.com and look at this related pdf:

Claisen-Schmidt(C-S) Condensation Based Organic Semiconductor Polymers

The Claisen-Schmidt condensation is between aromatic aldehydes and methyl ketones. Functional groups that can be readily attached to aromatic organic semiconductor intermediates by the Vilsmeir and Sonogishira (acetylene to ketone) reactions. This leads to new polymers with potentially unique semiconductor properties.

Thank you for reading these proposals.
Dr. Robert B. Login   rloginconsulting.com