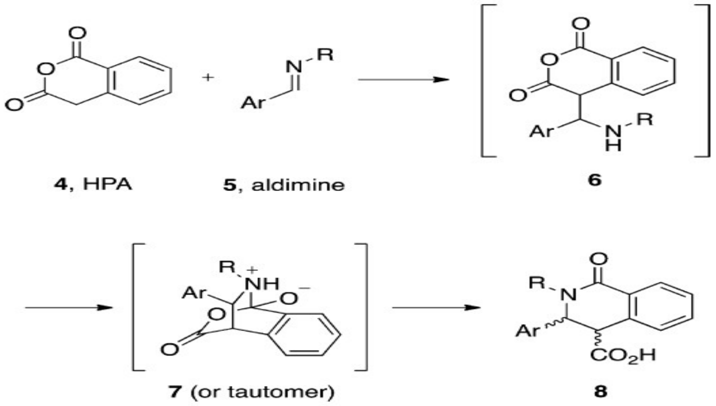
The Castagnoli-Cushman Polymerization Reaction

By: Dr. Robert B. Login rloginconsulting.com

Scheme 1. Formal Cycloaddition of Homophthalic Anhydride with Aldimines



Liu, J., Wang, Z., Levin, A., Emge, T. J., Rablen, P. R., Floyd, D. M., & Knapp, S. (2014). N-Methylimidazole promotes the reaction of homophthalic anhydride with imines. *The Journal of organic chemistry*, *79*(16), 7593-7599.

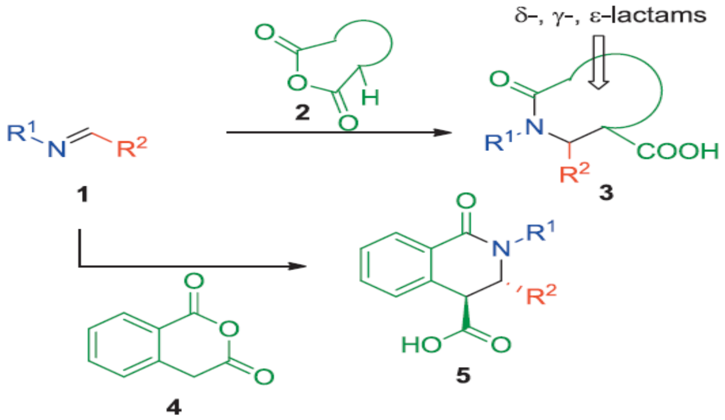


Fig. 1. The Castagnoli-Cushman reaction (CCR).

Chupakhin, E., Dar'in, D., & Krasavin, M. (2018). The Castagnoli-Cushman reaction in a three-component format. *Tetrahedron Letters*, *59*(26), 2595-2599.

Collar, A. G. (2019). *Enantioselective organocatalytic cycloaddition reactions between enolisable anhydrides and imines* (Doctoral dissertation, University of Dublin). Detailed review!

Homoaromatic anhydride Synthesis:

The synthesis of homophthalic acid or anhydride(4), the basic starting rm is well known, suggesting that its synthesis can be applied to other compounds.

Homophthalic acid may be obtained by the oxidation of indene,[3,4] the reduction of phthalonic acid,[5,6] and the hydrolysis of *o*-carboxyphenylacetonitrile.[7] Other methods are listed in an earlier volume.[3]

Homophthalic acid has been prepared from naphthalene[1] or tetralin[2] via phthalonic acid; by hydrolysis of *o*-cyanobenzylcyanide;[3] by oxidation of β-indanone with alkaline permanganate solution;[4] from α-indanone by chromic acid oxidation,[5] by nitrosation, Beckmann rearrangement, and hydrolysis,[6] or by nitrosation, hydrolysis, and hydrogen peroxide oxidation;[7] from *o*-toluic acid by bromination of the acid chloride followed by treatment with ethanol and sodium cyanide and hydrolysis with 50% sulfuric acid;[8] from indene by oxidation with chromic and sulfuric acid;[9] and from *o*-acetylbenzoic acid by Willgerodt reaction with morpholine and sulfur followed by hydrolysis of the dimorpholide.[10] The oxidation of indene by alkaline permanganate produces homophthalic acid[11] and phthalic acid;[12] oxidation with chromic acid leads to a purer product.[13] The hydrolysis of *o*-carboxyphenylacetonitrile yields homophthalic acid.[14]
The procedure described here is a modification of that described by Meyer and Vittenet[9] and Whitmore and Cooney.[15]
Homophthalic anhydride has been obtained by heating the acid alone,[1] and by refluxing with acetyl chloride[14] or with acetic anhydride.[16]

1. Graebe and Trümpy, *Ber.*, **31**, 375 (1898).
2. Davies and Poole, *J. Chem. Soc.*, **1928**, 1616.
3. Gabriel and Otto, *Ber.*, **20**, 2224, 2502 (1887).
4. Benedikt, *Ann.*, **275**, 354 (1893).
5. Ingold and Piggott, *J. Chem. Soc.*, **123**, 1497 (1923).
6. Perkin and Robinson, *J. Chem. Soc.*, **91**, 1082 (1907).
7. Perkin, Roberts, and Robinson, *J. Chem. Soc.*, **101**, 232 (1912).
8. Price, Lewis, and Meister, *J. Am. Chem. Soc.*, **61**, 2760 (1939).
9. Meyer and Vittenet, *Compt. rend.*, **194**, 1250 (1932); *Ann. chim.*, (10) **17**, 274 (1932).
10. Schwenk and Papa, *J. Org. Chem.*, **11**, 798 (1946).
11. Hensler and Schieffer, *Ber.*, **32**, 29 (1899).
12. Cooney, PhD. thesis, Polytech. Inst. Brooklyn, 1943.
13. Fieser and Pechet, *J. Am. Chem. Soc.*, **68**, 2577 (1946).
14. Wislicenus, *Ann.*, **233**, 102 (1886); *Org. Syntheses*, **22**, 61 (1942).
15. Whitmore and Cooney, *J. Am. Chem. Soc.*, **66**, 1237 (1944).
16. Dieckmann, *Ber.*, **47**, 1432 (1914).

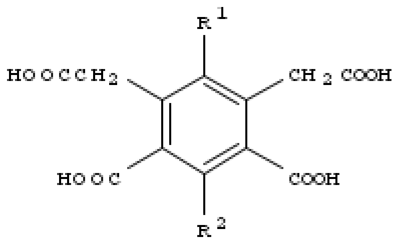
Organic Syntheses, Coll. Vol. 5, p.612 (1973); Vol. 44, p.62 (1964).

Stanoeva, E. R., & Khaimova, M. A. (1984). Homophthalic anhydrides and their application to the synthesis of heterocyclic compounds. *Chemistry of Heterocyclic Compounds*, *20*(12), 1305-1315. *Early review with additional synthesis procedures.*

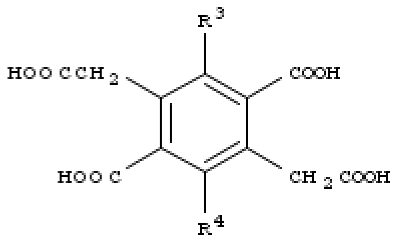
I presented the above so I could suggest how to synthesize di-homophthalic di functional compounds. Looking at Sci-Finder I found only two examples of such monomers:

1. Liquid crystal orientation agent containing polyamic acid and/or polyimide
By Nishikawa, Michinori; Iwamoto, Satoshi; Hota, Yoshitomo; Matsuki, Yasuo
From Jpn. Kokai Tokkyo Koho (1999), JP 11012357 A 19990119, Language: Japanese, Database: CAPLUS
The orientation agent comprises a polyamic acid and/or a polyimide (obtained by dehydration cyclization of the polyamic

acid) prepd. from a diamine compd. and ≥1 tetracarboxylic dianhydride from I and/or II [R_{1-4} = H, halo, C_{1-3} halogenated alkyl, C_{1-3} alkoxy, C_{1-3} alkyl]. The agent shows good orientation property, stability, and scratch resistance on rubbing treatment.



I



II

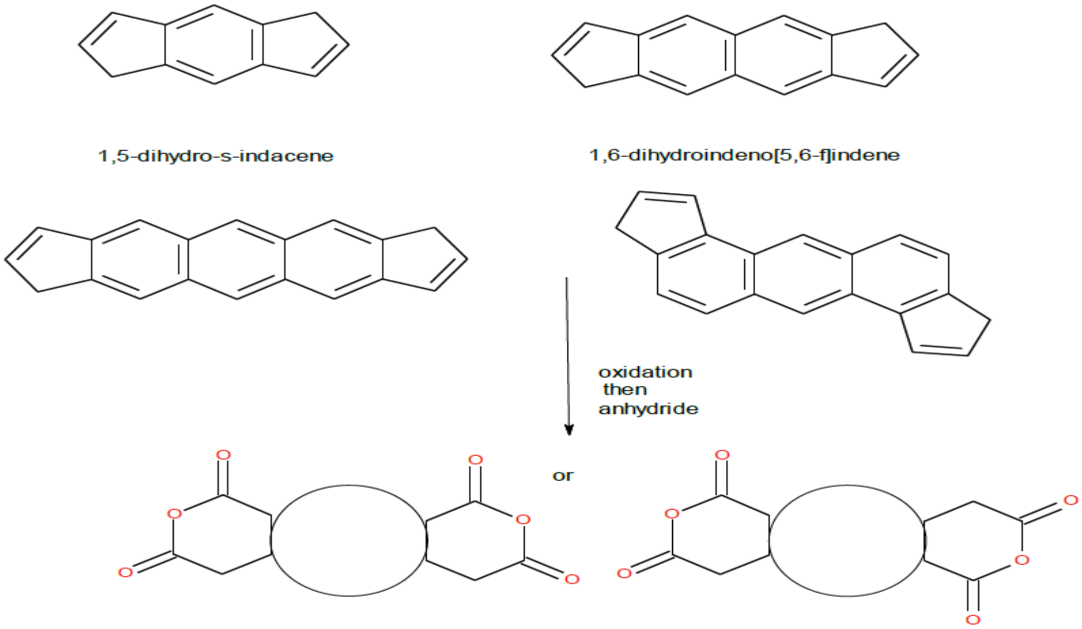
2. Synthesis of polyimides from 2,5-di(carboxymethyl)terephthalic dianhydride and diamines

By Ueda, Mitsuru; Takahashi, Masayoshi; Hishiki, Shohei; Imai, Yoshio

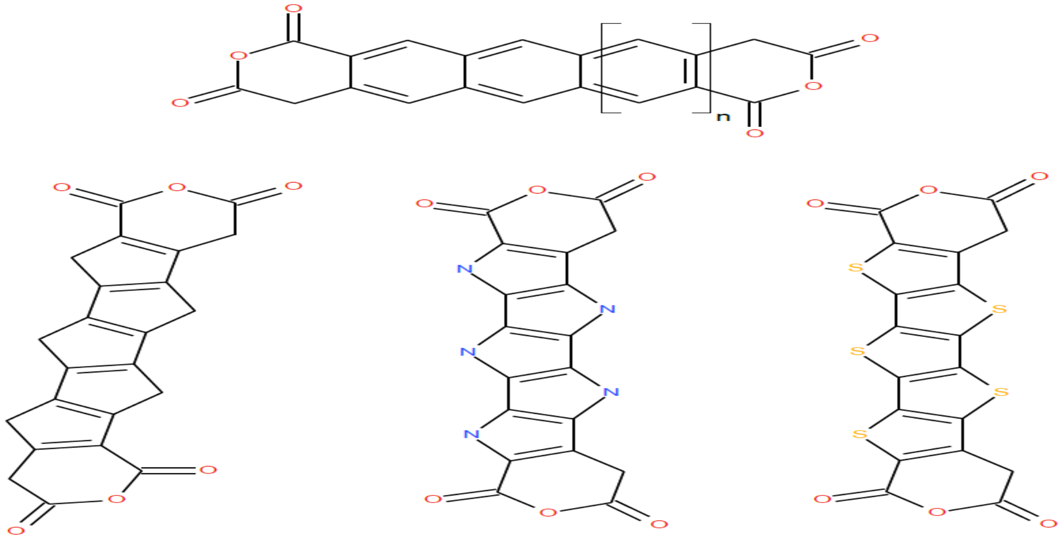
From Journal of Polymer Science, Polymer Chemistry Edition (1979), 17(8), 2459-68. Language: English, Database: CAPLUS, DOI:10.1002/pol.1979.170170818

2,5-Bis(carboxymethyl)terephthalic dianhydride [71402-71-6] was synthesized from pyromellitic dianhydride [89-32-7] in six steps and treated with diamines to prep. polyimides in two steps. The polyimides were insol. in org. solvents. Thermogravimetric anal. in air and N indicated that rapid decompn. began at >400° for arom. polyimides. The intermediate polyamic acids had inherent viscosities 0.1-0.7 and were converted to the polyimides by thermal cyclodehydration.

Sci-Finder had nothing else! My idea is to propose many other di-homo aromatic types:



Scheme 1: I show indacene and indene derivative synthesis route but the schematic di-homo derivatised circles could be any number of other aromatic structures.

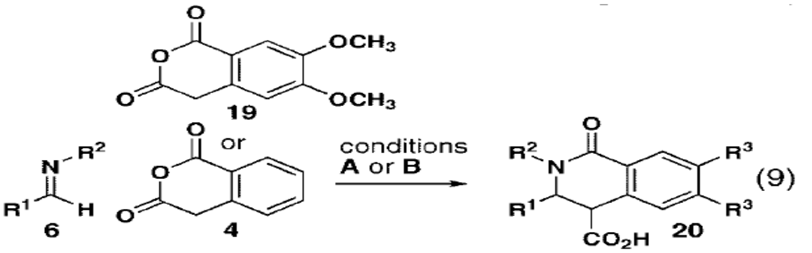


Scheme 2: Other possible anhydrides. Just several random examples with numerous other possibilities not shown.

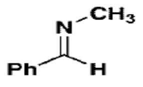
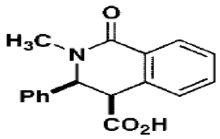
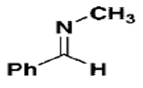
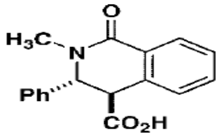
Obviously there are numerous synthetic routes to the desired di-functional compounds other than through the indacene etc oxidation route. Their structures would depend on the application of these compounds in subsequent CCR polymerization.

Once you have the di-homo derivative in hand the next step is to select a highly active di-imine.

Table 3. Reactions of Imines with Homophthalic Anhydride



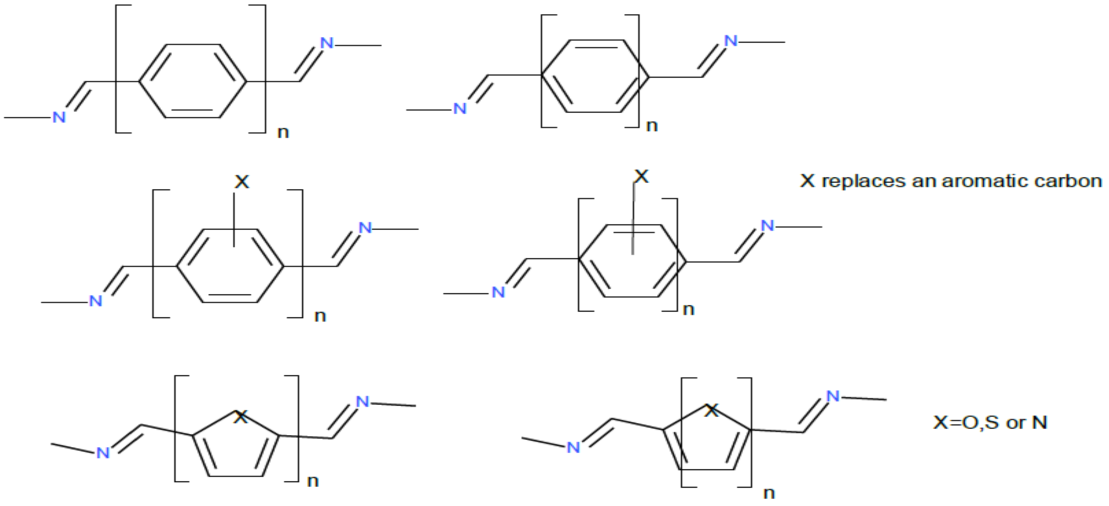
A: $CHCl_3$, 23 °C, 30min. (Cushman, ref. 3)
B: $ClCH_2CH_2Cl$, 10 min., reflux, 23 °C; 10% NaOH (aq), HCl (aq). (Haimova, ref 4,)

entry	substrate	product	yield, dr (**A** or **B**)
1			96%, 66:33 (**A**)
2			>95:5 (**B**)

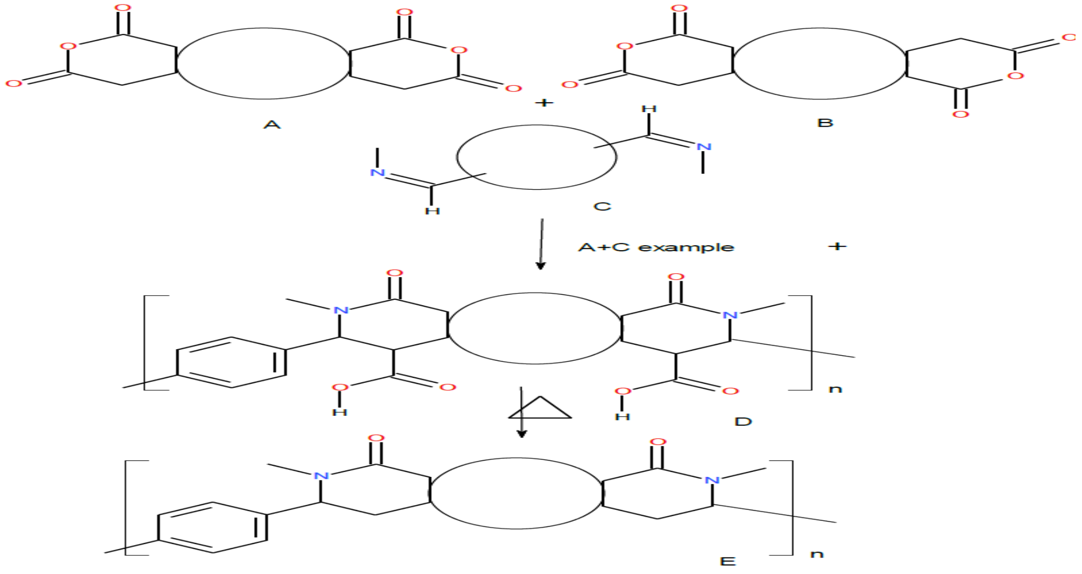
“Anhydrides possessing a functional group capable of facilitating enolate formation at one terminus are much more reactive toward imines than succinic or glutaric anhydride. This reactivity difference is most apparent with homophthalic anhydrides, which react readily with imines at ambient temperature. In addition, the reaction exhibits kinetic selectivity for the formation of the syn-diastereomer.”

González-López, M., & Shaw, J. T. (2009). Cyclic anhydrides in formal cycloadditions and multicomponent reactions. *Chemical reviews*, *109*(1), 164-189.

Above is an excellent review that indicates that the homophthalic anhydride is the most reactive anhydride but I'm assuming that phenyl imine because it results in high yields is also very reactive. At this point I don't know if the stereo chemistry would be important to this polymerization?

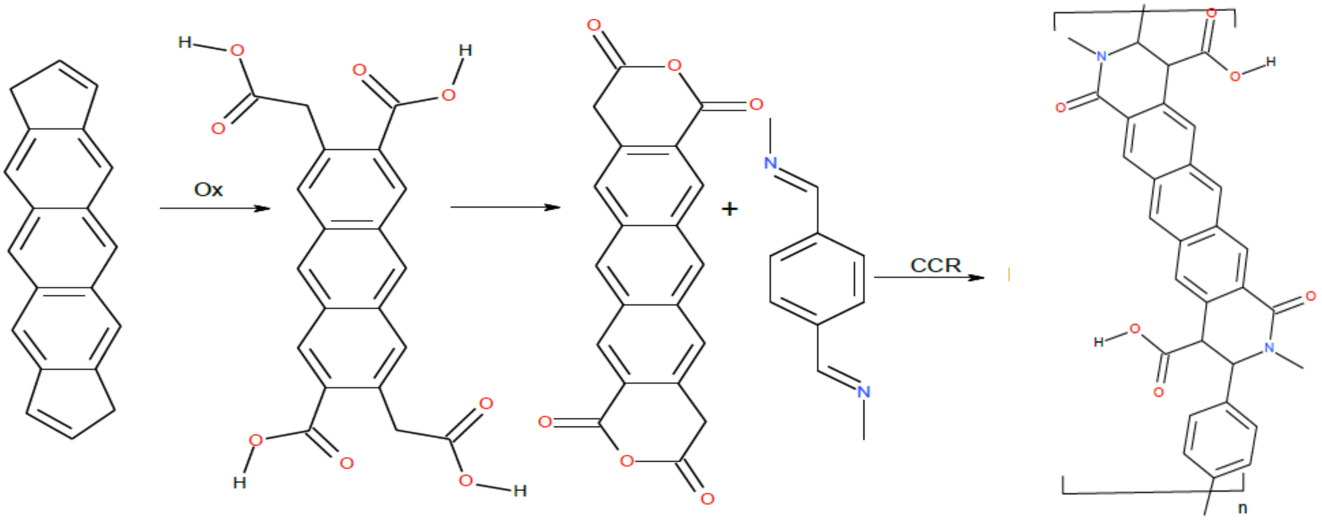


Scheme 3: A few imine examples that I think would be very reactive.



Scheme 4: With the undefined aromatic signified by the circles, polymerization would

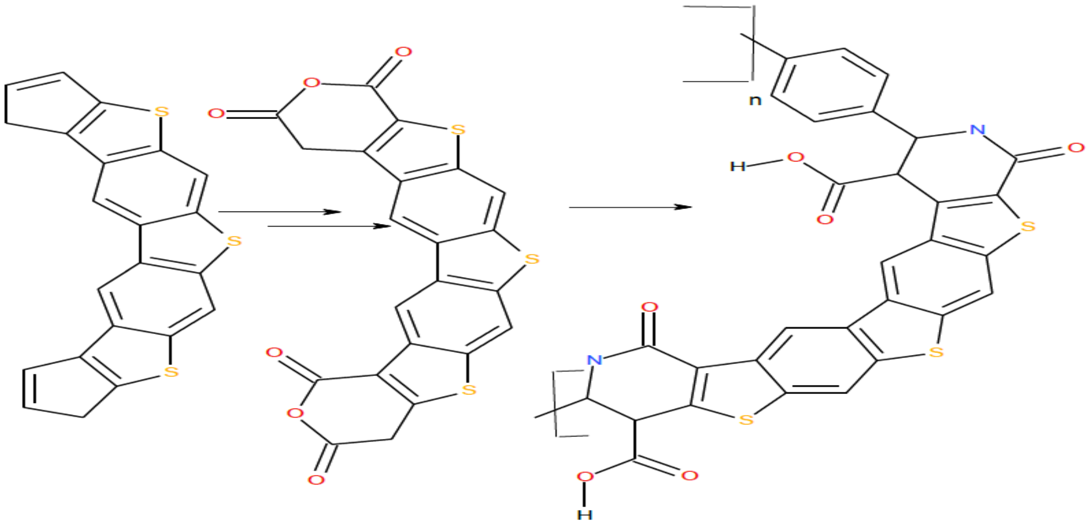
result in D above but under the rite conditions would decarboxylate to form E.



Scheme 5: An anthracene based example.

Now the hard part, to suggest applications for these polymers?

The anthracene based polymer of scheme 3 might form useful ionic films and membranes or ion exchange resins if cross-linked. Such films would be hydrophilic and might be gels in water when the carboxylic groups are neutralized. In addition as coatings on hot surfaces, decarboxylation could occur resulting in tough spongy coatings.



Scheme 6: Thiophene derivative polymer. I show this to suggest that conductive polymers could be designed and synthesized.

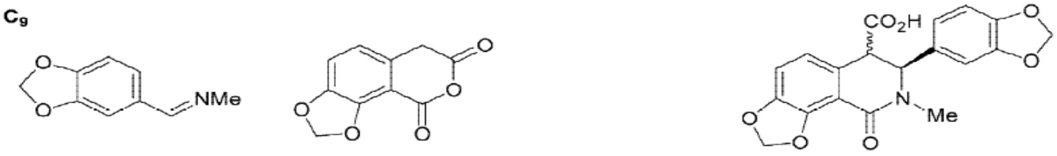
Finally, the CCR reaction can be run at room temperature. The ingredients are soluble in many low cost convenient solvents. This is important because the said reaction could be run on flexible plastic films without the need for excessive heat or no heat at all.

In addition, this CCR can be painted on surfaces after mixing the components that then would fill all the cracks and crevices. If a CCR designed adhesive could be used medicinally to bind wounds and bones and because of its polymerization it would be of low toxicity or non-toxic.

“This reactivity difference is most apparent with homophthalic anhydrides,
which react readily with imines at ambient temperature.”

González-López, M., & Shaw, J. T. (2009). Cyclic anhydrides in formal cycloadditions and multi component reactions. *Chemical reviews*, *109*(1), 164-189.

C_9



	β:α
MeCN, 82°, 1 h	67:33
MeCN:Et_3N (9:1), rt, 40 min	58:42
$MeNO_2$, rt, 30 min	38:62
t-BuOH, rt, 27 min	23:77
THF, rt, 65 min	20:80
neat, rt, 1 min	20:80
MeCN, –22°, 57 min	20:80
CH_2Cl_2, rt, 15 min	17:83
CH_2Cl_2, –78°, 72 min	11:89
DCE, 83°, 103 min	11:89
$PhCH_2CN$, 183°, 59 min	8:92

Maryanoff, B. E., Zhang, H. C., Cohen, J. H., Turchi, I. J., & Maryanoff, C. A. (2004). Cyclizations of N-acyliminium ions. *Chemical reviews*, *104*(3), 1431-1628.

Looking at the above references, I'm struck by the fact that the CCR could be run neat and would react in 1 minute. Even if somewhat longer, if both components are soluble and compatible then my above ideas would be possible.

Thank you for reading this proposal!
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