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Decarboxylation-Based Traceless Linking with Aroyl Acrylic Acids

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Abstract: β-Keto carboxylic acids are known to decarboxylate readily. In our pursuit to synthesize β-indolinyl propiophenones, we have exploited this chemistry as a mean of establishing a traceless handle. 2-Aroyl acrylic acids have been esterified to a trityl resin, after which Michael-type addition of indolines have been performed. Upon cleavage, the products are decarboxylated, and the β-indolinyl propiophenones are isolated. The reaction conditions have been optimized, and a small library has been prepared. © 1998 Elsevier Science Ltd. All rights reserved.

In solid phase organic synthesis the starting material must be bound to the resin through a functional group, e.g. OH, NH_2 or COOH. This functionality is then usually present in the final product in one form or another, but this is not always desirable. Therefore, several so-called traceless linkers have been developed recently.[1-9] In our efforts to synthesize a library of β-indolinyl propiophenones, we have developed a traceless linker method, in which the handle can be removed by a simple decarboxylation. Traceless linking by decarboxylation is new. An apparatus patent from 1994 holds a figure with similar chemistry as an example, but the patent includes no details on this reaction and no mentioning of decarboxylation in the text.[10] Also, cyano acetamidines have very recently been synthesized on solid-phase in a reaction involving decarboxylation.[11]

β-Keto carboxylic acids are known to decarboxylate easily via a six-ring transition state.[12] In 2-aroyl acrylic acids (Fig. 1), the presence of the carbon-carbon double bond inhibits decarboxylation. 2-Aroyl acrylic acids are thus quite stable, and several of these compounds are commercially available (from Apin Chemicals Ltd., Oxon, UK). The conjugated double bond acts as an acceptor in Michael-type additions. Upon double bond saturation the decarboxylation may proceed.

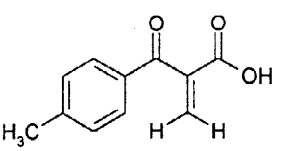

Fig. 1. Aroyl acrylic acid (commercially available).

We have utilized the features of 2-aroyl acrylic acids in a traceless linker synthesis of β-amino ketones, or more specifically β-indolinyl propiophenones. The compounds were synthesized in the following manner (Fig.

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2): The 2-aroyl acrylic acids were esterified to a resin. Upon Michael-type addition of indolines, the products were cleaved from the resin and allowed to decarboxylate.

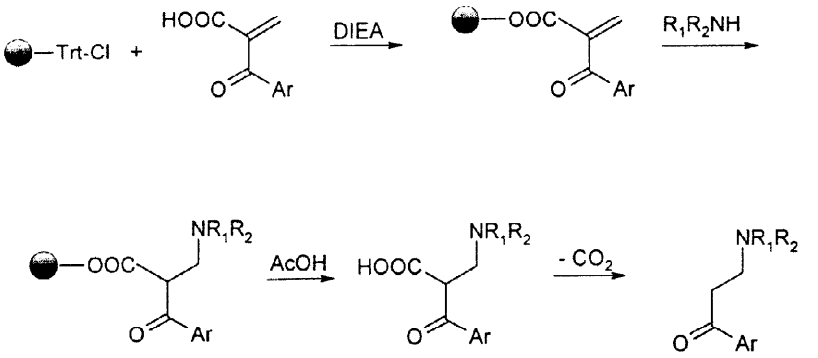


Fig. 2. The traceless linker synthesis of β-amino ketones.

The reaction was optimized using indoline and 2-(4-methylbenzoyl)-acrylic acid as model starting materials to give **1**. Trityl chloride resin was the resin of choice, as problems were encountered under both coupling and cleavage when a Wang resin was used. While optimizing the reaction conditions, it was found that up to 20 equivalents of indoline were necessary to obtain reaction completion in an overnight reaction at room temperature. It was also found that cleavage in 10% AcOH/DCM followed by solvent removal did not lead to decarboxylation. Decarboxylation could be achieved by cleaving in glacial acetic acid, and allowing the cleavage solution to stand 8 hours before freeze-drying the sample.

Surprisingly, it was discovered that an oxidized impurity (Fig. 3) was present in the final product, although no oxidants were used throughout the synthesis. Weigel et al. have previously shown that some β-amino ketones form similar oxidation products when exposed to ultraviolet light in the presence of atmospheric oxygen.[13] This type of oxidation proceeds via cyclopropanol intermediates. Further experimentation with our model reaction showed that in our case the oxidation could take place in the absence of ultraviolet light, but that the oxidation was dependent upon the presence of atmospheric oxygen. Furthermore, it was found that the by-product was formed in conjunction with the decarboxylation step. The formation could be reduced considerably by performing the cleavage and decarboxylation under inert conditions.

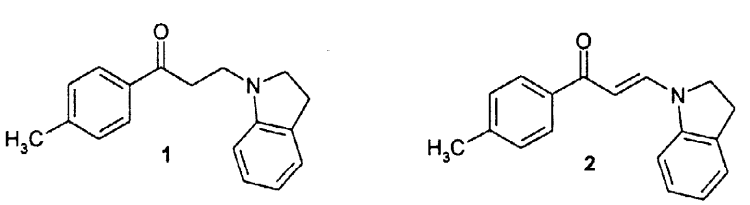


Fig. 3. The desired product (**1**) and the oxidized by-product (**2**), structures verified by ^{1}H- and ^{13}C-NMR.[14]

As can be seen by the HPLC traces below, running the synthesis with 20 equivalents indoline, and cleaving under inert conditions, yields the desired β-amino ketone with only a small amount of the by-product.

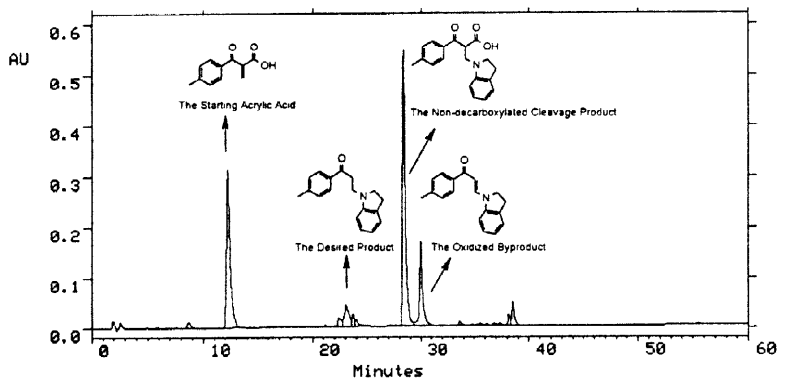


Fig. 4. First stages of solid phase optimization using 5 equivalents of indoline and cleaving with 10% acetic acid/DCM (non-inert).

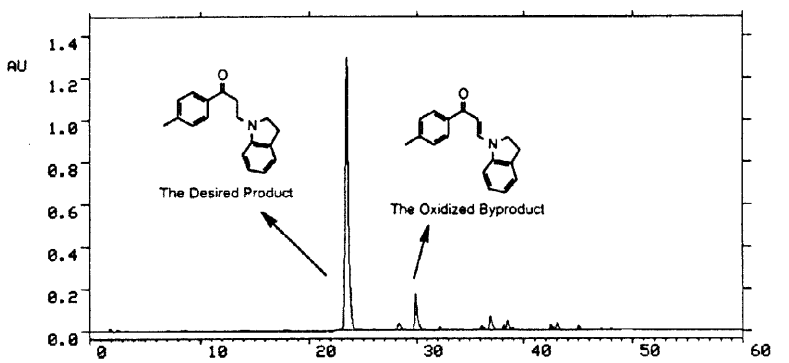
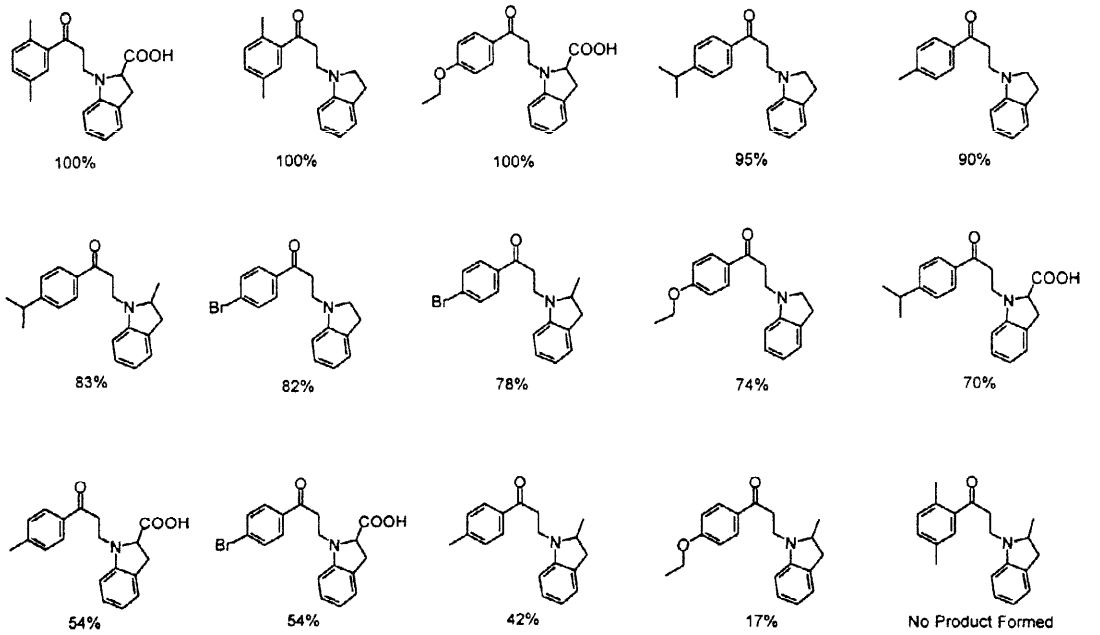


Fig. 5. The optimized synthesis using 20 equivalents of indoline and cleavage in glacial acetic acid under inert atmosphere.

A small library was synthesized by combining five 2-aroyl acrylic acids with three indolines. Several nitro-indolines were also investigated, but it was found that they were not strong enough nucleophiles to undergo the reaction under the prevailing conditions. The decarboxylated products were analyzed for purity using photo-diode array HPLC. The results are shown below. Indoline reacted well with all the 2-aroyl acrylic acids, yielding a purity greater than 70% in all cases. 2-Methyl indoline was the worst reactant, giving the three lowest purities. The structures of six of the products were confirmed using ^{1}H-NMR. All compound gave the expected MS data.

In conclusion, decarboxylation has been shown to be a viable method of achieving traceless linking in the synthesis of β-indolinyl propiophenones. The formation of an oxidized by-product has been accounted for, and it was found that resin cleavage under inert conditions could hinder its formation. We are currently working on modifying the method so it can be used with aliphatic amines, but the preliminary results indicate that quite different reaction conditions are required. The method may be expanded to include other nucleophiles or Diels-Alder dienes, and work is continuing along those lines.



References and Notes

1. Chenera, B., Finkelstein, J.A.; Veber, D.F. *J. Am. Chem. Soc* **1995**, *117*, 11999.
2. Plunkett, M.J.; Ellman, J.A. *J. Org. Chem.* **1997**, *62*, 2893.
3. Brown, A.R., Rees, D.C., Rankovic, Z.; Morphy, J.R. *J. Am. Chem. Soc.* **1997**, *119*, 3288.
4. Conti, P., Demont, D., Ottenheijm, H.C.J.; Leysen, D. *Tetrahedron Lett.* **1997**, *38*, 2915.
5. Hughes, A. *Tetrahedron Lett.* **1996**, *37*, 7595.
6. Gayo, L.M.; Suto, M.J. *Tetrahedron Lett.* **1997**, *38*, 211.
7. Zhao, X.Y., Jung, K.W.; Janda, K.D. *Tetrahedron Lett.* **1997**, *38*, 977.
8. Szardenings, A.K., Burkoth, T.S., Lu, H.H., Tien, D.W.; Campbell, D.A. *Tetrahedron* **1997**, *53*, 6593.
9. Kim, S.W., Sang, S.A., Koh, J.S., Lee, J.H., Ro, S.R.; Cho, H.Y. *Tetrahedron Lett.* **1997**, *38*, 4603
10. Cody, D.R., DeWitt, S.H.H., Hodges, J.C., Kiely, J.S., Moos, W.H., Pavia, M.R., Roth, B.D., Schroeder, M.C., Stankovic, C.J. *U.S. Patent 5,324,483* **1994**.
11. Zaragoza, F. *Tetrahedron Lett.* **1997**, *38*, 7291.
12. Jencks, A. in *Catalysis in Chemistry and Enzymology*, McGraw-Hill: New York, 1969, pp. 116-120.
13. Weigel, W., Schiller, S., Reck, G.; Henning, H.G. *Tetrahedron Lett.* **1993**, *34*, 6737.
14. Structure **1**, ^{1}H-NMR (DMSO-d_6) δ: 7.91 (d, 2H, J=8.5), 7.30 (d, 2H, J=8.0), 7.12 (m, 2H), 6.71 (t, 1H, J=7.0), 6.60 (d, 1H, J=8.0), 3.62 (t, 2H, J=6.5), 3.45 (t, 2H, J=8.0), 3.28 (t, 2H, J=7.5), 3.00 (t, 2H, J=8.5), 2.45 (t, 3H). ^{13}C: 199.1, 152.0, 144.5, 134.8, 130.6, 129.7, 128.6, 127.8, 124.9, 118.4, 107.6, 53.6, 44.8, 36.0, 29.0, 22.1. PD-MS: 265 (M+).

    Structure **2**, ^{1}H-NMR (DMSO-d_6) δ: 8.25 (d, 1H, J=12.6), 7.73 (d, 2H, J=8.0), 7.08 (m, 4H), 6.96 (d, 1H, J=7.5), 6.83 (t, 1H, =7.0), 5.90 (d, 1H, J=12.6), 3.80 (t, 2H, J=8.0), 3.12 (t, 2H, J=8.6), 2.27 (s, 3H). ^{13}C: 189.1, 144.3, 142.3, 141.5, 137.6, 131.4, 29.4, 128.4, 126.3, 125.9, 123.4, 109.4, 96.9, 48.6, 28.0, 21.9. PD-MS: 263 (M+).