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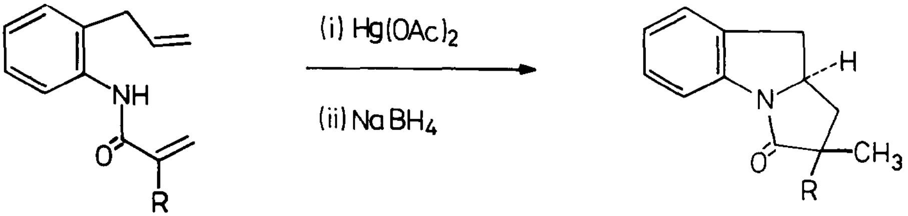
CYCLIZATIONS OF MERCURY AND PALLADIUM SUBSTITUTED ACYRYLANILIDES

Samuel Danishefsky* and Eiji Taniyama
Department of Chemistry, Yale University, New Haven, CT 06511

Summary: Cyclizations via reductive coupling of a mercurial acrylanilide and carbometallation of a palladium derivative, each formed via amidometallation, follow a similar course.

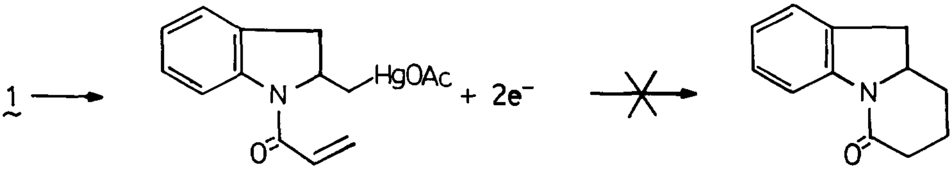
Ureidomercuration of N-Cbz-o-allylaniline followed by intermolecular reductive coupling with acrylonitrile, de-protection and cyclization provides a route to the benzoindolizidinone 6.[1] In the light of our findings pertaining to the intramolecular reductive coupling of mercurials,[2] a more convergent possibility, implied in the sequence 1 → 1a → 6, presented itself.

Accordingly, the acrylanilide 1 was treated with mercuric acetate in the usual way.[1] T.l.c. analysis indicated the disappearance of starting material. The presumed 1a was treated with sodium borohydride.[3] Chromatography of the resultant product on silica gel afforded a 34% yield of 3[4] R=αH, δCH_3 1.25,dJ=7Hz(3) and an 11% yield of 4[4],R=βH; δ$CH_3$1.35,d,J=7Hz(3). A single product 5[4] (δ1.25,dJ=7Hz(3), δ1.33,dJ=7Hz(3)) was obtained from a similar reaction sequence on substrate 2. In this case, a 28% yield of recovered starting material was isolated. Since disappearance of starting material was indicated at the mercuration stage, reductive retro-amidomercuration is apparently competitive with reductive cyclization. In neither case was there any indication for the formation of compound 6.



1 R=H
2 R=CH_3

3 R=α-H
4 R=β-H
5 R= CH_3

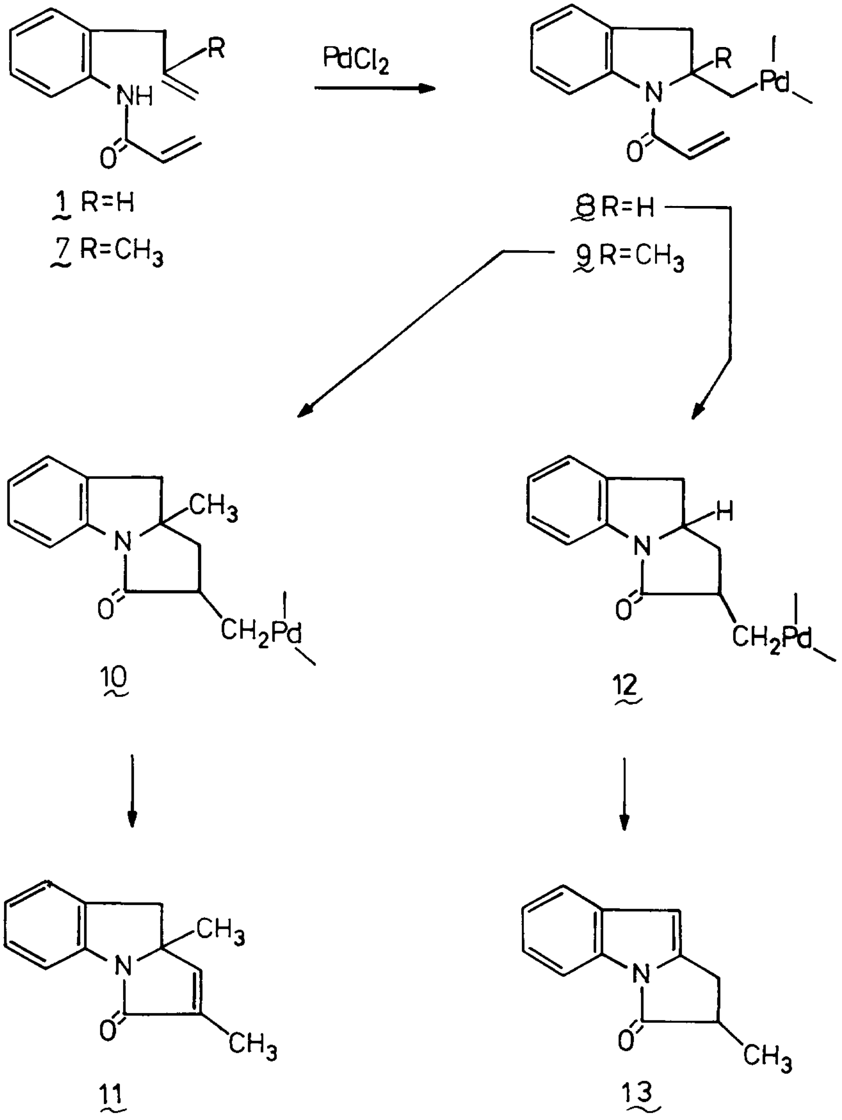


1a

6

Cyclization to produce the 5- rather than the 6- membered ring was reminiscent of the interesting findings of Hegedus,[5,6] wherein compound **7** suffers palladium mediated cyclization to afford **11** presumably via intermediates **9** and **10**. Of course, with substrate **7** β-hydride elimination is precluded at the stage of **9** by the quarternary carbon (R=Me).

To probe more closely the degree of similarity between the two processes, acrylanilide **1** was subjected to amidopalladation. Reaction of **1** with $PdCl_2$ (ϕ C≡N)$_2$ in tetrahydrofuran for 23 hr. at rt. afforded a 55% yield of **13**.[4] Presumably, this compound arises from retro-hydrido and hydrido-palladations starting with intermediate **12**. Thus, carbopalladation (**8** → **12**) is easily competitive with β-hydride elimination - a fact not implicit in the Hegedus experiment.[5]



1 R=H
7 R=CH$_3$

8 R=H
9 R=CH$_3$

10

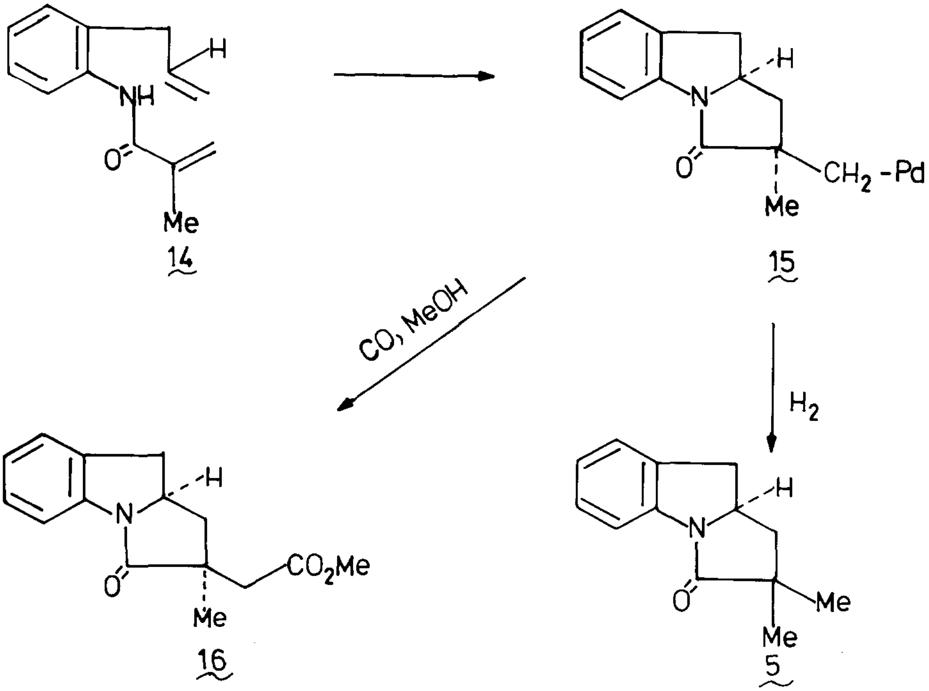
12

11

13

Since the sequence from the postulated **12** to the observed **13** is rather complicated, additional support for the proposed pathway was sought. Methacrylanilide **14** was subjected to the same process as **1**. It was recognized that the β-quarternary carbon, in what would be the corresponding intermediate **15**, would preclude the retro-hydridopalladation step required for indole formation.[7] The system, resulting from treatment of **14** with $PdCl_2$ $(ØC{\equiv}N)_2$ in tetrahydrofuran at rt. for 23 hr., was treated with hydrogen. There was obtained a 23% yield of the previously encountered **5**. More remarkably, when the palladation product was treated with CO-methanol-triethylamine, there was obtained, albeit only in 5% yield, the tricyclic methyl ester, **16**.[4,8]

In the palladium mediated reaction the proposed sequence of amidometallation to bicyclic product followed by carbometallation to afford a 5-membered ring is thus strongly supported. The formation of the corresponding 5-membered ring in the mercury case (cf. **1a** → **3**) may involve carbometallation or might best be viewed in terms of a "metal-free" radical cyclization. Experiments intended to address questions of this kind, as well as to clarify more fully the synthetic potentialities of such transformations, will be undertaken.



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References

1. S. Danishefsky and E. Taniyama, *Tetrahedron Lett.*, preceding paper
2. S. Danishefsky, S. Chackalamannil and B. J. Uang, *J. Org. Chem.*, **47**, 2531 (1982)
3. The intermolecular version of this reaction was developed by B. Giese and associates. See: B. Giese, H. Horler and W. Zwick, *Tetrahedron Lett.* 931 (1982); B. Giese and K. Heuck, *Chem. Ber.* **114**, 1572 (1981).
4. The structure of this compound is consistent with its infrared nmr and mass spectral properties.
5. L. S. Hegedus, G. F. Allen and D. J. Olsen, *J. Amer. Chem. Soc.*, **102**, 3583 (1980) For a more recent variation of this reaction see: L. S. Hegedus and J. M. McKearin, *ibid*, **104**, 2445 (1982).
6. That the cyclization of the mercurial occurs in the "anti-Michael" sense is no doubt related to the radical nature of the process, cf. C. L. Hill and G. M. Whitsides, *ibid*, **96**, 87 (1974).
7. In the Hegedus work,[5] at higher temperature, a palladium specie corresponding to **15** undergoes a most interesting fragmentation re-combination sequence, leading to a 6-membered ring.
8. Only one stereoisomer was noted. In view of the poor yield the significance of this finding cannot be evaluated. The stereochemical assignment for compound **16** is based on a comparison of its nmr spectrum with those of compounds **3**, **4** and **5**. Full spectral details will be published in a full paper.

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