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Formation of Aromatic Rings through Enamine Annulation

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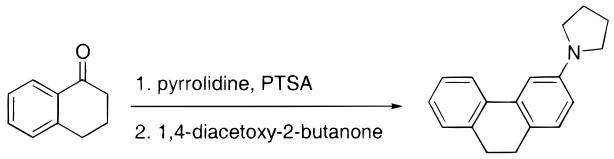
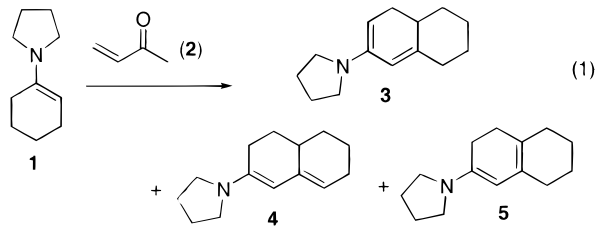
ABSTRACT



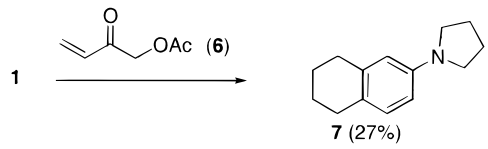
Condensation of pyrrolidine enamine of ketones with 1,4-diacetoxy-2-butanone provides a new, concise synthetic route to substituted benzenes, dihydroindenes, tetrahydronaphthalenes, and di- and octahydrophenanthrenes. The reaction produced modest yields with regiocontrol of the secondary amine substituent.

Condensation of enamines with α,β-unsaturated carbonyl compounds provides a convenient, one-step method for constructing nonaromatic rings.[1] This procedure has been used extensively in the synthesis of alkaloids, steroids, and terpenes.[2] One example of this transformation is the reaction of 1-(1-pyrrolidino)cyclohexene (**1**) with methyl vinyl ketone (**2**) to give hexahydronaphthalenes **3**−**5** in a combined yield of 78% (eq 1).[3]



(1)

Recently, we found that the reaction of enamine **1** with 1-acetoxy-3-buten-2-one (**6**)[4] gave a single product, 6-(1-pyrrolidino)-1,2,3,4-tetrahydronaphthalene (**7**), in 27% isolated yield (eq 2). The observed ^{1}H and ^{13}C NMR chemical shifts and the ^{1}H−^{1}H coupling constants for **7** documented the site of pyrrolidine substitution and that cyclization proceeded with aromatization. The finding that reaction of **1** with **6** yielded an aromatic product while the corresponding reaction with **2** did not indicated that the acetoxy moiety in **6** was necessary for the formation of the annulated benzene ring.



(2)

We attributed the modest yield of **7**, in part, to the lability of **6**. Compound **6** was observed to undergo polymerization during overnight storage at 0 °C.[4] Accordingly, we determined whether 1,4-diacetoxy-2-butanone (**8**) could be employed in place of **6**. Reaction of **1** with **8** in benzene at

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(1) (a) Cook, A. G. *Enamines, Synthesis, Structure, and Reaction*, 2nd ed.; Marcel Dekker: New York, 1998; Chapter 7, p 347. (b) Chinchilla, R.; Backvall, J. E. *The Chemistry of Enamines*; Rappoport, Z., Ed.; John & Wiley Sons: New York, 1994; Chapter 18, p 993.

(2) (a) Kobayashi, K.; Furuta, Y.; Matsuoka, H.; Uchida, M.; Morikawa, O.; Konishi. H. *Chem. Lett.* **1999**, *6*, 503. (b) Murphy, W. S.; Bertrand, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4115. (c) Li, J.; Trivedi, B. K.; Rubin, J. R.; Roth, B. D. *Tetrahedron Lett.* **1998**, *39*, 6111. (d) Schwarz, J. B.; Meyers, A. *J. Org. Chem.* **1998**, *63*, 1619. (e) Kao, B. C.; Doshi, H.; Reyes-Rivera, H.; Titus, D. D.; Yin, M.; Dalton, D. R. *J. Heterocycl. Chem.* **1991**, *28*, 1315.

(3) House, H. O. H.; Trost, B. M.; Magin, R. W.; Carlson, R. G.; Frank, R. W.; Rasmusson, G. H. *J. Org. Chem.* **1965**, *30*, 2512.

(4) Hennion, G. F.; Kupiecki, F. P. *J. Org. Chem.* **1953**, *18*, 1601.

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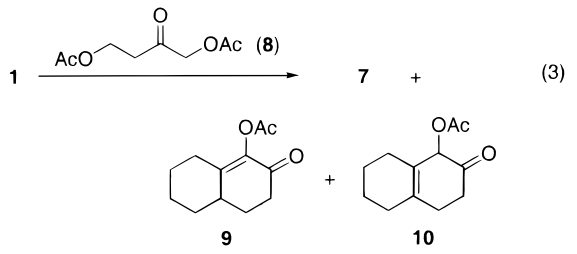
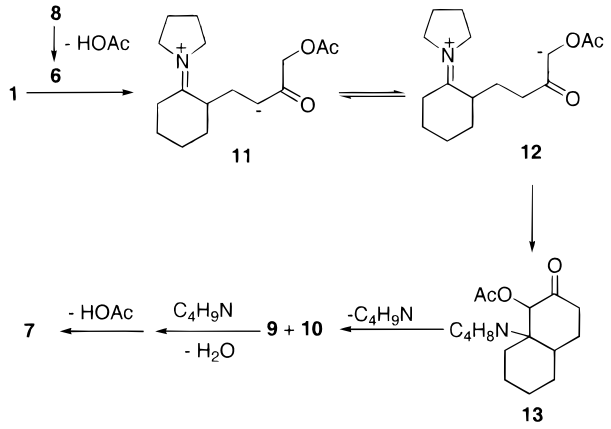
room temperature afforded **7** (47% yield) along with a binary mixture (~ 7%) (eq 3). Spectroscopic analysis suggested that the binary mixture consisted of 1-acetoxy-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (**9**) and 1-acetoxy-1,4,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (**10**) in an approximately 2:1 ratio, respectively. Key to our assignments were the observation of two downfield ^{13}C NMR signals, at 191.4 and 206.4 ppm, which we have attributed to the carbonyl carbons in **9** and **10**, respectively. Reducing the reaction time from 18 to 4 h decreased the yield of **7** to 3% and increased the combined yield of **9** and **10** to approximately 41%.



These initial findings suggested a pathway for the formation of **7** from **1** and **8** (Scheme 1). Michael addition of

Scheme 1



enamine **1** to the in situ generated **6** gives zwitterion **11**. This species is in equilibrium with **12**, which cyclizes to **13**. Loss of pyrrolidine from **13** generates **9** or **10**. Condensation of pyrrolidine with the newly formed ketone **9** or **10** and loss of H_2O and HOAc provides the aromatic derivative **7**. This pathway is an extension of an earlier route proposed for the formation of compounds **3**−**5**.[3]

Attempts to further improve the yield of **7** were unsuccessful. Higher temperatures (60 °C) and longer reaction times (24 h) did not improve the yield, and inclusion of pyrrolidine (3 equiv) led to only trace amounts of **7**.[5]

The generality of this one-step, aromatic annulation procedure was investigated (Table 1). Ketones, varying in

Table 1. Products from Pyrrolidine Enamines of Ketones and **8**

entry	starting ketone	enamine(s)	product (yield %)[a]
1	**14**	**15**	**16** (34)
2	**17**	**18**	**19** (28)
3	**20**	**21**	**22** (60)
4	**23**	**24a** **24b**	**25** (47)
5	**26**	**27**	**28** (42)
6	**29**	**30**	**31** (41)
7	**32**	**33**	**34** (65)
8	**35**	**36a** **36b**	**37** (35)

[a] Isolated yields based on starting ketones.

structure, were used to generate the corresponding aromatic derivatives. For ketones in entries 1−6, the corresponding enamine was prepared by refluxing (3 h) an anhydrous benzene solution of the ketone (1−2 mmol), pyrrolidine (2 equiv), and catalytic amounts of *p*-toluenesulfonic acid (PTSA) with a modified Dean−Stark apparatus.[6] For ketones in entries 7 and 8, enamine formation required a longer reaction time (30 h) and a larger excess of pyrrolidine (10 equiv).[7] The enamines obtained were concentrated in vacuo, and the crude enamines were directly added to an anhydrous benzene solution containing **8** (1.5 equiv). The reaction proceeded at room temperature (18 h), and the products were isolated by preparative TLC.

(5) Compound **8** is unstable in the presence of amines (i.e., pyrrolidine, triethylamine, DBU). 1,7-Diacetoxy-3-methylene-2,6-heptanedione was obtained in 50% yield when a benzene solution of **8** and triethylamine (1 equiv) was stirred at room temperature (1 h).

(6) Masamune, T.; Takasngi, M.; Murai, A. *Tetrahedron* **1971**, *27*, 3369.
(7) Hellberg, L. H.; Milligan, R. J.; Wike, R. N. *J. Chem. Soc. C* **1970**, 35.

We observed that acyclic (entry 1), carbocyclic (entries 2−4, 7, and 8), and heterocyclic (entries 5 and 6) ketones underwent aromatization upon treatment with **8**. The isolated yields are based on the starting ketones and were from 28 to 65%. Interestingly, we observed only a single product for ketones **23** (entry 4)[8] and **35** (entry 8) even though the ^{1}H and ^{13}C NMR spectra for the corresponding enamines **24** and **36**, respectively, showed the presence of two isomers. Products **25** and **37**, obtained in these reactions, were derived from the major enamine isomers **24a** and **36a**, respectively. Attempts to condense the pyrrolidine enamine from *N*-methyl-4-piperidinone with **8** failed to give a cycloadduct.

In conclusion, we have found a concise enamine-induced benzoannulation method that affords substituted benzene, dihydroindene, tetrahydronaphthalene, and di- and octahydrophenanthrene compounds. The reaction produced modest yields with regiocontrol of the secondary amine substituent.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **7**, **9**, **10**, **16**, **19**, **22**, **25**, **28**, **31**, **34**, and **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL000093P

(8) Gurowitz, W. D.; Joseph, M. A. *Tetrahedron Lett.* **1965**, *3*, 4433.