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HETEROCYCLIC SYNTHESIS VIA THALLATION AND SUBSEQUENT PALLADIUM-PROMOTED OLEFINATION

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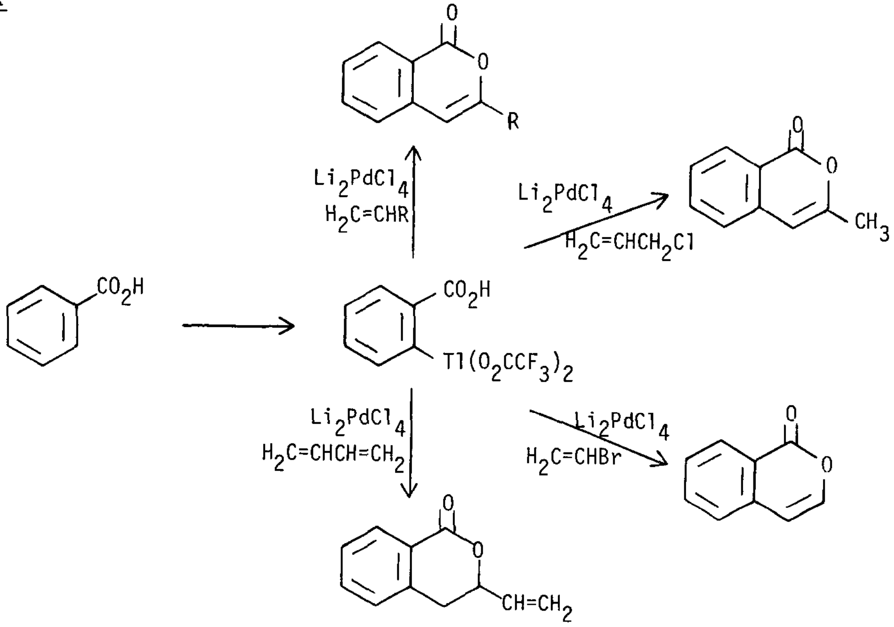
Summary: The thallation and subsequent palladium-promoted olefination of *p*-tolylacetic acid, *N*-methylbenzamide, benzamide and acetanilide provides a novel new route to a variety of important oxygen and nitrogen heterocycles.

We recently reported that the thallation and subsequent palladium-promoted olefination of benzoic acid provides a highly convenient new route to a variety of isocoumarins and 3,4-dihydroisocoumarins (Scheme I).[1] At this time we wish to report that the thallation-

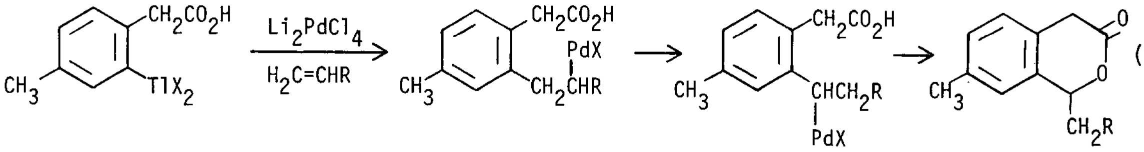
Scheme I



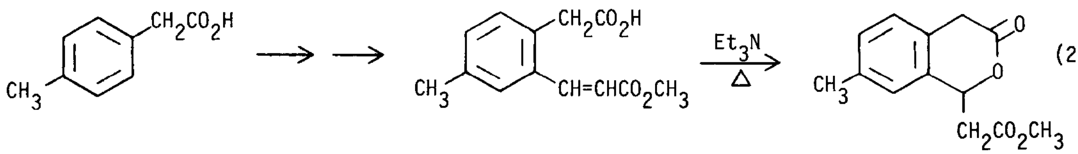
olefination of a number of other functionally substituted arenes known to give a high percentage of ortho-thallated intermediate[2,3] affords a convenient route to a wide variety of important heterocyclic ring systems. The results are summarized in Table I.

Thallation of the arenes listed in Table I was accomplished using the following variations of the earlier published procedures:[1-3] p-tolylacetic acid (25°C, 48 h), N-methylbenzamide (reflux, 36 h), benzamide (reflux, 24 h), acetanilide (25°C, 48 h), m-methoxybenzyl alcohol (arene addition at 0°C, 25°C, overnight). The resulting organothallium compounds were allowed to crystallize from solution and were reacted further as indicated in footnote a in Table I.

While the majority of the subsequent palladium-promoted olefination reactions give the anticipated product, several exceptions have been noted. For example, the reaction of the ortho-thallated benzoic acid and 3,3-dimethyl-1-butene gives 3-t-butylisocoumarin,[1] but the corresponding reaction of the thallated p-tolylacetic acid (entry 1) affords a saturated six-membered ring lactone. This reaction, best run in methylene chloride, appears to proceed via rearrangement and subsequent displacement of the corresponding benzylic palladium compound (eq. 1). Such displacements have been reported previously in the literature.[4] The thallated p-tolylacetic acid also reacts with methyl acrylate and catalytic amounts of Li_2PdCl_4 (entry 2) to stop at the corresponding styrene derivative which cyclizes upon refluxing with Et_3N (eq. 2).

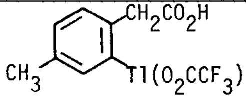
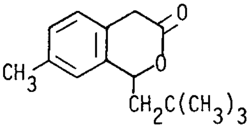
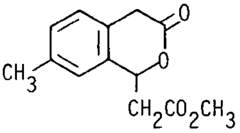
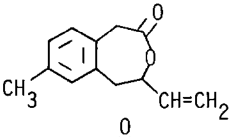
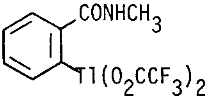
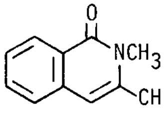
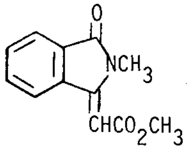
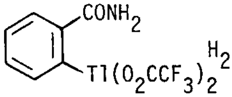
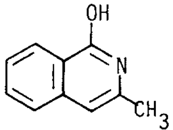
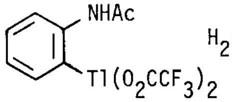
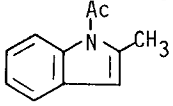
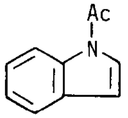
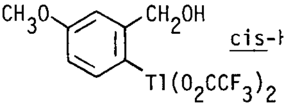
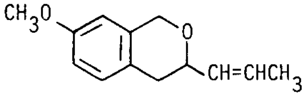


(1)



(2)

Table I. Heterocyclic Synthesis via Thallation and Subsequent Palladium-Promoted Olefination

Entry	Thallated Arene	Olefin (2 equiv)	Olefination Conditions[a]	Product	% Isolated Yield
1		$H_2C{=}CHCH(CH_3)_3$	CH_2Cl_2; 2 Et_3N/ 2 K_2CO_3/50°C/5h		77
2		$H_2C{=}CHCO_2CH_3$	0.1 Li_2PdCl_4/ 48h; Et_3N/Δ		71
3		$H_2C{=}CHCH{=}CH_2$	CH_2Cl_2; 2 Et_3N/ 2 K_2CO_3/50°C/5h		69
4		$H_2C{=}CHCH_2Cl$	---; 80°C/5h		61
5		$H_2C{=}CHCO_2CH_3$	---; 1.5 NaH/ 80°C/5h		52
6		$H_2C{=}CHCH_2Cl$	---; Δ/5h		60
7		$H_2C{=}CHCH_2Cl$	---; 1.5 NaH/ 80°C/5h		45
8		$H_2C{=}CHBr$	---; 1.5 NaH/ 80°C/5h		45
9		cis-$H_2C{=}CHCH{=}CHCH_3$	CH_2Cl_2/20h; 2 Et_3N/2 Na_2CO_3/ Δ/5h		54

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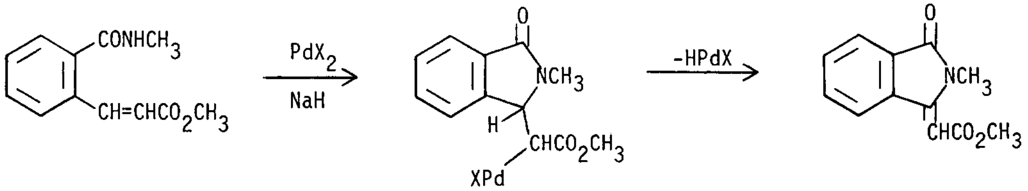
[a] Olefination was carried out using 1 equiv Li_2PdCl_4 in CH_3CN at 25°C for 16h unless otherwise indicated; base and/or heat were then introduced as indicated.

The reaction of N-methylbenzamide and methyl acrylate (entry 5) is unusual in that cyclization apparently involves a palladium-promoted process and not a simple Michael addition (eq. 3). An unsaturated lactam, rather than the anticipated saturated lactam, is formed in fair yield.



(3)

The thallation-olefination of benzamides and acetanilides would appear to be a particularly valuable route to the isocarbostyril, isoquinolone and indole ring systems. We are continuing to explore the scope and limitations of the thallation-olefination approach to heterocycles.

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References

1. Larock, R. C.; Varaprath, S.; Lau, H. H.; Fellows, C. A. J. Am. Chem. Soc. **1984**, 106, 0000.
2. McKillop, A.; Hunt, J. D.; Zelesko, M. J.; Fowler, J. S.; Taylor, E. C.; McGillivray, G.; Kienzle, F. J. Am. Chem. Soc. **1971**, 93, 4841.
3. Taylor, E. C.; Kienzle, F.; Robey, R. L.; McKillop, A.; Hunt, J. D. J. Am. Chem. Soc. **1971**, 93, 4845.
4. Horino, H.; Inoue, N. Heterocycles **1978**, 11, 281.

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