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SYNTHESIS OF 1,2,4-TRIAZINE-(2H,4H)-3,5-DIONE ANTICOCCIDIAL AGENTS VIA PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS

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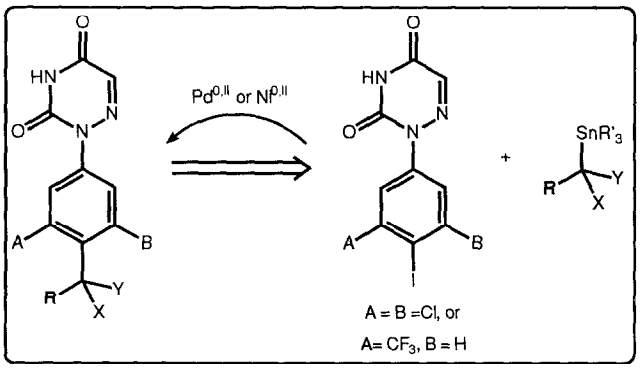
Abstract: Palladium-mediated coupling of 2-(4-iodoaryl)-1,2,4-triazine-(2H,4H)-3,5-diones with variously substituted vinylstannanes has been examined in efforts to explore the SAR of novel triazine anticoccidials. Conventional procedures were employed for the large-scale preparation of key iodoaryltriazine intermediates while a new method - employing a modified Shapiro reaction - was developed for the synthesis of 1,1-substituted vinylstannanes.

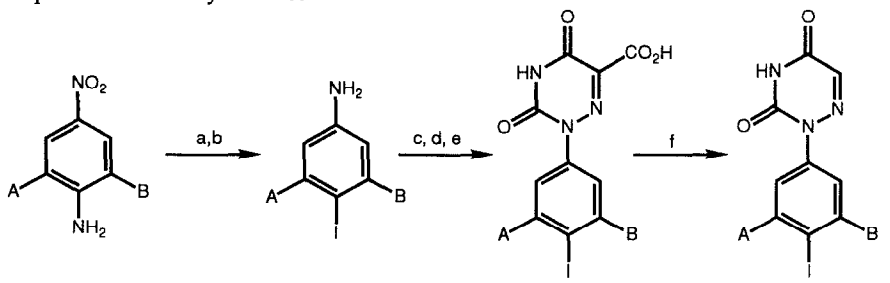
In 1960, weak anticoccidial activity was noted for 6-azauracil, the parent structure for the 1,2,4-triazine-(2H,4H)-3,5-diones ("triazines").[1] Over the past three decades, extensive synthetic investigations of substituted triazines have been conducted at several pharmaceutical companies, culminating in the identification of a number of potent, well tolerated, broad spectrum anticoccidial agents.[2] Recent innovations in transition metal-mediated aromatic couplings suggested that this methodology might be amenable for the preparation of novel entries in the triazine series. Following synthetic and QSAR analyses[3] of the triazines, a working model for triazine anticoccidial activity was proposed which would incorporate features important for high potency and acceptable consumer safety (i.e., toxicology and drug residues). A retrosynthetic analysis of this model is provided in Figure 1 below.

Figure 1. Retrosynthetic analysis of triazine target model.



Previous preparations of substituted triazines have involved linear, multi-stepped synthetic routes.[2] An analysis of the potency model to be challenged synthetically suggested a convergent route to a series of novel compounds through the utilization of transition metal mediated coupling of various organostannanes with iodoaryltriazine intermediates. The preparation of the two required iodoaryltriazines was anticipated to be straightforward based on our previous work in this area.[2,4] The challenge of this approach centered on the preparation and ultimate coupling of the assorted stannanes with these aryliodides.

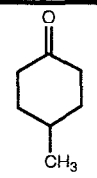
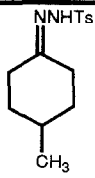
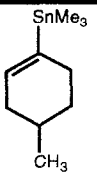
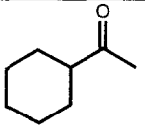
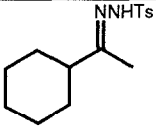
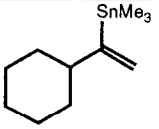
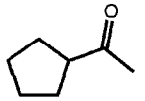
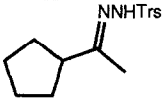
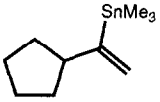
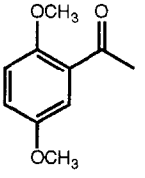
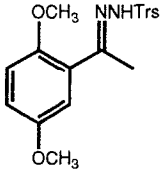
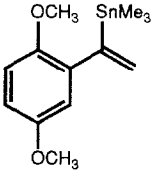
Figure 2. Preparation of iodoaryltriazines.



Key: Isolated yields are not optimized and refer to A=B=Cl, and (A=CF_3, B=H), respectively.(a) H_2S0_4, $NaNO_2$; KI, H_2O, 22% (37%); (b) $SnCl_2$, H_2O/EtOH, reflux, 60% (73%); (c) HCl, $NaNO_2$; $EtO_2CNHCOCH_2CN$, pyr., 88% (65%); (d) KOAc/HOAc, reflux, 90% (56%); (e) HCl/HOAc, reflux, 83% (96%); (f) $HSCH_2CO_2H$, 170 °C, 32% (45%).

Following several approaches involving Stille-type coupling of aryl iodides[5] and vinyltriflates[6] with hexamethylditin to produce our requisite aryl/vinyl stannane coupling partners, we elected to prepare these species through a modified Shapiro reaction employing either p-toluenesulphonyl- ("tosyl-"), or 2,4,6-triisopropylphenylsulphonyl- ("trisyl-") hydrazones derived from the corresponding ketones.[7,8] Examples of these preparations are provided in Table 1 below.

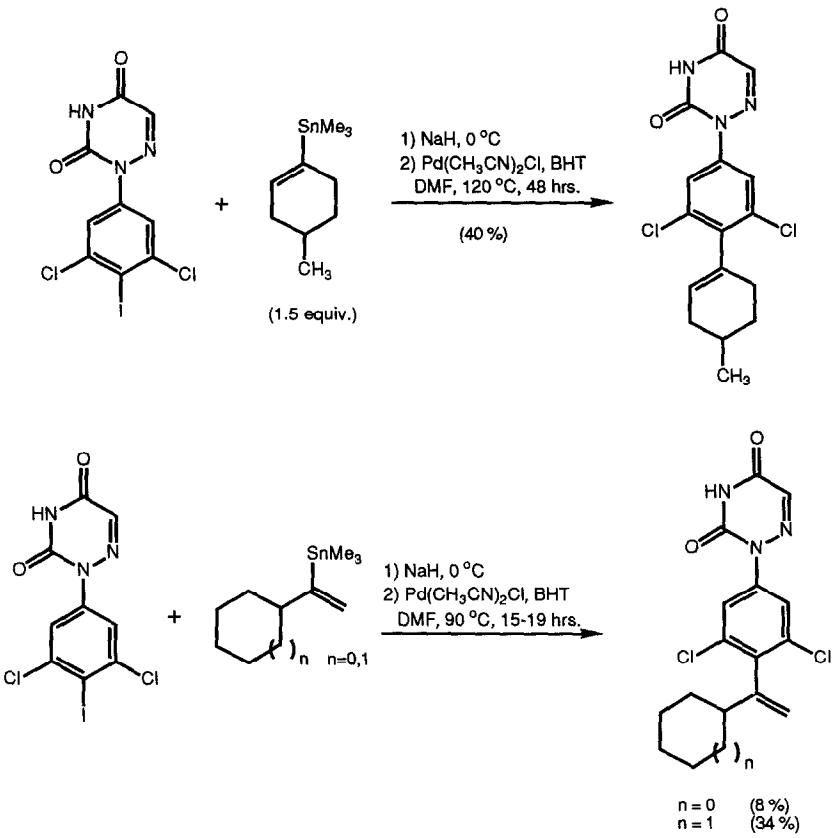
Table 1. Preparation of vinylstannanes via tosyl or trisylhydrazones.

Starting Ketone	Method[a]	Hydrazone (Yield)	Vinyl stannane (Yield)[b]
	A	 (70%)	 (19%)
	A	 (68%)	 (25%)
	B	 (67%)	 (91%)
	B	 (84%)	 (64-90%)

[a] Method A: p-$TsNHNH_2$, HCl, MeOH, 0 °C. Method B: $TrisylNHNH_2$, HCl, MeOH, 0 °C. [b] (i) 2.2 n-BuLi, THF, -78 °C; (ii) Me_3SnCl, THF, TMEDA, 0 °C.

We were gratified to find that coupling of hindered, ortho-substituted triazine aryl iodides with a variety of vinylstannnanes could be effected with the use of catalytic palladium species. In a typical procedure, the sodium salt of the triazine aryl iodide (10 mmol) was generated at 0 °C (NaH, DMF),[9] warmed to ambient temperature, treated with the vinyl stannane (15 mmol) and $Pd(CH_3CN)_2Cl_2$ (0.5-1.0 mmol) in DMF[10] and heated to 90-100 °C for 18-48 hrs.[11] The reaction mixture was cooled to room teperature, diluted with diethyl ether, washed with saturated NH_4Cl solution, dried over $MgSO_4$, and chromatographed (silica) to provide the desired coupled adducts. Figure 3 below provides representative examples of coupled triazine products based on the dichloroiodoaryltriazine precursor.

Figure 3. Palladium-Catalyzed Coupling Reactions - Synthesis of 3,5-Dichlorophenyltriazines.



As detailed above, a straightforward route to the synthesis of 4-substituted aryltriazines has been developed. A variety of tethered aryltriazines have been prepared by the above described palladium-mediated coupling procedure with modest to good yields observed for vinylstannane couplings to the sterically demanding 3,5-dichloro-4-iodoaryltriazine. Similar yields were obtained for the 3-trifluoromethyl-4-iodoaryltriazine series as well. Although triazine N4-methylation was observed in some cases, this transition metal mediated procedure

was generally compatible with the heteroaromatic triazine system. Attempted coupling with particularly unreactive vinylstannanes occasionally yielded 4-methylaryltriazines presumably due to methyl transfer from the tin species. While most of the new triazines demonstrated excellent *in vitro* activity ($IC_{50} < 1.0 \times 10^{-4}$ ppm),[12] none of these compounds proved active *in vivo* at doses below 16 ppm [13]

Acknowledgements: *In vitro* data was provided by Dr. R.C. Findly, and K.T. Murphy (Groton). *In vivo* results were courtesy of D.M. Newcomb (Terre Haute, IN).

References and Notes

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9. It was found during the course of our investigations that coupling of the triazine sodium salts reduced the relative percentage of triazine N4-methylation byproducts.

10. Several palladium(0) and palladium(II) species were examined in addition to bis(acetonitrile)palladium(II) dichloride, including tetrakis[illegible] dichloride, and dichloro[1,1' [illegible] superior to $Pd(CH_3CN)_2Cl_2$ [illegible] **1984**, *106*, 4833; Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.

11. Following reports from the Stille group, we found more consistent yields of coupled products through the inclusion of 2,6-di-*tert*-butyl-4-methylphenol as a catalytic antioxidant.

12. *In vitro* potencies were determined in an *Eimeria tenella* tissue culture model with Madin-Darby bovine kidney cells as host, and an enzyme-linked immunosorbent assay was performed as the endpoint. Olson, J.A. *Antimicrob. Agents Chemother.* **1990**, *34*, 1435.

13. Battery efficacy testing against *E. tenella* was based on the drug screen previously described. Chappel, L.R.; Howes, H.L.; Lynch, J.E. *J. Parasitol.* **1974**, *60*, 415.

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