Construction of Diarylmethane Compounds.

Synthesis of tolpropamine via Heck-Matsuda Reaction

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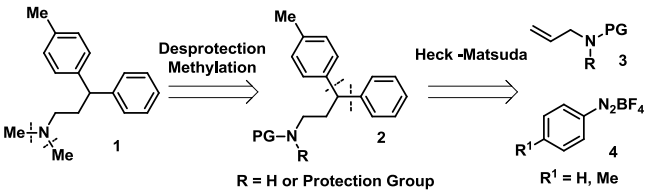
Keywords: Heck-Matsuda reaction, arenediazonium salts, diarylmethane compounds

INTRODUCTION

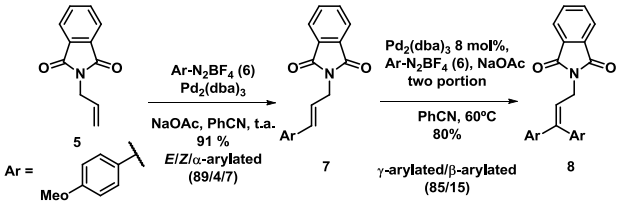
Tolpopramine is a antihistamine and antipruritic drug used for skin diseases treatment such as allergy and itch. Previous syntheses relied on the Witting reaction to obtain 1-phenyl-1-(p-tolyl)ethane followed by hydroaminomethylation reaction using rhodium catalysis. This methodology does not provide conditions for an enantiosselective reaction.[1] The compound **1** could be easily obtained from two Heck-Matsuda reactions from the *N*-protected allylamine **3**.[2]



Scheme 1. Retrosynthetic analysis.

RESULTS AND DISCUSSION

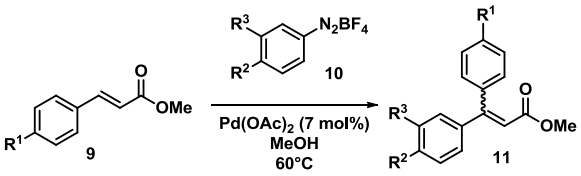
Studies regarding the bis arylation of *N*-phthalimide allylamine (**8**) with and tetrafluoroborate 4-methoxy-benzenediazonium salt (**6**) provided only moderate results.



Scheme 2: Conditions of bisarylation of Heck-Matsuda reaction

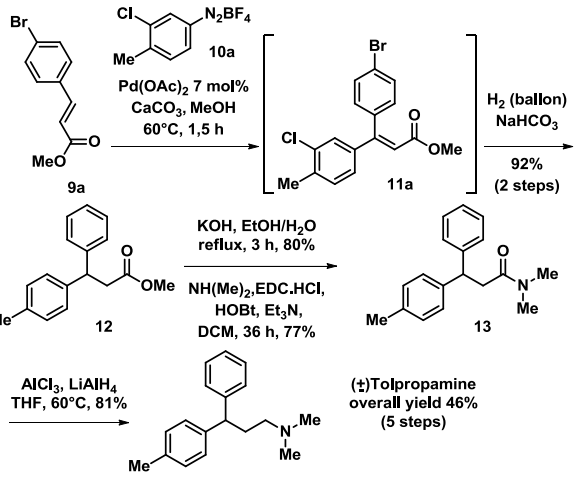
We then decided to optimize conditions to obtain the diarylated compounds from methyl cinnamate, 4-tolyl-diazonium tetrafluoroborate, methanol and $Pd(OAc)_2$ at 60°C.[3]

Table 1. Optimization of Heck-Matsuda reaction



Base (eq)	**10**	R^1	R^2	R^3	*E*/*Z*	Yield (%)
-	4	H	Me	H	-	trace
NaOAc (3)	2	H	Me	H	100/0	42
NaOAc (3)	4	H	Me	H	95/5	68
DTMPy(1)	1,5	H	Me	H	-	trace
NaOAc (3)	1,5	Me	Br	H	-	trace
NaOAc (3)	1,5	Br	Me	Cl	75/25	60
$CaCO_3$ (1)	1,5	H	Me	Cl	71/29	**88**
$CaCO_3$ (1)	1,5	Br	Me	Cl	**92/8**	**83**

With the conditions obtained for ester **11** then synthesized (±)-tolpropamine.



Scheme 3. Synthesis of (±)-tolpropamine.

CONCLUSION

The Hecck-Matsuda reaction from cinnamates is a efficient method to obtain diarylmethane compounds with high yield. This system can be easily modified to synthesis of 3,3-dipropylamine, like tolpropamine.

ACKNOWLEDGEMENTS

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REFERENCES

[1] Li, S., Huang, K., Zhang, J., Wu, W., Zhang, X. *Org. Lett.* **2013**, *15*, 1036
[2] Prediger, P., Barbosa, L. S. F.; Génisson, Y., Correia, C. R. D. *J. Org. Chem.* **2011**, *76*, 7737.
[3] Taylor, J. G.; Correia, C. R. D. *J. Org. Chem* **2011**, *76*, 857.