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A Novel Three-Component Reaction for the Diastereoselective Synthesis of 2*H*-Pyrimido[2,1-a]isoquinolines via 1,4-Dipolar Cycloaddition†

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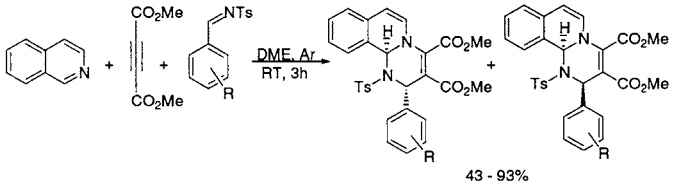
ABSTRACT



The 1,4-dipole derived from isoquinoline and DMAD has been shown to react readily with *N*-tosylimines resulting in the diastereoselective synthesis of 2*H*-pyrimido[2,1-a]isoquinoline derivatives.

The monumental work of Huisgen has established 1,3-dipolar cycloaddition[1,2] as the most important methodology for the construction of a wide range of five-membered heterocycles. Concomitantly, he also provided the conceptual framework for the related 1,4-dipolar cycloadditions and demonstrated the existence of 1,4-dipoles.[3]

Except for isolated reports,[4,5] such reactions nevertheless remained underexploited. A noteworthy development in this area has been the reaction of 1,4-dipoles incorporated into cross-conjugated betaines by Padwa.[6] Although the formation of a 1,4-dipole from isoquinoline and dimethyl acetylenedicarboxylate (DMAD) and its trapping by phenyl isocyanate, diethyl mesoxalate, and dimethyl azodicarboxylate were reported by Huisgen,[7] the utility of this reaction for the synthesis of six-membered heterocycles has not been explored so far. In the context of our ongoing investigations on heterocyclic construction via dipolar intermediates derived from nucleophilic species and DMAD,[8] we reasoned that the isoquinoline-DMAD dipole would readily react with acti-

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† This paper is dedicated to the memory of Professor R. H. Sahasrabudhey, who passed away on August 21, 2002.

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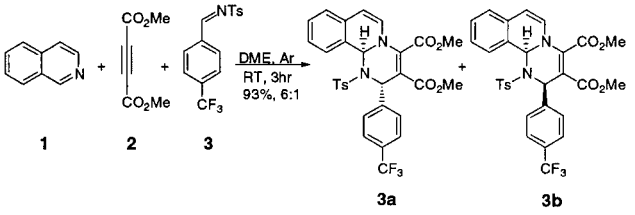
vated imines leading to pyrimido-isoquinolines in the process. The preliminary results of our studies attesting the validity of this approach are presented here.

Our studies were set to motion by dissolving isoquinoline, DMAD, and *N*-tosylimine **3** in DME and stirring the solution at room temperature under an argon atmosphere. An exceedingly facile reaction occurred with stereoselective formation of novel 2*H*-pyrimido[2,1-a]isoquinoline derivatives **3a** and **3b** in 93% yield in a 6:1 ratio (Scheme 1).

Scheme 1



The diastereomeric ratio was determined by ^{1}H NMR, and the major diastereomer **3a** was separated by crystallization and characterized by spectroscopic techniques. In the ^{1}H NMR, the two methoxy carbonyl groups were observed at δ 3.63 and 3.85 as two singlets, supporting the IR absorption at 1748 cm $^{-1}$. The ring junction proton was observed as a singlet at δ 6.13, and the other benzylic proton displayed a singlet at δ 5.90. Finally, the structure and configuration of the major diastereomer was ascertained to be **3a** by single-crystal X-ray analysis (Figure 1).

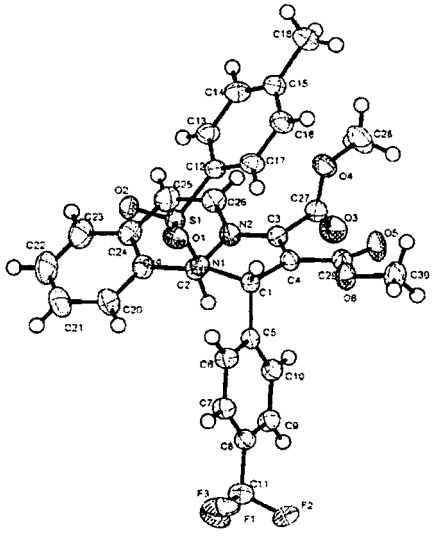
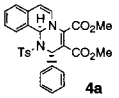
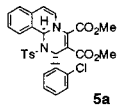
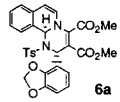
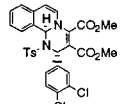
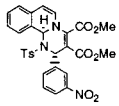
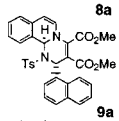
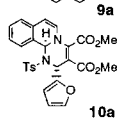


Figure 1. X-ray structure of compound **3a**.

The reaction was found to be applicable to a number of *N*-tosylimines, affording the 2*H*-pyrimido[2,1-a]isoquinoline derivatives in moderate to excellent yields and with impressive diastereoselectivity. The results are summarized in Table 1.

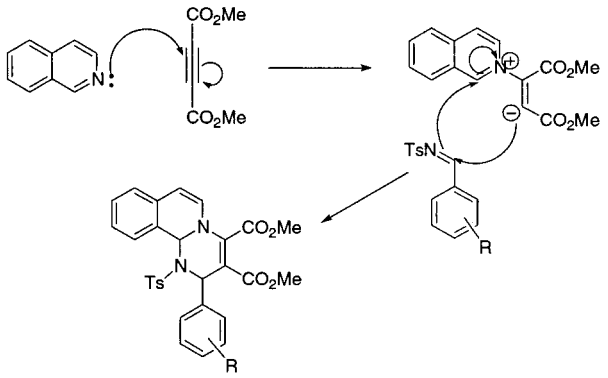
Table 1. Reaction of Isoquinoline and DMAD with Various *N*-Tosylimines

Entry	Tosylimine	Product [a]	Ratio [b]	Yield (%) [c]
1.	 4	 4a	6:1	43
2.	 5	 5a	10:1	92
3.	 6	 6a	5:1	56
4.	 7	 7a	5:1	60 (70)[d]
5.	 8	 8a	10:1	73
6.	 9	 9a	5:1	50 (89)[d]
7.	 10	 10a	5:1	45

[a] Structure of the major isomer is shown. [b] Determined by ^{1}H NMR. [c] Combined isolated yield of both isomers. [d] Recovered yield.

Mechanistically, the reaction can be considered to proceed via the initial formation of the 1,4-dipolar intermediate from isoquinoline and DMAD, followed by its trapping with *N*-tosylimine, to give the corresponding 2*H*-pyrimido[2,1-a]isoquinoline derivative (Scheme 2).

Scheme 2



It is worthy of note that pyrimido-isoquinoline derivatives manifest a number of important and therapeutically useful biological activities; some of them are potent antiallergics,

platelet-activating factor receptor antagonists, and mast cell activation inhibitors.[9]

In conclusion, we have devised a novel three-component reaction for the diastereoselective synthesis of 2*H*-pyrimido-[2,1-a]isoquinoline derivatives via 1,4-dipolar cycloaddition under mild conditions. Further investigations with different dipolarophiles are in progress.

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Supporting Information Available: General experimental procedures and IR, ^{1}H NMR, and ^{13}C NMR data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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