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Synthesis and Antibacterial Activity of Novel 1,3-Oxazine Derivatives

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In modern synthetic organic chemistry, heterocycles are vital for the development of pharmaceuticals, industrial chemicals and natural products.¹⁻¹¹ Among heterocycles, oxazines are of particular interest for their unique applications in drug discovery¹² and natural products chemistry.¹³ Oxazines play important roles as antihyperglycemic,¹⁴ antileishmanial,¹⁵ antitubercular,^{16,17} anti-ulcer,¹⁸ anticancer^{19,20} and antibacterial²¹ agents. In recent examples demonstrating the applicability of oxazines to drug discovery, Patil and his coworkers synthesized oxazines and found compounds with activity against *E. coli*, *S. aureus*, and strains of *Micrococcus* and *R. subtilis*.²² Kategaonkar and colleagues successfully prepared oxazines bearing naphthalene moieties and tested them against Gram positive (*B. subtilis*) and Gram negative (*E. coli*) organisms. The oxazines displayed strong inhibitory activity.²³ Oxazine derivatives were prepared by Chernov and coworkers and were found to have inhibitory activities against *S. aureus* and *E. coli*.²⁴ Recent developments in the preparation of oxazines have included green methods,²⁵ eco-friendly synthesis²⁶ and other up-to-date approaches.²⁷⁻³⁰ These reports spurred our own interest, and we now report our preliminary findings on the preparation of some novel 1,3-oxazine derivatives and their antibacterial activities. We were especially interested in preparing amide and morpholino derivatives because of their good druggability. In addition many heterocyclic systems having these functionalities possess antimicrobial, anti-inflammatory, and central nervous system activities.³¹⁻³³

In the event, the multicomponent reaction of benzaldehyde, phenylacetylene and urea in the presence of trifluoroacetic acid and acetic acid resulted in compound 1 (Scheme 1, 59%). Compound 1 was successfully acylated with 4-chlorobenzoyl chloride under an inert atmosphere to yield compound 2 (83%). In a similar vein, the reaction among

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