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# Synthesis and antibacterial evaluation of ureides of Baylis–Hillman derivatives☆

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**Abstract**—The synthesis of several 1-(2-cyano-3-aryl-allyl)-3-aryl-urea(thiourea) constructed from the reaction between allylamines generated from Baylis–Hillman acetates and substituted isocyanates and isothiocyanates has been described. Further, their cyclization in the presence of a base led to the formation of 5-arylmethyl-4-imino-3-aryl-3,4-dihydro-1*H*-pyrimidin-2-ones. All compounds were tested for their antibacterial activity. Few of the compounds showed superior activity or were equipotent to the standard antibacterial agents.

The emergence of resistant strains of bacteria has renewed the interest of several research groups in the development of new antibacterial compounds. The aryl ureas remain one of the simplest of chemicals to be used as antibacterials in clinics. For instance, diaryl urea triclocarban (Fig. 1) is essentially used in the disinfecting solutions in hospitals and households. The significance of ureides as antiinfectives including antibacterials was recently reviewed by us.[1] In our efforts concentrated toward generation of compounds of medicinal importance using Baylis–Hillman reaction as the key step, we envisioned the synthesis of new aryl urea derivatives in a straightforward manner by the reaction between the amines afforded by the Michael addition of ammonia or primary amine on the Baylis–Hillman derivatives and the commercially available aryl isocyanates. In principle, these open-chain aryl ureas can be easily cyclized in the presence of a base to yield the tetrahydropyrimidin-2-ones, the cyclic ureide analog. Such a synthetic strategy would give a library of novel ureides for antibacterial evaluation. In studies aimed toward these objectives, we have carried out the synthesis of several urea derivatives from the allylamines obtained from the acetates of the Baylis–Hillman adducts of acrylonitrile and successfully cyclized them to the corresponding tetrahydro-pyrimidin-2-ones. These compounds were evaluated for their antibacterial activity. During the preliminary in vitro screening, a few of the compounds exhibited significant antibacterial activity against several strains of bacteria, which prompted us to report our findings in this communication.

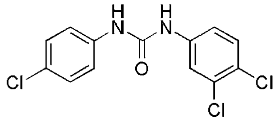

**Figure 1.** Triclocarban.

Initially, the Baylis–Hillman adducts **1a** and **1b** were prepared following the literature procedure.[2] Treatment of these compounds with methanolic ammonia or benzyl amine gave the corresponding amino derivatives **2a**, **3a** and **3b** as illustrated in Scheme 1.[3] The reaction of amines **2a**, **3a**, and **3b** with different isocyanates yielded the required urea derivatives (**4**–**7**). Interestingly, these ureas during the cyclization reaction in the presence of $K_2CO_3$ or NaH afforded products **8**–**11**. The loss of the benzyl moiety in these compounds was conclusively supported by spectroscopic data. Further support for the assigned structure of products **8**–**11** was made on the basis of alternate synthesis as outlined in Scheme 2. Treatment of acrylonitrile with benzyl amine in methanol led to the product **12** which was reacted with substituted isocyanate to give the urea derivative **13**.

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*Keywords*: Ureides; Baylis–Hillman; Antibacterial.

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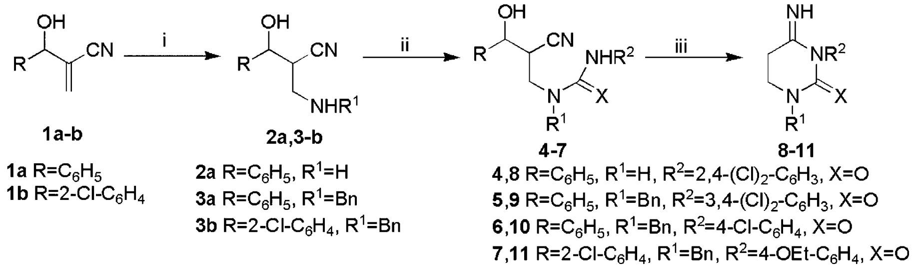
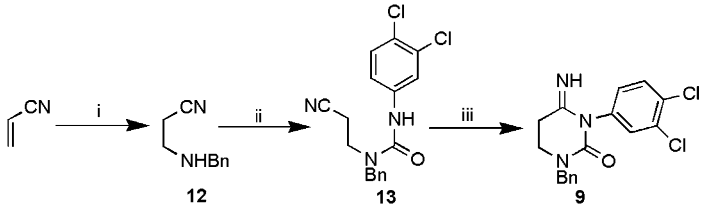
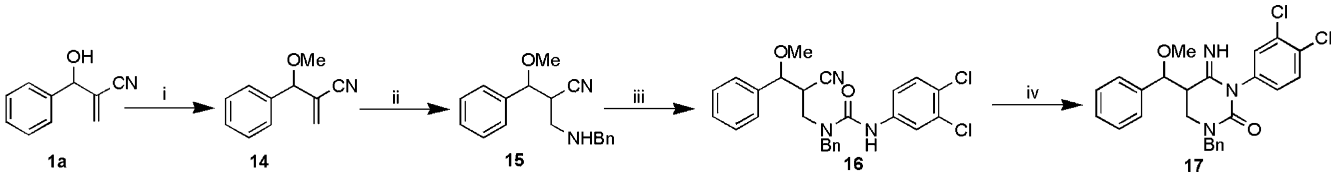


**Scheme 1.** Reagents and conditions: (i) methanolic ammonia, rt 8 h or $BnNH_2$, MeOH, rt 8 h; (ii) $R_2NCO$, THF, rt, 1.5–2 h; (iii) $K_2CO_3$, MeOH, reflux, 8–9 h or NaH, toluene, reflux, 8–9 h.

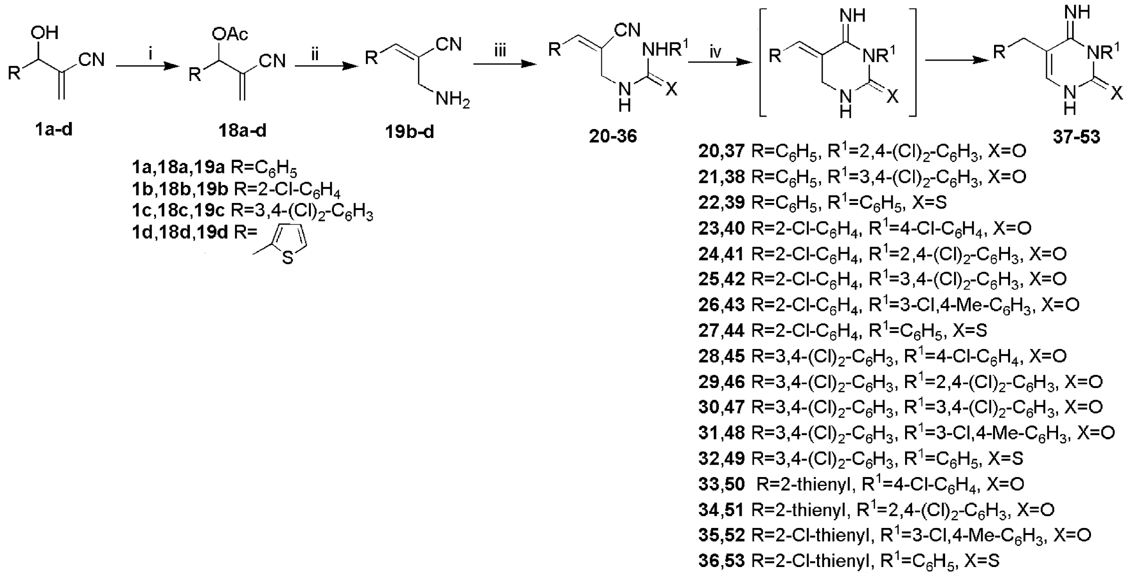


**Scheme 2.** Reagents and conditions: (i) $BnNH_2$, MeOH, rt, 3.5 h; (ii) $R_2NCO$, THF, rt, 1 h; (iii) NaH, toluene, reflux, 9 h.

Subsequently, the reaction between the urea **12** and NaH in refluxing toluene afforded the cyclized derivative **9**. It was presumed that in the presence of strong base such as $K_2CO_3$ or NaH the hydroxyl group present at the benzylic position triggers off the loss of the benzyl group as benzaldehyde. In order to validate, in a representative compound **1a** the hydroxyl group was converted to the methoxy group **14**.[4] Subsequently, it was reacted with benzyl amine and converted to the urea derivative **16**. The cyclization of urea **16** with NaH led to isolation of the methoxy derivative **17** in moderate yields as depicted in Scheme 3. This clearly showed that the elimination of the benzyl group is due to the presence of the hydroxyl moiety. In the light of these results



**Scheme 3.** Reagents and conditions: (i) $Ag_2O$, MeI, $CH_2Cl_2$, rt, 5 h; (ii) $BnNH_2$, MeOH, rt, 6 h; (iii) 3,4-$(Cl)_2$–$C_6H_3NCO$, THF, 45 min; (iv) NaH, toluene, reflux, 8 h.



**Scheme 4.** Reagents and conditions: (i) AcCl, pyridine, $CH_2Cl_2$, rt, 3 h; (ii) methanolic ammonia, rt, 1 h; (iii) $R_1NCO$, THF, rt, 1 h; (iv) $K_2CO_3$, MeOH, reflux, 8–9 h or NaH, toluene, reflux, 8–9 h.