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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

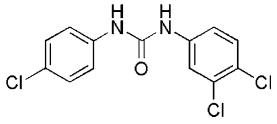

Figure 1. Triclocarban.

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.

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**.

Keywords: Ureides; Baylis–Hillman; Antibacterial.
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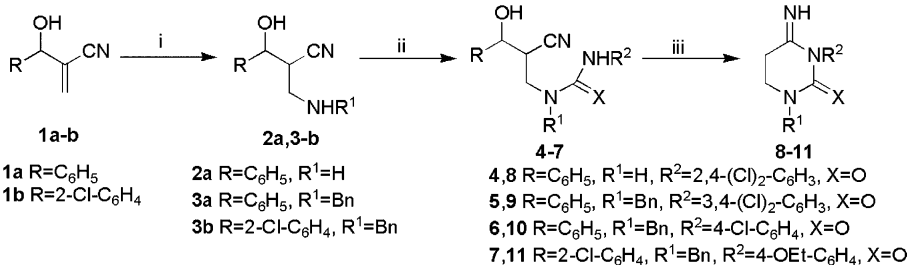
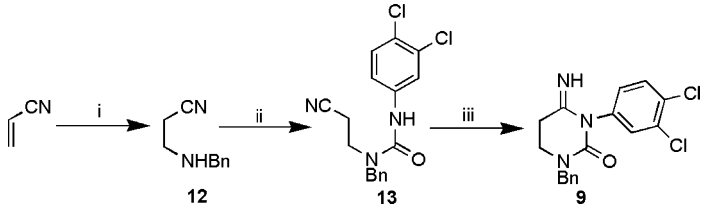
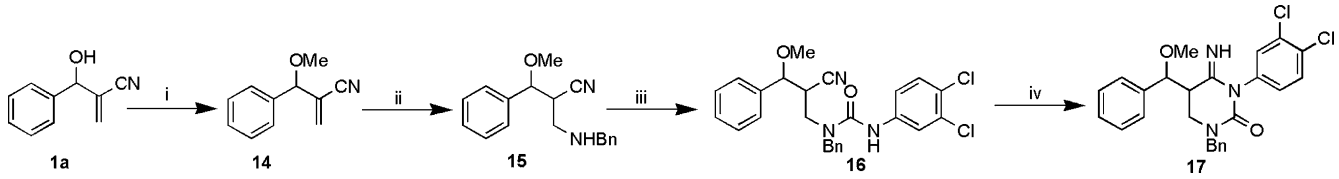


Scheme 1. Reagents and conditions: (i) methanolic ammonia, rt 8 h or $BnNH_2$, MeOH, rt 8 h; (ii) R_2NCO, THF, rt, 1.5–2 h; (iii) K_2CO_3, MeOH, reflux, 8–9 h or NaH, toluene, reflux, 8–9 h.

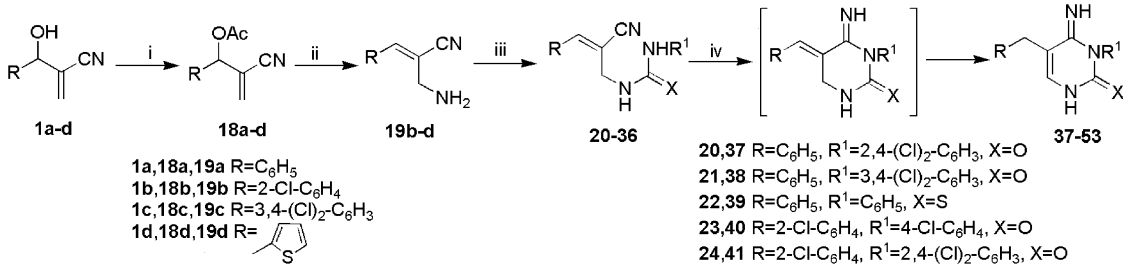


Scheme 2. Reagents and conditions: (i) $BnNH_2$, MeOH, rt, 3.5 h; (ii) R_2NCO, THF, rt, 1 h; (iii) NaH, toluene, reflux, 9 h.

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.

it was decided to evaluate the analogous reactions on the acetates of the Baylis–Hillman adducts as shown in Scheme 4. Accordingly, the Baylis–Hillman adducts **1a–d** were prepared and acetylated in the presence of pyridine and acetyl chloride. Treatment of acetates **18a–d** with methanolic ammonia furnished the allylamines **19a–d** as *Z*-isomer.[3a] The reaction between the allylamines and several commercially available iso(thio)cyanates yielded the required (thio)urea derivatives **20–36** in good yields as solids. These products (**20–36**) were cyclized in the basic medium to yield the respective 4-imino-tetrahydro-pyrimidin-2-ones **37–53** in moderate yields. The tautomerization of the benzylidene double bond from an exocyclic to an endocyclic position was supported by the NMR data. All the compounds generated during the study gave satisfactory spectroscopic and analytical data.[5] The ureas **4–7**, **16**, **20–36**, and cyclized products **17** and **37–53** were evaluated [6] against the susceptible Gram-positive and the Gram-negative bacteria including *Staphylococcus aureus*, *Streptococcus faecalis*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa* strains and the results are summarized in Table 1. Among all the compounds screened, **16**, **17**, **30**, **32**, and **46** exhibited significant antibacterial activity with low MIC values. Only two other compounds, **25** and **29**, show prominent activity against the *E. coli*.

It was interesting to discover that all active compounds bear 3,4-dichloro-phenyl group which is a sub-structure

Table 1. Yields, physical characteristics and antibacterial activities of reported compounds

Compound	Yield (%)	Physical state, mp (°C)	Antibacterial activity MIC (μg mL^{-1})				
			Sa	Sf	Kp	Ec	Pa
4	81	White solid, 160–162	>50	>50	>50	>50	>50
5	79	White solid, 142–144	>50	>50	>50	>50	>50
6	51	White solid, 86–88	25	50	50	12.5	50
7	59	White solid, 168–169	>50	>50	>50	>50	>50
8	82	White solid, 208–210	50	50	50	25	50
16	77	Yellow oil	**3.12**	**6.25**	**3.12**	**3.12**	**50**
17	38	Brown solid, 140–144	**1.56**	**3.12**	**3.12**	**1.56**	**50**
20	66	White solid, 173–175	>50	>50	>50	50	>50
21	70	White solid, 173–174	>50	>50	>50	>50	>50
22	54	White solid, 148–149	50	50	50	50	50
23	72	White solid, 212–213	>50	>50	>50	>50	>50
24	74	White solid, 214–216	>50	>50	>50	>50	>50
25	78	White solid, 185–186	>50	>50	>50	1.56	>50
26	60	White solid, 165–166	>50	>50	>50	>50	>50
27	60	White solid, 150–152	>50	>50	50	>50	>50
28	73	White solid, 203–205	>50	>50	>50	>50	>50
29	63	White solid, 205–206	>50	>50	>50	6.25	>50
30	63	White solid, 201–202	**1.56**	**1.56**	**1.56**	**0.78**	**50**
31	77	White solid, 176–177	>50	>50	>50	>50	>50
32	60	White solid, 160–161	**1.56**	**3.12**	**3.12**	**1.56**	**25**
33	58	White solid, 212–213	>50	>50	>50	>50	>50
34	62	White solid, 206–207	>50	>50	>50	>50	>50
35	55	White solid, 220–221	>50	>50	>50	>50	>50
36	62	White solid, 161–163	>50	>50	50	>50	>50
37	58	White solid, 207–210	50	25	50	50	50
38	63	White solid, 185–187	50	50	50	50	50
39	60	White solid, 210–212	>50	>50	>50	>50	>50
40	44	White solid, 197–199	>50	>50	>50	>50	>50
41	65	White solid, 204–206	>50	>50	50	>50	>50
42	40	White solid, 214–215	>50	50	>50	50	>50
43	43	White solid, 216–217	50	50	>50	50	50
44	58	Pale yellow solid, 212–213	>50	25	>50	>50	>50
45	57	White solid, 208–209	>50	>50	>50	>50	>50
46	59	White solid, 147–149	**3.12**	**3.12**	**3.12**	**3.12**	**25**
47	40	White solid, 199–200	25	25	50	25	50
48	43	White solid, 210–211	>50	50	50	>50	>50
49	51	Pale yellow solid, 205–206	>50	25	50.0	>50	>50
50	40	White solid, 197–199	>50	>50	>50	>50	>50
51	39	White solid, 118–120	>50	>50	>50	>50	>50
52	55	White solid, 190–192	>50	50	>50	>50	>50
53	50	Pale yellow solid, 210–212	>50	>50	>50	>50	>50
Norfloxacin			0.3	0.78	0.36	0.36	0.78
Gentamycin sulfate			6.25	0.78	0.78	0.02	25.0
Ampicillin			0.09	0.02	0.01	0.02	50.0

Sa, *Staphylococus aureus*; Sf, *Streptococcus fecaelis*; Kpn, *Klebsiella pneumoniae*; Ec, *Escherichia coli*; Pa, *Pseudomonas aeruginosa*.
ND, not done.

unit of triclocarban. Compound **16**, an open-chain urea derivative, showed significant antibacterial effect with 2-fold better activity than the standard gentamycin for *S. aureus*. In comparison, the cyclized derivative **17** showed marked activity against *S. aureus* with MIC of 1.56 μg mL^{-1}, which was 2-fold better than **16** and 4-fold better than the standard gentamycin. Both these compounds also elicit significant antibacterial activity against other *P. aeruginosa* and were found to be equipotent to the ampicillin. In the series represented by compounds **20**–**53**, the open-chain urea analogs were found to show better antibacterial activity than the cyclic dihydro-pyrimidin-2-one system. Within the urea derivatives, the most potent in vitro antibacterial effect was demonstrated by compounds **30** and **32** in relation to all evaluated strains of bacteria, while compounds **25** and **29** show potent responses against *E. coli* only. Although compounds **30** and **32** were equipotent against *S. aureus*, compound **30** was 2-fold more active for *S. fecaelis*, *K. pneumoniae*, and *E. coli* and was 2-fold less active for *P. aeruginosa* than compound **32**. Compounds **25** and **29** with MIC of 1.56 and 6.25 μg mL^{-1}, respectively, against *E. coli* were the only other actives in the series. These results indicated that in open chain aryl ureas, in comparison to the thiourea group, only the compounds bearing urea moiety show antibacterial effect. On the other hand, the presence of 3,4-dichlorophenyl group was essential for antibacterial activity in this class of compounds. The replacement of the phenyl group with a heteroaryl group has negative effect on the antibacterial activity. Unfortunately except for compound **46**, most of the cylclic ureide analogs were found to be inactive. Compound **46** with MIC of 3.12 μg mL^{-1} against *S. aureus* was 2-fold more active than gentamycin and with MIC of 25 μg mL^{-1} against *P. aeruginosa* was equipotent to the same drug. Compound **47**, the cyclic derivative of urea **30**, shows mild activity only thereby indicating that even the presence of two 3,4-dichlorophenyl groups did not have influence on antibacterial activity. The biological evaluation of this limited set of compounds shows that the cyclized compound 1-benzyl-3-(3,4-dichloro-phenyl)-4-imino-5-(methoxyphenyl-methyl)-tetrahydro-pyrimidin-2-one (**17**) elicits better antibacterial activity than its open chain urea precursor (**16**). On the contrary, the 1-(2-cyano-3-aryl-allyl)-3-aryl-ureas (**20**–**35**) were better antibacterial as compared to their cyclic analogs 5-arylmethyl-4-imino-3-aryl-3,4-dihydro-1*H*-pyrimidin-2-ones (**36**–**53**).

In summary, we have discovered potent antibacterial activity in new aryl ureas which can be easily afforded from the Baylis–Hillman chemistry. Further work is underway to optimize the SAR in the related structures by introducing more diversity.

Acknowledgments

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5. 1-Benzyl-1-[3-(4-chloro-phenyl)-2-cyano-3-methoxy-propyl]-3-(3,4-dichloro-phenyl)-urea (**16**). ν_{max} (neat) 1663 (CONH), 2248 (CN), 3401 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ = 3.25 (s, 3H, OCH_3), 3.47–3.56 (m, 2H, CH_2), 3.80–3.84 (m, 1H, C*H*CN), 3.87–3.90 (m, 1H, C*H*OCH_3), 4.79 (s, 2H, CH_2Ph), 7.24–7.69 (m, 12H, ArH), 9.07 (s, 1H, NH); mass (FAB+) *m/z* 502 (M^++1), 504 (M^++3); EI-HRMS, calcd for $C_{25}H_{22}Cl_3N_3O_2$ 501.0778, found: 501.0782.
1-Benzyl-5-[(4-chloro-phenyl)-methoxy-methyl]-3-(3,4-dichloro-phenyl)-4-imino-tetrahydro-pyrimidin-2-one (**17**). ν_{max} (KBr) 1640 (CONH), 3317 (NH) cm^{-1}, ^1H NMR (DMSO-d_6, 200 MHz) δ = 3.24 (m, 1H, C*H*CH_2), 3.32 (s, 3H, OCH_3), 3.34 (d, 2H, *J* = 4.0 Hz, CH_2N), 3.62 (d, 1H, *J* = 6.1 Hz, C*H*OCH_3), 4.33 (s, 2H, CH_2Ph), 6.90 (br s, 1H, ArH), 7.10 (s, 1H, ArH), 7.30–7.36 (m, 8H, ArH), 9.02 (s, 1H, NH); mass (FAB+) *m/z* 502 (M^++1); EI-HRMS, calcd for $C_{25}H_{22}Cl_3N_3O_2$ 501.0778, found: 501.0787.
1-[3-(2-Chloro-phenyl)-2-cyano-allyl]-3-(3,4-dichloro-phenyl)-urea (**25**). ν_{max} (KBr) 1649 (CONH), 2214 (CN), 3343 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ = 4.14 (d, 2H, *J* = 5.4 Hz, CH_2NH), 6.96 (br, 1H, CH_2N*H*), 7.34 (s, 1H, ArH), 7.45–7.51 (m, 5H, =CH and ArH), 7.84–7.86 (m, 2H, ArH), 9.11 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, 50.32 MHz) δ = 42.9, 114.6, 117.6, 118.4, 119.4, 123.1, 127.9, 129.6, 130.1, 130.8, 131.3, 132.0, 133.2, 140.3, 140.7, 155.0; mass (FAB+) *m/z* 381 (M^++1); EI-HRMS, calcd for $C_{17}H_{12}Cl_3N_3O$ 379.0046, found: 379.0055.
1-[2-Cyano-3-(3,4-dichloro-phenyl)-allyl]-3-(3,4-dichloro-phenyl)-urea (**30**). ν_{max} (KBr) 1684 (CONH), 2219 (CN), 3322 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ = 4.09 (d, 2H, *J* = 5.4 Hz, CH_2NH), 6.92 (t, 1H, *J* = 6.0 Hz, CH_2N*H*), 7.28 (dd, 1H, J_1 = 2.2 Hz, J_2 = 8.0 Hz, ArH), 7.37 (s, 1H, =CH), 7.48 (d,1H, *J* = 8.0 Hz, ArH), 7.77 (s, 2H, ArH), 7.85 (d, 1H, *J* = 2.2 Hz, ArH), 7.98 (s, 1H, ArH), 9.16 (s, 1H, NH), mass (FAB+) *m/z* 416 (M^++1); EI-HRMS, calcd for $C_{17}H_{11}Cl_4N_3O$ 412.9656, found: 412.9655.
1-[2-Cyano-3-(3,4-dichloro-phenyl)-allyl]-3-phenyl-thiourea (**32**). ν_{max} (KBr) 1593 (CSNH), 2210 (CN), 3167 (NH) cm^{-1}, ^1H NMR (DMSO-d_6, 200 MHz) δ = 4.65 (d, 2H, *J* = 6.0 Hz, CH_2NH), 6.35 (t, 1H, *J* = 6.0 Hz, CH_2N*H*, replaceable with D_2O), 7.28 (s, 1H, =CH), 7.32–7.49 (m, 5H, ArH), 7.59 (s, 1H, ArH), 7.93–7.97 (m, 2H, ArH); mass (FAB+) *m/z* 362 (M^++1), 364 (M^++3); EI-HRMS, calcd for $C_{17}H_{11}Cl_4N_3S$ 361.0207, found: 361.0214.
5-(3,4-Dichloro-benzyl)-3-(2,4-dichloro-phenyl)-4-imino-3,4-dihydro-1*H*-pyrimidin-2-one (**46**). ν_{max} (KBr) 1656 (CONH), 3308 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ = 3.73 (s, 2H, CH_2), 7.29 (d, 1H, =CH), 7.56–7.60 (m, 5H, ArH), 7.86 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6, 50.32 MHz) δ = 31.5, 129.0, 130.3, 130.5, 130.7, 131.2, 133.0, 134.6, 141.3, 156.9; mass (FAB+) *m/z* 414 (M^+), 416 (M^++2); EI-HRMS, calcd for $C_{17}H_{11}Cl_4N_3O$ 412.9656, found: 412.9658.

6. Bacterial strains: five pathogenic bacteria namely *Streptococcus faecalis*, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* were obtained from our departmental culture collection and maintained on nutrient agar slants at 37 °C.[7] The purity of all the cultures was checked before MIC determination. MIC determination. Minimum inhibitory concentration of compounds was tested by standard micro broth dilution method. Briefly, testing was performed in flat bottom 96 well tissue culture plates (CELLSTAR® Greiner bio-one GmbH, Germany) in Muller Hinton broth (Titan biotech Ltd, India) for bacterial strains. Initial inoculum of bacterial strains was maintained at $1–5 \times 103$ cells/ml. The plates were incubated in a moist chamber at 37 °C and absorbance at 492 nm was recorded on VersaMax microplate reader (Molecular Devices, Sunnyvale, USA) after for 24 h. MIC was determined as 90% inhibition of growth with respect to the growth control by using SOFTmax Pro 4.3 Software (Molecular Devices, Sunnyvale, USA).

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