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Cu(Otf)2 Catalyzed Regioselective N3-Arylation Of Biginelli 4-Aryl-3,4-Dihydropyrimidin-2(1H)-One Using Symmetrical Diaryliodonium Salt

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ABSTRACT

The Biginelli reaction is a simple one pot three-component condensation of an aldehyde, β-ketoester and urea in presence of a catalytic quantity of acid to produce biologically important 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) scaffolds.[1-4] However, the classical Biginelli reaction fails to produce N3-arylated dihydropyrimidones using *N*-arylurea as one of the reacting component. In this case, N1-arylated DHPMs are obtained as the sole product.[12] Therefore; there is a necessity to perform N3-arylation of DHPMs to furnish decorated cyclic urea analogues.

Keywords: Aldehyde, β –Ketoester, Urea.

I. INTRODUCTION

Scheme 1: Synthesis of Biginelli DHPM's by using N-Substitued urea

Literature survey has revealed that the N-arylation of Biginelli DHPMs is more challenging and less explored reaction in comparison to the N-arylation of N-H heterocycles such as imidazole, pyrazole, triazoles, tetrazoles, benzimidazoles, indazoles and DNA/RNA nucleobases.[13]

N-arylation of uracil and its derivatives using diaryliodonium salts is a noteworthy literature report for the regioselective synthesis of N1 or N3-arylated uracil.[32]

Scheme 2: Regioselective synthesis of N1 or N3-arylated uracil

Uracil and Biginelli DHPMs are structural analogues of cyclic urea and therefore, we intrigued with the possibility of N-arylation of DHPMs. In continuation of our work on structural post modification of the Biginelli compounds using Hypervalent iodine reagents,[33] herein we report an efficient $Cu(OTf)_2$ mediated C-N cross-coupling reaction of DHPMs with diaryliodonium salts. The reaction regioselectively performs N3-arylation of DHPMs in good yields (Scheme 12).

Scheme 3: N3-Arylation of Biginelli 4-Aryl-6-methyl-3,4-dihydropyrimidine-2(1H)-one derivatives using diaryliodonium triflates

The N-arylation of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **1a** using various arylating agents was selected as a model reaction (Table 1). The reaction of iodobenzene as arylating agent with **1a** failed to produce N3-arylated DHPM **3a** under copper catalysis (entries 1-3). Various solvents and bases were screened in order to get the optimized condition. The reaction did not proceed in DMF while poor yields were obtained in dioxane and acetonitile (entries 4-6). Toluene was found to be the best solvent for the reaction (entry 7). Various bases such as t-BuOK, NaOH and K_2CO_3 were screened for the N-arylation of DHPM's using **2a** (entries 7-10). The number of side products was observed using t-BuOK and NaOH as bases, while the reaction proceeds smoothly with 1.2 equivalents of K_2CO_3. The chloride and tetrafluoroboarate as counter anion was not much

effective in comparison to the triflate anion (entries 11-12). By increasing the quantity of Ph_2IOTf from 1.2 to 1.5 equivalents, the yield of product **3a** increased up to 77% (entry 13). Thus the optimized condition for the N3-arylation of DHPMs is the use of diaryliodonium triflate (1.5 equiv), K_2CO_3 (1.2 equiv), and $Cu(OTf)_2$ (20 mol%).[34]

Table 1. Optimization condition for N3-arylation of Biginelli 3,4-dihydropyrimidones

Entry	Arylating agent	Base (1.2 equiv)	Catalyst	Solvent	Yield (%)
1	PhI (1 equiv)	K_2CO_3	CuI	DMF	0
2	PhI (1 equiv)	Cs_2CO_3	CuI	DMF	0
3	PhI (1 equiv)	Cs_2CO_3	$Cu(OTf)_2$	Toluene	0
4	Ph_2IOTf (1.2 equiv)	K_2CO_3	$Cu(OTf)_2$	DMF	0
5	Ph_2IOTf (1.2 equiv)	K_2CO_3	$Cu(OTf)_2$	Dioxane	21
6	Ph_2IOTf (1.2 equiv)	K_2CO_3	$Cu(OTf)_2$	Acetonitrile	56
7	Ph_2IOTf (1.2 equiv)	*t*-BuOK	$Cu(OTf)_2$	Toluene	59
8	Ph_2IOTf (1.2 equiv)	NaOH	$Cu(OTf)_2$	Toluene	37
9	Ph_2IOTf (1.2 equiv)	K_2CO_3	$Cu(OTf)_2$	Toluene	68
10	Ph_2IOTf (1.5 equiv)	*t*-BuOK	$Cu(OTf)_2$	Toluene	39
11	Ph_2IBF_4 (1.5 equiv)	K_2CO_3	$Cu(OTf)_2$	Toluene	69
12	Ph_2ICl (1.5 equiv)	K_2CO_3	$Cu(OTf)_2$	Toluene	43
13	Ph_2IOTf (1.5 equiv)	K_2CO_3	$Cu(OTf)_2$	Toluene	77

Under the optimized conditions, N3-arylation of various Biginelli DHPMs derivatives was performed using three different symmetrical diaryliodonium triflates (Table 2). The reaction was found to be regioselective for N3-arylation (entries **3a-j**) and no isomeric N1-arylated product was isolated. This may be attributed to the lower nucleophilicity or reactivity of N1 over N3 amide nitrogen due to enamine moiety. The electron withdrawing and donating substituents on C4-aryl groups were tolerated during the reaction. The reaction of N1-aryl DHPMs also furnished N3-arylated product in good yields (entries **3i-j**). All the products were characterized by IR, NMR (^1H and ^{13}C), and LCMS analysis.

Table 2: N3-Arylation of Biginelli DHPMs using symmetrical diaryliodonium triflates[a]

[a]**Reaction conditions:** 4-Aryl-6-methyl-3,4-dihydropyrimidine-2(1H)-one derivatives (1 mmol), diaryliodonium triflate (1.5 mmol), $Cu(OTf)_2$ (20 mol%) and K_2CO_3 (1.2 mmol) in 10 mL toluene under reflux for 8–12 h.

A plausible mechanism for the N3-arylation of Biginelli 4-aryl-6-methyl-3,4-dihydropyrimidine-2(1H)-one (DHPM's) is depicted in Scheme 15. In the first step the DHPMs undergo deprotonation on reaction with K_2CO_3 to give the intermediate **A** which can attack the electrophilic iodine of diaryliodonium salt to form the intermediate **B**. The tendency of **B** for reductive elimination of iodobenzene results in the N3-arylation of DHPMs. The success of this reaction is due to the electrophilic nature of diaryliodonium salts along with super leaving group ability of phenyliodino group.

Scheme 4: A plausible mechanism for N3-Arylation of Biginelli DHPMs using symmetrical diaryliodonium triflates

II. CONCLUSION

we have demonstrated a direct method for regioselective N3-arylation of Biginelli DHPMs using symmetrical diaryliodonium salts under thermal conditions leading to formation of the highly decorated cyclic urea analogues. The merits of the methodology are (i) Provides a easy access to N3-arylated DHPMs which is, generally, not feasible via Biginelli three-component reaction involving N-arylurea as one of the substrate (ii) Very efficient methodology for the N3-arylation of N1-unsubstitued DHPM's (iii) A wide range of N3-arylated DHPMs derivatives were obtained in good to moderate yields and (iv) The reaction is operationally simple, highly effective and displayed a broad functional group tolerance.

III. REFERENCES

[1]. Kappe, C. O. Eur. J. Med. Chem. 2000, 35, 1043.
[2]. Kappe, C. O. Acc. Chem. Res. 2000, 33, 879.
[3]. Kappe, C. O. Tetrahedron 1993, 49, 6937.
[4]. Zanatta, N.; Fantinel, L.; Fernandes, L. S.; Wouters, A. D.; Bonacorso, H. G.; Martins, M. A. P. Synthesis 2008, 21, 3492.
[5]. Zigeuner, G.; Hamberger, H.; Blaschke, H., Sterk, H. Monatsh. Chem. 1966, 97, 1406.
[6]. Namazi, H.; Mirzaei, Y. R.; Azamat, H. J. Heterocyclic Chem. 2001, 38, 1051. (b) Zigeuner, G., Knopp, C. Monatsh. Chem. 1970, 101, 1541.
[7]. George, T.; Tahrlramani, R.; Metha, D. V. Synthesis 1975, 405.
[8]. Kappe, C. O. Liebigs Ann. Chem. 1990, 505.