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Ps-Al(OTf)$_3$ Promoted efficient and novel synthesis of substituted *N*-aryl lactams

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Dedicated my Doctoral Mentor Dr. Suprabhat Ray, on the occasion of his 75th Birthday
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Abstract: Polystyrene-supported aluminium triflate (Ps-Al(OTf)$_3$ promoted, efficient and novel, one-pot method for the synthesis of substituted *N*-aryl lactams through the reaction of various kinds of corresponding substituted arenes with a variety of *ω*-azido alkanoic acids at room temperature, by *in-situ* involvement of Friedel-Crafts reaction followed by intramolecular Schmidt rearrangement was developed, afforded good to excellent yields.

Keywords: Substituted arenes; *ω*-Azido alkanoic acids; Substituted *N*-aryl lactams; Ps-Al(OTf)$_3$.

1. Introduction

Substituted *N*-aryl lactam moiety has been encountered in the varieties of structurally diverse biologically potent natural products and drug candidates [1] and have also been attracted much attention due to their diverse arrays of potential biological activities such as anti-cancer [2], anti-microbial [3], anti-diabetic [4], anti-CNS [5], anti-convulsants [6] and agrochemicals[7] *etc.* Moreover, this structural moiety has also been explored as an useful synthon for the syntheses of structurally diverse complex heterocycles such as benzo-[*a*]-quinazolidine-2-ones [8], hexahydropyrido-[3,4-*c*] [1,5]-benzothiazepines [9], 5-(diethoxyphosphoryl)-1-aryl-2-alkyl/aryl-2,3-dihydro-4-pyridones [10], 3-aminopiperidines [11], methyl indolo-[2,3-*a*]-quinazolidin-2-acetate [12] and synthesis of various alkaloids such as guettardine, 15-epiguettardine [13], *E*-azaburnamine [14], makaluvamine A & C [15], veiutamine [16] and synthesis of fundamental tetracyclic skeleton of ervitsine and 20-*de*-ethylidine-6,16-dihydro-analoques [17]. In view of their importance and wide applications, their syntheses have gained considerable attention, therefore, become a focus of synthetic organic chemistry.

Traditional synthesis of substituted *N*-aryl lactams involved through the direct coupling reaction of substituted aryl halides with cyclic amides catalyzed by a transition metal catalyst [18]. So far significant improvements have been achieved in Pd-catalyzed amide arylation reactions [19] but the method remains hard to apply these reactions to large and industrial scale syntheses due to high cost of Pd and the difficulty in removing Pd residues from the polar reaction products. An alternative method for aryl amidation involves through the Cu catalyzed Goldberg reaction between cyclic amides and aryl iodides [20]. This method is attractive from economic standpoint because Cu is much cheaper than Pd. Despite this advantage, the Goldberg reaction is not a popular reaction in organic chemistry due to the necessity to use temperatures as high as 210°C, highly polar aprotic solvents, strong bases such as alkoxides and NaH, large amounts of the nucleophile and often large amounts of Cu catalysts. In recent years, much effort has been directed in order to search for better catalytic systems for this reaction. Several kinds of efficient ligands have been used to promote this reaction such as diamines [21], diimines [22], aminoacids [23], *β*-ketoesters [24], and diols [25]. Some of the other multi-step synthetic routes for the synthesis of substituted *N*-aryl lactams have also been reported [26]. Majority of the above mentioned routes are associated with several drawbacks such as low reactivity, requirement of large amount of catalysts and ligands, costly, toxic and moisture sensitive nature of catalysts, harsh reaction conditions, tedious work-up, longer reaction times, generation of toxic byproducts and few of them also involved two or more steps. Therefore, there is continued interest in developing new, efficient, and safer protocols employing mild reaction conditions.

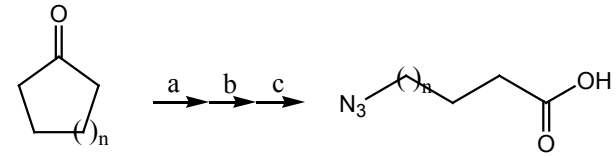
We report herein an efficient and mild protocol for the synthesis of substituted *N*-aryl lactams starting from their corresponding substituted arenes using a variety of *ω*-azido alkanoic acids mediated by polystyrene-supported aluminium triflate Ps-Al(OTf)$_3$ at room temperature. To the best of our knowledge, this is the first report for the efficient and mild synthesis of substituted *N*-aryl lactams from the corresponding substituted arenes using Ps-Al(OTf)$_3$ at room temperature involving interesting chemistry thus exploring a novel synthetic route. Ps-Al(OTf)$_3$ was prepared by the exchange reaction between cross-linked polystyrene supported $AlCl_3$ (Ps–$AlCl_3$) and triflic acid in Freon-113 under reflux conditions following the reported standard procedure [27].

2. Results and Discussion

The *ω*-azido alkanoic acids **4**, **5**, **6** are key intermediates for this single-step coupling methodology and have been synthesized from their corresponding cyclic ketones **1**, **2**, **3** respectively, following the standard reported (**Scheme 1**) procedure [28]**.** Initially, a reaction of 1,2-dimethoxybenzene **7** with a 4-azidobutanoic acid **5** (n = 1) using Ps-Al(OTf)$_3$ in dry DMSO was tried at room temperature (entry 1) and the corresponding 1,2-dimethoxy *N*-aryl lactam product formation was indeed realized. The product formation was further confirmed through the appearance of an amidic peak at ~1665 cm^{-1} in IR. The identification of the desired products were further confirmed through the various spectroscopic and analytical techniques and were also correlated by our previously reported authentic samples [29]. This reaction was also tried in various dry organic solvents such as chloroform, acetonitrile, methanol, acetone, DMSO, DMF, CH_2Cl_2 *etc.* and thus found that dry DMSO was found to best among all in carrying out this transformation at room temperature. Then, we optimized the versatility of this method through the reaction of a variety of 3,4,5-substituted arenes **7** containing electron donating/electron withdrawing groups with different kinds of

ω-azido alkanoic acids **4**, **5**, **6** (**Scheme 2**) using Ps-Al(OTf)$_3$ at room temperature. Thus, a variety of *N*-aryl lactams were synthesised and characterized through the IR, NMR, and mass spectral data. It was further realized that the yields of the *N*-aryl lactam was depend upon the type of substitution on the aromatic ring of the corresponding arene used. Furthermore, by introducing an electron donating group at aromatic nucleus of arene led to increasing yield of the corresponding substituted *N*-aryl lactam and by introducing electron withdrawing groups led to decrease in yield as mentioned in Table 1.

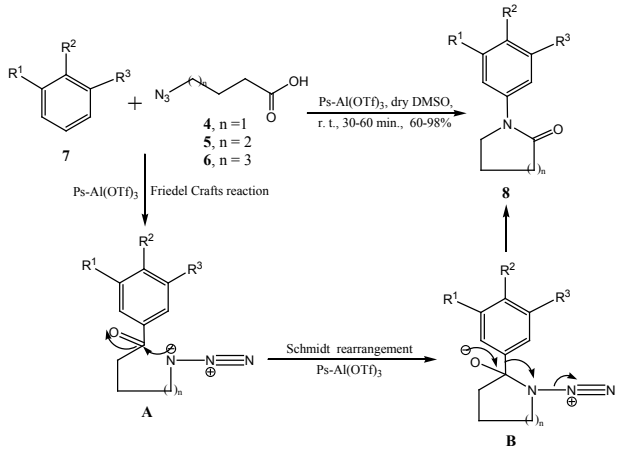
We proposed that triflate of ω-azido alkanoic acids will form intermediate **A** through the Friedel-Crafts acylation reaction, which on subsequent 1,2-shift (*i.e.* C-N) of aryl migration of intermediate **B** through the Schmidt rearrangement led to the formation of the desired substituted *N*-aryl lactam **8** (Scheme 3).



1, n = 1, Cyclopentanone
2, n = 2, Cyclohexanone
3, n = 3, Cycloheptanone

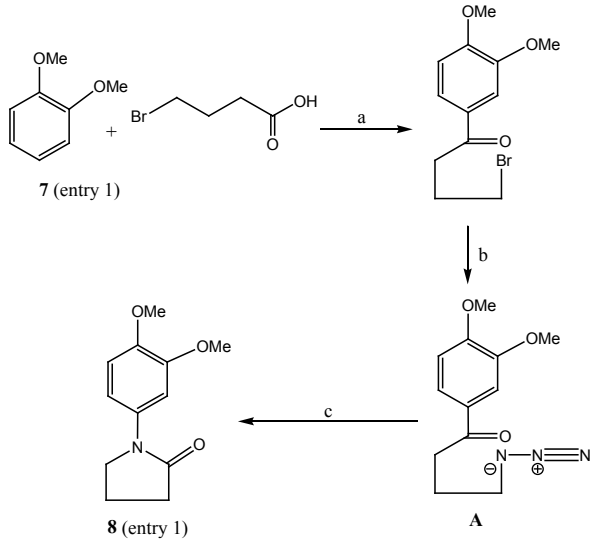
4, n =1
5, n = 2
6, n = 3

Scheme 1: Reagents and conditions: (a) HCO_2H/H_2O_2, water, 97%; (b) 48% HBr/H_2SO_4, 94%; (c) NaN_3, DMF, 98%.



Scheme 2: (a) Reagents and conditions: Ps-Al(OTf)$_3$, dry DMSO, r. t., 30-60 min., 60-98%; (b) Proposed mechanism of formation of substituted *N*-aryl lactams of general formula **8**.

To further validate this methodology, a reaction of 1,2-dimethoxybenzene was tried with previously synthesized 4-bromobutanoic acid employing Ps-Al(OTf)$_3$ afforded the corresponding acylated bromoproduct through the Friedel-Crafts reaction, which on treatment with NaN_3 afforded the corresponding 4-azidoacylated compound **A**. Treatment of compound **A** with Ps-Al(OTf)$_3$ afforded the corresponding *N*-aryl lactam through the Schmidt rearrangement (**Scheme 3**). The spectral data of the synthesized compound was correlated with the *N*-aryl lactam compound (entry 1) synthesized through the direct coupling method.



Scheme 3: (a): Ps-Al(OTf)$_3$, dry DMSO, 30 min., r. t., 95%; (b) NaN_3, 2h, DMF, 98%; (c) Ps-Al(OTf)$_3$, dry DMSO, 20 min., r. t., 92%.

3. Conclusion

In conclusion, we have developed an efficient and novel method for the synthesis of substituted *N*-aryl lactams through the

reaction of corresponding arenes with ω-azido alkanoic acids employing Ps-Al(OTf)$_3$ at room temperature. This is a new and one-pot method using catalytic amount of Ps-Al(OTf)$_3$ which afforded high yields (60-98%) of the desired substituted *N*-aryl lactams in shortest reaction time (30-60 min.) involving novel chemistry and dominates over the reported procedures in respect of milder reaction conditions, high yields, and shorter reaction time.

4. Experimental

Chemicals were procured from Merck, Aldrich, and Fluka chemical companies. Reactions were carried out under an atmosphere of nitrogen. IR spectra were recorded on Bomem MB-104–FTIR spectrophotometer, whereas NMRs were obtained on an AC-300F instrument [^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz)] using $CDCl_3$ and TMS as internal standard. Mass

Table 1: Synthesis of substituted *N*-aryl lactams of general formula **8**[a] of Scheme 2.

Entry	R^1	R^2	R^3	n	Time (min.)	Isolated Yield (%)	Reference
1	OMe	OMe	H	1	35	92	[29]
2	OMe	H	OMe	1	35	90	[29]
3	OMe	OMe	OMe	1	30	98	[29]
4	OMe	H	OMe	2	35	88	[29]
5	OMe	OMe	OMe	2	30	96	[29]
6	OMe	OMe	H	2	35	85	[29]
7	OMe	OMe	H	3	40	80	[29]
8	OMe	H	OMe	3	40	82	[29]
9	OMe	OMe	OMe	3	35	89	[29]
10	Me	Me	H	1	40	90	[29]
11	Me	H	Me	1	40	88	[29]
12	Me	Me	Me	1	35	93	[29]
13	Me	Me	H	2	40	87	[29]
14	Me	H	Me	2	40	85	[29]
15	Me	Me	Me	2	35	94	[29]
16	Me	Me	H	3	45	79	[29]
17	Me	H	Me	3	45	83	[29]
18	Me	Me	Me	3	40	85	[29]
19	NO_2	H	NO_2	1	50	72	[29]
20	NO_2	NO_2	H	1	50	75	[29]
21	NO_2	NO_2	NO_2	1	55	70	[29]
22	NO_2	H	NO_2	2	50	69	[29]
23	NO_2	NO_2	H	2	50	71	[29]
24	NO_2	NO_2	NO_2	2	55	65	[29]
25	NO_2	H	NO_2	3	55	67	[29]
26	NO_2	NO_2	H	3	55	65	[29]
27	NO_2	NO_2	NO_2	3	60	60	[29]

[a]All the products were characterized by IR, NMR and mass spectral data.

spectra were recorded using a Bruker Esquire 3000 spectrophotometer. Elemental analysis were conducted by means of a Carlo-Erba EA 1110-CNNO-S analyzer and agreed favourably with the calculated values.

General Procedure

An equimolar amount of substituted arene and the corresponding ω-azido alkanoic acid were taken in dry DMSO (25 ml) and stirred for 10 min. at room temperature. To this, 1/10th molar amount (with respect to arene) of Ps-Al(OTf)$_3$ was added slowly in 2-3 small portions. The reaction was continued until completion (*cf* Table 1) as confirmed by TLC. The reaction mixture was filtered and filtrate was poured into distilled water (50 ml) and extracted with ethyl acetate thrice (3x30). The organic layer was separated and dried over anhydrous sodium sulphate and then concentrated to afford the corresponding substituted *N*-aryl lactam compound.

1-(3,4-Dimethoxyphenyl)piperidin-2-one (Entry 1)[29]

Colorless oil.

IR (Neat): 1055, 1155, 1206, 1250, 1270, 1325, 1350, 1390, 1475, 1593, 1670, 2840, 2930 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$) δ = 1.92-1.95 (m, 4H), 2.55 (t, J = 6.2 Hz, 2H), 3.61 (t, J = 5.5 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 6.77-6.78 (m, 2H), 6.86-6.88 (m, 1H)ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 23.4, 32.7, 52.0, 55.7, 55.8, 110.0, 111.2, 118.0, 136.4, 147.6, 149.0, 170.0ppm; MS (EI, 70 eV) *m*/*z* (%): 235 (M^+, 100), 220, 166; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{13}H_{17}O_3N$ (M^+) 235.1208, found 235.1205.

1-(3,5-Dimethoxyphenyl)pyrrolidin-2-one (Entry 2)[29]

White solid, m.p.: 85-86^{o}C.

IR (CH_2Cl_2): 1069, 1154, 1208, 1249, 1275, 1324, 1347, 1393, 1478, 1598, 1697, 2841, 2958 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.14 (tt, J = 8.4 Hz, J = 6.6 Hz, 2H, CH_2), 2.61 (t, J = 8.4 Hz, 2H, CH_2), 3.80 (s, 6H, OCH_3), 3.83 (t, J = 6.6 Hz, 2H, CH_2), 6.27 (t, J = 2.4 Hz, 1H, Ar), 6.86 (d, J = 2.4 Hz, 2H, Ar)ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 17.8, 32.9, 48.9, 55.3, 96.4, 98.3, 141.1, 160.7, 174.3ppm; MS (EI, 70 eV) *m/z* (%): 221 (M+, 100), 192 (23), 178 (9), 166 (75), 162(7), 151 (5), 136 (12), 122(6), 108(5); Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14, H, 6.83, N, 6.33%; Found: C, 64.99, H, 6.85, N, 6.25%.

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