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COMMUNICATION

An efficient and novel approach for the synthesis of substituted *N*-aryl lactams

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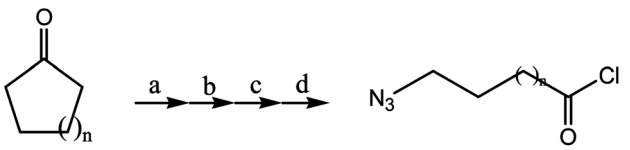
A quick, efficient, one-pot method for the synthesis of substituted *N*-aryl lactams through the reaction of various kinds of corresponding substituted arenes with a variety of ω-azido alkanoic acid chlorides using a Lewis acid (*i.e.* $EtAlCl_2$) at room temperature, through the *in situ* involvement of a Friedel–Crafts reaction followed by intramolecular Schimdt rearrangement was developed, and afforded good to excellent yields.

Substituted *N*-aryl lactam moieties have been encountered in a plethora of structurally diverse natural products and drug candidates[1] and have also attracted much attention due to their diverse arrays of potential biological activities such as anti-cancer,[2] antimicrobial,[3] anti-diabetic,[4] anti-CNS,[5] anti-convulsant[6] and have been used as agrochemicals[7] *etc.* Moreover, this structural moiety has also been explored as a 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] for the synthesis of various alkaloids such as guettardine, 15-epiguettardine,[13] *E*-azaburnamine,[14] makaluvamine A&C,[15] veiutamine;[16] and for the synthesis of the fundamental tetracyclic skeleton of ervitsine and 20-*de*-ethylidine-6,16-dihydro analogues.[17] In view of their importance and wide applications, their syntheses have gained considerable attention, and therefore have become a focus of synthetic organic chemistry.

Traditional synthesis of substituted *N*-aryl lactams involved the direct coupling reaction of substituted aryl halides with cyclic amides catalyzed by a transition metal catalyst such as Pd and Cu.[18–20] In recent years, several kinds of efficient ligands have been used to promote this reaction such as diamines,[21] diimines,[22] amino acids,[23] β-ketoesters,[24] and diols.[25] Some other multi-step synthetic routes for the synthesis of substituted *N*-aryl lactams have also been reported.[26] The majority of the above mentioned routes are associated with several drawbacks such as low reactivity, requirement of large amounts 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 a 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. In the present communication, we report herein a novel and efficient synthetic route for the synthesis of substituted *N*-aryl lactams starting from their corresponding substituted arenes and a variety of ω-azido alkanoic acid chlorides catalyzed by a Lewis acid, ethylaluminium dichloride (*i.e.* $EtAlCl_2$), at room temperature. To the best of our knowledge, this is the first report of the efficient and mild synthesis of substituted *N*-aryl lactams starting from their corresponding substituted arenes and ω-azido alkanoic acid chlorides employing a catalytic amount of $EtAlCl_2$ at room temperature. Furthermore, this is a one-pot method involving the sequential Friedel–Crafts reaction followed by Schmidt rearrangement catalyzed by $EtAlCl_2$ and thus we explore a novel synthetic route for the synthesis of substituted *N*-aryl lactams, wherein the chemistry is totally different from the previously reported various kinds of metal mediated coupling reactions.

The ω-azido alkanoic acid chlorides **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 procedure[27] (Scheme 1). Initially, a reaction of 1,2-dimethoxybenzene **7** with 4-azidobutanoic acid chloride **4** (n = 1) using a catalytic amount of $EtAlCl_2$ in dry CH_2Cl_2 was tried at room temperature (entry 1) and the corresponding 1,2-dimethoxy *N*-aryl lactam product



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) $HCOOH–H_2O_2$, water, 97%; (b) 48% $HBr–H_2SO_4$, 94%; (c) NaN_3, DMF, 98%; (d) oxalyl chloride, benzene, 98%.

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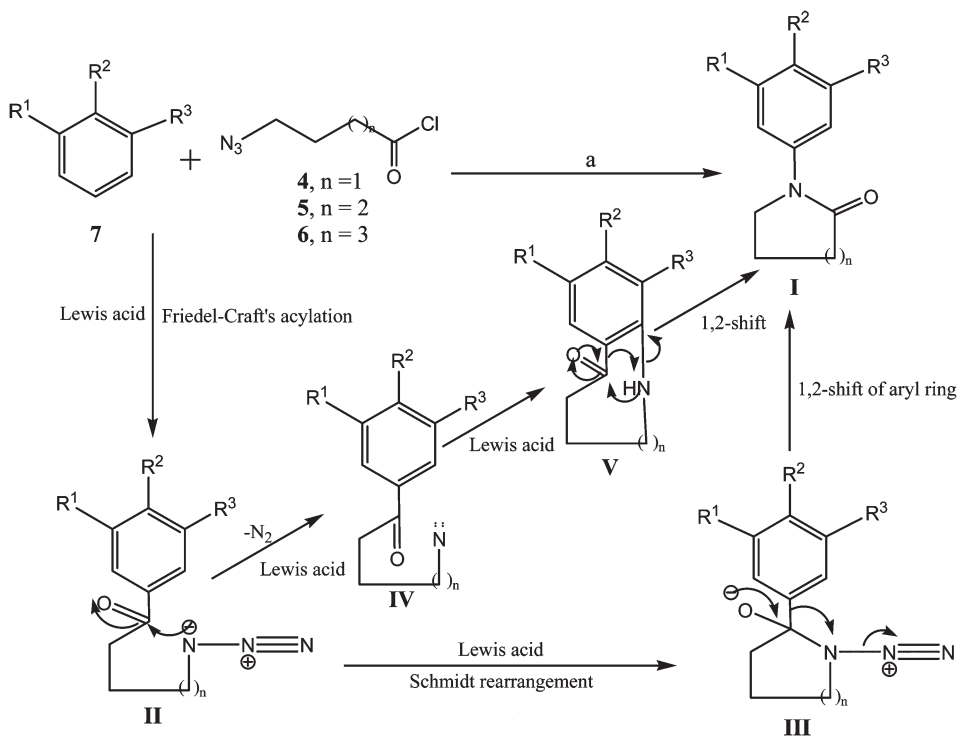
formation was indeed realized. The formation of the product was confirmed through the appearance of an amidic peak at ~1662 cm^{-1} in the IR spectra and was further confirmed through various spectroscopic and analytical techniques (see the Experimental section). This reaction was tried in various dry organic solvents such as chloroform, acetonitrile, methanol, acetone, DMSO, DMF, CH_2Cl_2 *etc.*, and thus dry CH_2Cl_2 was found to be the best among all in carrying out this transformation at room temperature. This reaction was also carried out in a variety of Lewis acids (*i.e.* BF_3OEt_2, $AlCl_3$, BF_3, CF_3SO_3H, Me_3B, $EtAlCl_2$) and $EtAlCl_2$ was found to be the best among all in achieving high yields of the desired products. Then, we optimized the versatility of this method through the reaction of a variety of 3,4,5-substituted arenes **7** containing electron releasing/electron withdrawing groups with different kinds of ω-azido alkanoic acid chlorides **4**, **5**, **6** (Scheme 2) employing a catalytic amount of $EtAlCl_2$ 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 yield of the *N*-aryl lactam was dependent upon the type of substitution on the aromatic ring of the corresponding arene used. It was further realized that introducing an electron releasing group at the aromatic nucleus of the arene led to an increasing yield of the substituted *N*-aryl lactam and introducing electron withdrawing groups led to a decrease in the yield as mentioned in Table 1.

We propose that the Lewis acid will facilitate the reaction of ω-azido alkanoic acid chlorides **4**, **5**, **6** with the corresponding substituted arene **7** which will form the acylated intermediate **II** through Friedel–Crafts acylation reaction. Nucleophilic attack of

Table 1 Conversion of various substituted arenes into substituted *N*-aryl lactams of general formula **I**[a]

Entry no.	R^1	R^2	R^3	*n*	Time (min)	Isolated yield (%)
1	OMe	OMe	H	1	25	93
2	OMe	H	OMe	1	25	91
3	OMe	OMe	OMe	1	20	98
4	OMe	H	OMe	2	25	89
5	OMe	OMe	OMe	2	20	97
6	OMe	OMe	H	2	25	85
7	OMe	OMe	H	3	30	83
8	OMe	H	OMe	3	30	82
9	OMe	OMe	OMe	3	25	89
10	Me	Me	H	1	30	92
11	Me	H	Me	1	30	90
12	Me	Me	Me	1	25	94
13	Me	Me	H	2	30	89
14	Me	H	Me	2	30	88
15	Me	Me	Me	2	25	95
16	Me	Me	H	3	35	80
17	Me	H	Me	3	35	85
18	Me	Me	Me	3	30	87
19	COOMe	H	COOMe	1	40	74
20	COOMe	COOMe	H	1	40	77
21	COOMe	COOMe	COOMe	1	50	71
22	COOMe	H	COOMe	2	40	70
23	COOMe	COOMe	H	2	40	72
24	COOMe	COOMe	COOMe	2	50	68
25	COOMe	H	COOMe	3	50	68
26	COOMe	COOMe	H	3	50	67
27	COOMe	COOMe	COOMe	3	50	65

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

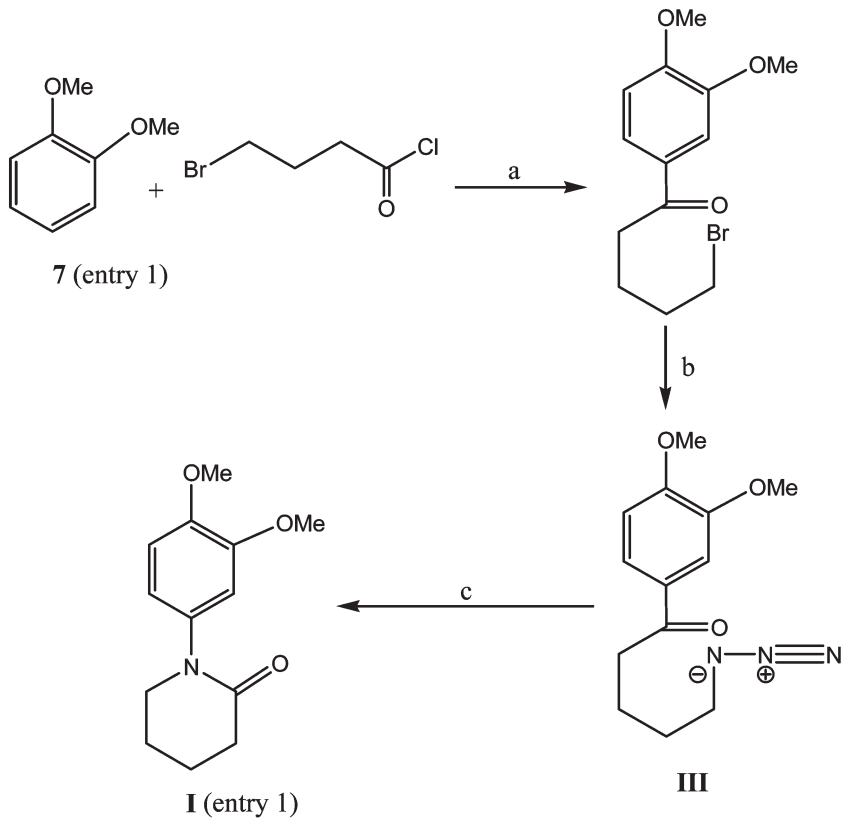


Scheme 2 Reagents and conditions: (a) $EtAlCl_2$, dry CH_2Cl_2, 20–50 min, 65–98%; and proposed mechanism of formation of substituted *N*-aryl lactams of general formula **I**.

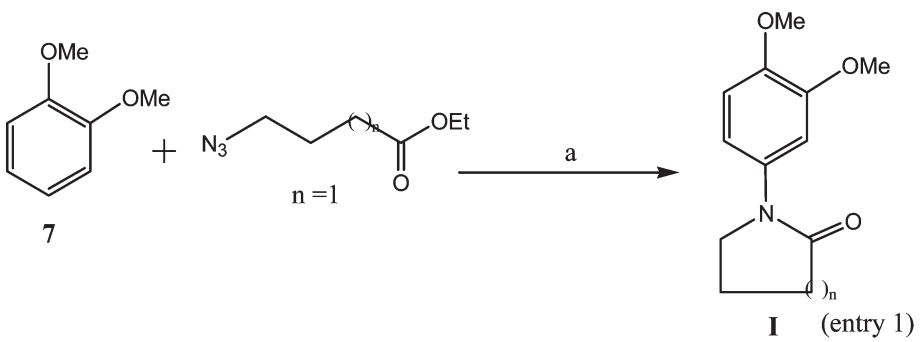
one of the nitrogen atoms of azide on the carbonyl functionality of acylated intermediate **II** generated intermediate **III** which on subsequent 1,2-shift (*i.e.* C–N) of aryl migration through Schmidt rearrangement using the same Lewis acid led to the formation of the desired substituted *N*-aryl lactam of general formula **I** (Scheme 2). Furthermore, the acylated compound **II** may also form nitrene intermediate **IV** which on subsequent C–H insertion may form intermediate **V**, electronic rearrangement of **V** may lead to the formation of the corresponding *N*-aryl lactam of general formula **I**.

To further validate this methodology, a reaction of 1,2-dimethoxybenzene was tried with previously synthesized 4-bromobutanoic acid chloride employing $EtAlCl_2$ and this afforded the corresponding acylated bromo product through Friedel–Crafts reaction, which on treatment with NaN_3 afforded 4-azidoacylated compound **III**. Treatment of compound **III** with $EtAlCl_2$ afforded the corresponding *N*-aryl lactam through the Schmidt rearrangement (Scheme 3). The spectral data of the synthesized compound were correlated with the *N*-aryl lactam compound (entry 1) synthesized through the direct coupling method.

Another control for the formation of substituted *N*-aryl lactam was further confirmed through the reaction of 1,2-dimethoxy benzene with a previously synthesized ω-azido alkanoic ester employing a catalytic amount of $EtAlCl_2$ in dry CH_2Cl_2 (Scheme 4). The formation of the corresponding *N*-aryl lactam (entry 1) was confirmed through spectroscopic and analytic techniques and was further confirmed through the data of the previously synthesized authentic sample.



Scheme 3 (a) $EtAlCl_2$ dry CH_2Cl_2, 50 min, 95%; (b) NaN_3, 2 h, DMF, 98%; (c) $EtAlCl_2$, dry CH_2Cl_2, 25 min, 93%.



Scheme 4 Reagents and conditions: (a) $EtAlCl_2$, CH_2Cl_2, rt, 25 min, 91%.

In conclusion, we have developed an efficient and novel one-pot method for the synthesis of substituted *N*-aryl lactams through the reaction of corresponding arenes with a variety of ω-azido alkanoic acid chlorides employing a catalytic amount of $EtAlCl_2$ at room temperature. This is a new and efficient method that afforded high yields (65–98%) of the desired substituted *N*-aryl lactams in the shortest reaction time (20–50 min), through the sequential Friedel–Crafts reaction followed by intramolecular Schimdt rearrangement, and thus provides a novel synthetic route for the synthesis of a variety of substituted *N*-aryl lactams wherein the chemistry is totally different from the previously reported metal mediated coupling reactions.

Experimental

Typical experimental procedure for the synthesis of substituted *N*-aryl lactams

An equimolar amount of substituted arene and the corresponding ω-azido alkanoic acid chloride were taken in dry CH_2Cl_2 (25 ml), and stirred for 10 min at room temperature. To this, a 1/10th molar amount (with respect to arene) of Lewis acid (*i.e.* $EtAlCl_2$) was added slowly in 2–3 small portions at room temperature. The reaction was continued until completion (*cf.* Table 1) as confirmed by TLC. The reaction mixture was then poured into distilled water (50 ml) and extracted with dichloromethane. The organic layer was separated and dried over anhydrous sodium sulphate and then concentrated to afford the desired substituted *N*-aryl lactam compound.

Data of selected compounds

1-(3,4-Dimethoxyphenyl)piperidin-2-one (Table 1, entry 1, $C_{13}H_{17}O_3N$). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{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, 170.0; MS (EI) *m*/*z* 235 (M+, 100), 220, 166; HRMS (EI) *m*/*z* calcd for $C_{13}H_{17}O_3N$ (M+) 235.1208, found 235.1208.

1-(3,5-Dimethoxyphenyl)pyrrolidin-2-one (Table 1, entry 2, $C_{12}H_{15}NO_3$). White solid, m. p. = 85–86 °C; IR (CH_2Cl_2): ν = 1069, 1154, 1208, 1249, 1275, 1324, 1347, 1393, 1478, 1598, 1697, 2841, 2958 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): 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); ^{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, 174.3; MS (EI) *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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