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REGULAR ARTICLE

A sequential one-pot tandem approach for the synthesis of 4-tosyl-5-aryloxazoles from carboxylic acids

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Abstract. An efficient method for the synthesis of 4-tosyl-5-aryloxazoles directly from aromatic carboxylic acids has been reported. The method involves the conversion of aromatic carboxylic acids to tosyl carboxylates by treating with tosyl chloride in the presence of potassium carbonate and its subsequent reaction with tosylmethyl isocyanide in the presence of sodium hydride to get 4-tosyl-5-aryloxazoles.

Keywords. Oxazole; tosylmethylisocyanide; tandem; cyclization; one-pot.

1. Introduction

Oxazole is a commonly encountered moiety in antimicrobial,[1] antifungal,[2] anticancer[3] and anti-tuberculosis agents.[4] Also they are present in lipid peroxidation inhibitors,[5] neurotrophic factor inducers,[6] LSD 1 inhibitors,[7] T-type calcium and sodium channel blockers,[8] phosphodiesterase[9] and GSK-3 inhibitors.[10] As a result, there is a continuing interest in the development of new methods for the synthesis of oxazoles.

Vast numbers of synthetic methods for oxazoles are reported in the literature. Thus, we focussed our interest on the synthesis of oxazoles from isocyanides. The most widely used and popular method is van Leusen strategy which makes use of aldehydes and tosylmethyl isocyanide (TosMIC).[11] The modification of this strategy makes use of solid phase equivalent TosMIC,[12] quaternary ammonium hydroxide ion exchange resin as a catalyst,[13] ultrasound as promoters[14] and ionic liquid [bmim]Br[15] as reaction media. Katritzky and co-workers have replaced TosMIC by benzotriazolyl methyl isocyanide in original van Leusen method.[16] Alternative approaches are reaction of active methylene isocyanides with phenyl carboxylates,[17] multicomponent reaction of amines, aldehydes, ketones and α-acidic isocyanides,[18] Schöllkopf condensation of lithiated methyl isocyanides with carboxylic acid chlorides,[19] oxidative decarboxylation-cyclization of α-oxo carboxylates and isocyanides,[20] cycloaddition of isocyanides with methyl ketones,[21] cycloaddition of active methylene isocyanides with acid chlorides in flow reactor.[22] Cuprous iodide catalysed cyclization of isocyanide enones,[23] Ugi/Robinson–Gabriel synthesis[24] and conversion of carboxylic acid to acid chlorides followed by reaction with ethyl isocyanoacetate.[25]

The above-reported methods suffer from limitations such as the use of costly transition metal catalysts,[20] unstable substrates[22,25] and elevated temperatures.[20,21] Recently, we reported the synthesis of oxazoles directly from arylmethyl alcohols and benzyl bromides, which is a remarkable change in van Leusen approach.[26] Based on literature survey, van Leusen's strategy has majorly employed unstable/highly reactive precursors (acid anhydrides/acid chlorides) for the synthesis of oxazoles.[27] The handling and storage of these reactive starting materials is one of the major shortcomings,

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whereas synthesis directly from simple carboxylic acids is not yet reported. Thus, we report herein a sequential one-pot tandem synthesis of 4-tosyl-5-aryloxazoles from carboxylic acids via tosyl carboxylate intermediates (13 examples).

2. Experimental

2.1 *Materials and methods*

The starting materials were purchased from commercial sources. The solvents were of analytical grade and were used without further purification. Reactions were monitored by thin-layer chromatography (TLC) using pre-coated sheets of silica gel 60 (Merck 60F254, 0.25 mm thickness) and visualization under UV light. Melting points were determined on SELACO melting point apparatus and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained using an Agilent NMR spectrometer. Chemical shifts (δ) are given in parts per million (ppm) using the residue solvent ($CDCl_3$ and DMSO-d6) peaks as a reference relative to TMS. Coupling constant (J) values are given in Hz. The mass spectral analysis was performed using Waters-Synapt G2 mass spectrometer. Infrared spectra were recorded on Shimadzu FT-IR model 8300 spectrophotometer.

2.2 *General procedure for the synthesis of 4-tosyl-5aryl-oxazoles* **3a–3m**

To a solution of aromatic carboxylic acid **1** (2 mmol) in THF (5 mL), potassium carbonate (2 mmol) was added and stirred for 5–10 min. Later, tosyl chloride (2 mmol) was added and continued stirring. The disappearance of carboxylic acid was monitored by TLC. The reaction mass was cooled to 0 °C and tosylmethylisocyanide (2 mmol) was added followed by the addition of suspension of sodium hydride (2 mmol) in THF (2 mL). The reaction mixture was stirred for 1 h. After the completion of reaction monitored by TLC, water (25 mL) was added to the reaction mixture and extracted with ethyl acetate (25 mL × 2). The combined organic layer was washed in water (25 mL), brine (25 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to get crude products which were purified by column chromatography using 10% ethyl acetate in hexane.

2.2a *Characterization data of 5-phenyl-4-tosyloxazole (**3a**)*: White solid, Yield 91%, 0.54 g, M.p.: 142–144 °C; IR (KBr, cm^{-1}): $\bar{\upsilon}$ 683, 1022, 1043, 1267, 1567, 2920; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H, Me), 7.30 (d, J = 8.4 Hz, 2H, Ar-H), 7.46–7.50 (m, 3H, Ar-H), 7.83 (s, 1H, Ar-H), 7.88 (d, J = 8.4 Hz, 2H, Ar-H), 7.95–7.97 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.6, 125.5, 128.5, 128.8, 129.0, 129.4, 129.8, 130.9, 137.2, 144.9, 149.0, 152.7; HRMS (ESI): Anal. Calcd for $C_{16}H_{13}NO_3S$: 299.0616; Found: 300.0699 $[M+1]^+$ Author /Editor difference in calcd. and found (1 unit, here and for others) is due to comparison between M and M $^{+\cdot}$ Data given in SI are comparable.

2.2b *Characterization data of 5-(4-fluorophenyl) -4-tosyloxazole (**3b**)*: White solid, Yield 93%, 0.59 g, M.p.: 96–98 °C; IR (KBr, cm^{-1}): $\bar{\upsilon}$ 685, 1025, 1048, 1255, 1575, 2931; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H, Me), 7.17–7.24 (m, 2H, Ar-H), 7.31 (d, J= 7.6 Hz, 2H, Ar-H), 7.82 (s, 1H, Ar-H), 7.87 (d, J= 8.4 Hz, 2H, Ar-H), 7.97–8.00 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.6, 115.8, 116.0, 121.7, 128.2, 129.8, 129.9, 131.2, 131.3, 136.9, 145.1, 151.7, 165.4; HRMS (ESI): Anal. Calcd for $C_{16}H_{12}FNO_3S$: 317.0522; Found: 318.0608 $[M+1]^+$.

2.2c *Characterization data of 5-(4-chlorophenyl) -4-tosyloxazole (**3c**)*: White solid, Yield 88%, 0.58 g, M.p.: 110–112 °C; IR (KBr, cm^{-1}): $\bar{\upsilon}$ 692, 1018, 1038, 1255, 1581, 2914; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H, Me), 7.31 (d, J= 7.6 Hz, 2H, Ar-H) 7.46–7.50 (m, 2H, Ar-H) 7.84–7.94 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.90, 119.2, 123.5, 124.2, 125.5, 126.2, 132.5, 137.0, 140.4, 144.5, 146.7, 147.3; Anal. Calcd for $C_{16}H_{12}ClNO_3S$: 333.0226; Found: 334.0309 $[M+1]^+$.

2.2d *Characterization data of 5-(4-bromophenyl) -4-tosyloxazole (**3d**)*: White solid, Yield 86%, 0.65 g, M.p.: 116–118 °C; IR (KBr, cm^{-1}): $\bar{\upsilon}$ 675, 1025, 1050, 1265, 1569, 2931; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H, Me), 7.31 (d, J= 7.6 Hz, 2H, Ar-H) 7.62 (d, J= 10.8 Hz, 2H, Ar-H), 7.84–7.87 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.7, 125.0, 126.3, 128.9, 130.5, 131.1, 132.2, 132.6, 137.5, 145.9, 150.1, 152.3; HRMS (ESI): Anal. Calcd for $C_{16}H_{12}BrNO_3S$: 376.9721; Found: 377.9806 $[M+1]^+$ and 379.978 $[M+3]^+$.

2.2e *Characterization data of 5-(2-bromophenyl) -4-tosyloxazole (**3e**)*: White solid, Yield 81%, 0.61 g, M.p.: 112–114 °C; IR (KBr, cm^{-1}): $\bar{\upsilon}$ 685, 1032, 1068, 1282, 1585, 2932; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H, Me), 7.25–7.30 (m, 2H, Ar-H), 7.39–7.47 (m, 2H, Ar-H) 7.54 (d, J= 7.6 Hz, 1H, Ar-H) 7.68 (d, J= 7.6 Hz, 1H, Ar-H), 7.83 (d, J= 7.6 Hz, 2H, Ar-H), 7.92 (d, J= 1.2 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.6, 123.7, 127.1, 127.3, 128.3, 129.7, 132.4, 132.8, 133.4, 136.7, 145.0, 150.4, 151.9, 153.4; HRMS (ESI): Anal. Calcd for $C_{16}H_{12}BrNO_3S$: 376.972; Found: 377.9804 $[M+1]^+$ and 379.9786 $[M+3]^+$.

2.2f *Characterization data of 5-(p-tolyl)-4-tosyloxazole (**3f**)*: White solid, Yield 85%, 0.53 g, M.p.: 120–122 °C; IR (KBr, cm^{-1}): $\bar{\upsilon}$ 689, 1028, 1048, 1278, 1589, 2941; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 6H, Me_2), 7.29 (d, J= 8.0 Hz, 4H, Ar-H) 7.81–7.88 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.6, 123.3, 128.9, 129.6, 129.9, 130.4, 134.0, 137.9, 142.1, 145.6, 149.7, 153.8; HRMS (ESI): Anal. Calcd for $C_{17}H_{15}NO_3S$: 313.0773; Found: 314.0856 $[M+1]^+$.

2.2g *Characterization data of 5-(m-tolyl)-4-tosyloxazole (**3g**)*: White solid, Yield 84%, 0.52 g, M.p.: 96–98 °C; IR (KBr, cm^{-1}): $\bar{\upsilon}$ 692, 1038, 1053, 1275, 1575, 2939; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 6H, Me_2), 7.24–7.43 (m, 4H,

Ar-H), 7.23–7.77 (m, 2H, Ar-H), 7.84–7.88 (m, 3H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.6, 21.7, 126.2, 128.2, 128.4, 128.8, 129.0, 129.8, 131.8, 137.1, 138.3, 145.0, 149.2, 152.9, 160.3; HRMS (ESI): Anal. Calcd for $C_{17}H_{15}NO_3S$: 313.0773; Found: 314.0858 $[M+1]^+$.

2.2h *Characterization data of 5-(o-tolyl)-4-tosyloxazole (***3h***)*: White solid, Yield 78%, 0.48g, M.p.: 62–64 °C; IR (KBr, cm^{-1}): $\bar{\upsilon}$ 695, 1035, 1074, 1289, 1591, 2935; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H, Me), 2.41 (s, 3H, Me), 7.26–7.31 (m, 4H, Ar-H), 7.41 (d, J = 7.6 Hz, 2H, Ar-H), 7.78 (d, J = 8.0 Hz, 2H, Ar-H), 7.90 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.0, 21.6, 125.5, 128.1, 128.8, 129.7, 129.9, 130.3, 131.1, 131.5, 137.1, 138.2, 144.9, 150.1, 153.4; HRMS (ESI): Anal. Calcd for $C_{17}H_{15}NO_3S$: 313.0773; Found: 314.08588 $[M+1]^+$.

2.2i *Characterization data of 5-(3,4-dimethylphenyl)-4-tosyloxazole (***3i***)*: White solid, Yield 80%, 0.52 g, M.p.: 76–78 °C; IR (KBr, cm^{-1}): $\bar{\upsilon}$ 666, 1039, 1055, 1283, 1588, 2915; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.31 (s, 6H, $(Me)_2$), 2.41 (s, 3H, Me), 7.24 (t, J = 4.4 Hz, 1H, Ar-H), 7.29 (d, J = 8.0 Hz, 2H, Ar-H),7.69–7.72 (m, 2H, Ar-H), 7.81 (s, 1H, Ar-H), 7.88 (d, J = 8.4 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.8, 19.8, 21.6, 122.9, 126.6, 128.2, 129.7, 129.8, 129.8, 134.7, 136.4, 137.2, 140.2, 144.8, 148.9, 153.2; HRMS (ESI): Anal. Calcd for $C_{18}H_{17}NO_3S$: 327.0929; Found: 328.1015 $[M+1]^+$.

2.2j *Characterization data of 5-(4-methoxyphenyl)-4-tosyloxazole (***3j***)*: White solid, Yield 78%, 0.51 g, M.p.: 84–86 °C; IR (KBr, cm^{-1}): $\bar{\upsilon}$ 689, 1042, 1056, 1276, 1589, 2945; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H, Me), 3.87 (s, 3H, OMe), 7.00 (d, J = 9.2 Hz, 2H, Ar-H), 7.24–7.31 (m, 2H, Ar-H), 7.78–7.95 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.6, 55.4, 114.0, 117.9, 128.1, 128.3, 129.7, 129.9, 130.6, 137.3, 144.8, 148.6, 161.6; HRMS (ESI): Anal. Calcd for $C_{17}H_{15}NO_4S$: 329.0722; Found: 330.0806 $[M+1]^+$.

2.2k *Characterization data of 5-(3-methoxyphenyl)-4-tosyloxazole (***3k***)*: White solid, Yield 81%, 0.53 g, M.p.: 60–62 °C; IR (KBr, cm^{-1}): $\bar{\upsilon}$ 691, 1038, 1085, 1284, 1575, 2941; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H, Me), 3.87 (s, 3H, OMe), 7.02–7.05 (m, 1H, Ar-H), 7.24–7.41 (m, 3H, Ar-H), 7.52–7.59 (m, 2H, Ar-H), 7.83–7.89 (m, 3H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.6, 55.4, 113.9, 117.3, 121.2, 126.5, 128.2, 129.6, 129.8, 135.7, 137.0, 145.0, 149.0, 152.4, 159.4; HRMS (ESI): Anal. Calcd for $C_{17}H_{15}NO_4S$: 329.0722; Found: 330.0804 $[M+1]^+$.

2.2l *Characterization data of 5-(3,4-dimethoxyphenyl)-4-tosyloxazole (***3l***)*: White solid, Yield 75%, 0.54 g, M.p.: 134–136 °C; IR (KBr, cm^{-1}): $\bar{\upsilon}$ 686, 1028, 1056, 1278, 1575, 2957; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H, Me), 3.97 (s, 6H, $(OMe)_2$), 6.97 (d, J = 8.4 Hz, 1H, Ar-H), 7.25–7.31 (m, 2H, Ar-H), 7.58 (d, J = 8.0 Hz, 1H, Ar-H), 7.79 (s, 1H, Ar-H), 7.87 (d, J = 8.0 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.6, 55.1, 55.9, 110.9, 111.9, 115.9, 118.0, 122.2, 128.1, 129.7, 137.4, 144.8, 148.4, 148.8, 151.2, 152.6; HRMS (ESI): Anal. Calcd for $C_{18}H_{17}NO_5S$: 359.0827; Found: 360.0909 $[M+1]^+$.

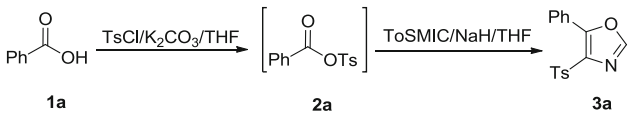
2.2m *Characterization data of 5-([1,1′-biphenyl]-3-yl)-4-tosyloxazole (***3m***)*: White solid, Yield 82%, 0.61 g, M.p.: 128–130 °C; IR (KBr, cm^{-1}): $\bar{\upsilon}$ 689, 1035, 1043, 1267, 1569, 2925; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H, Me), 7.24–7.49 (m, 5H, Ar-H), 7.69–7.66 (m, 2H, Ar-H), 7.73 (d, J = 8.4 Hz, 2H, Ar-H), 7.86–7.93 (m, 3H, Ar-H), 8.06–8.08 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 100M Hz): δ 21.6, 124.3, 127.1, 128.0, 128.3, 128.5, 128.9, 129.7, 131.7, 135.6, 137.0, 139.8, 143.6, 144.9, 149.1, 152.5; HRMS (ESI): Anal. Calcd for $C_{22}H_{17}NO_3S$: 375.0929; Found: 376.1013 $[M+1]^+$.

2.3 *X-ray crystallographic study of compound (***3m***)*

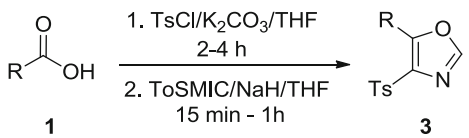
The single crystal X-ray diffraction data of the compound **3m** was generated on a Rigoku SMART Lab model, Japan; it uses Cu source and works at room temperature in monochrome beam method. The structure was established by direct methods and refined on F^2 by full matrix least square methods using the SHELXS program.

3. Results and Discussion

Initially, to optimize the reaction condition, we took a synthesis of tosyl benzoate 2a by the reaction of benzoic acid 1a with tosyl chloride in the presence of base and solvent, and subsequent reaction of **2a** with tosylmethyl isocyanide in the presence of a base in the same solvent to get 4-tosyl-5-phenyl oxazole **3a**. Thus, we conducted reactions in the presence of bases such as potassium carbonate, sodium hydride and triethylamine and in solvents such as DMF, THF, acetonitrile and toluene. The desired product 3a was obtained in 91% yield in the presence of potassium carbonate in the first step and sodium hydride in the second step with THF as solvent (Scheme 1).



Scheme 1. Synthesis of 4-tosyl-5-phenyloxazole **3a** from benzoic acid **1a**.



Scheme 2. Synthesis of 4-tosyl-5-aryloxazole **3**.

Table 1. Substrate scope for the synthesis of 4-tosyl-5-aryloxazole **3**.

Entry	R (**1**,**3**)	% Yield (**3**)	Entry	R (**1**,**3**)	% Yield (**3**)
1	C_6H_5	91 (**3a**)	8	2-Me-C_6H_4	78 (**3h**)
2	4-F-C_6H_4	93 (**3b**)	9	3,4-Me_2-C_6H_3	80 (**3i**)
3	4-Cl-C_6H_4	88 (**3c**)	10	4-MeO-C_6H_4	78 (**3j**)
4	4-Br-C_6H_4	86 (**3d**)	11	3-MeO-C_6H_4	81 (**3k**)
5	2-Br-C_6H_4	81 (**3e**)	12	3,4-$(MeO)_2$-C_6H_3	75 (**3l**)
6	4-Me-C_6H_4	85 (**3f**)	13	[1,1′-biphenyl]-4-yl	82 (**3m**)
7	3-Me-C_6H_4	84 (**3g**)			

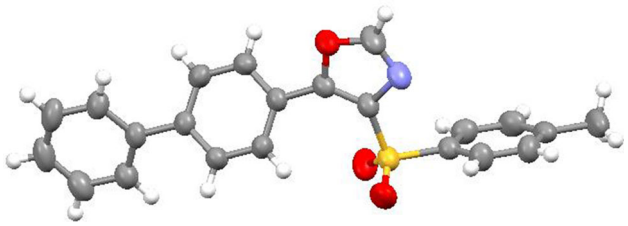


Figure 1. ORTEP diagram of 4-tosyl-5-(1,1′-biphenyl-4-yl)-oxazole (**3m**).

With the optimized reaction conditions in hand, we examined the general applicability of the protocol for the synthesis of 4-tosyl-5-aryloxazole **3** (Scheme 2). Thus, various *para*-substituted aromatic carboxylic acids bearing inductively electron withdrawing halogens (F, Cl and Br) gave 4-tosyl-5-(4-fluro/chloro/bromophenyl)-oxazoles **3b–d** in 86–93% yield (entries 2–4, Table 1). Notably, yield gradually decreases with a decrease in electronegativity of substituted halogen. Further, 2-bromobenzoic acid furnished 4-tosyl-5-(2-bromophenyl)oxazole **3e** in 81% yield (entry 5, Table 1), which is less when compared with 4-tosyl-5-(4-bromophenyl)-oxazole **3d** which is obtained in 86% yield (entry 4, Table 1) probably due to steric factors. On the other hand, substituted aromatic carboxylic acids bearing inductively electron releasing methyl group at various positions afforded corresponding 4-tosyl-5-(4/3/2-methylphenyl)oxazoles **3f–h** in 78–85% yield (entries 6–8, Table 1). Similarly, 3,4-dimethylbenzoic acid gave 4-tosyl-5-(3,4-dimethylphenyl)oxazole **3i** in 80% yield (entry 9, Table 1). In addition, substituted aromatic carboxylic acids bearing electron releasing methoxy groups at various positions furnished 4-tosyl-5-(3/4-methoxyphenyl)oxazoles **3j** and **3k** in 78 and 81% yield respectively (entries 10 and 11, Table 1). Similarly, 3,4-dimethoxybenzoic acid gave 4-tosyl-5-(3,4-dimethoxyphenyl)oxazole **3l** in 75% yield (entry 12, Table 1). Finally, [1,1′-biphenyl]-4-carboxylic acid afforded corresponding oxazole **3m** in 82% yield (entry 13, Table 1). The mechanism of the reaction is similar to our earlier reported research.[28] The structure of one of the oxazoles **3m** was confirmed by single crystal X-ray diffraction studies (CCDC reference number 1833176)[29] and its ORTEP diagram is given in Figure 1.

4. Conclusion

In summary, we report an efficient method for the synthesis of 4-tosyl-5-aryloxazoles directly from aromatic carboxylic acids. The method involves the conversion of aromatic carboxylic acids into tosyl esters and their *in situ* reaction with tosylmethyl isocyanide to access 4-tosyl-5-aryloxazoles. One-pot, simple, efficient and rapid reaction time are the noteworthy features of this protocol. Further investigations on isocyanide cyclization reactions are underway in our laboratory.

Supplementary Information (SI)

Crystallographic data for the compound **3m** reported in this paper had been deposited in the Cambridge Crystallographic Data Centre with ccdc reference number: 1833176. These data can be obtained free of charge from Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures. Supplementary Information containing general information, experimental details and characterization data of all the synthesized compounds is available at www.ias.ac.in/chemsci.

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29. CCDC 1833176 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures