



SILICA-SUPPORTED 2,4,6-TRICHLORO-1,3,5-TRIAZINE (SILICA-TCT): ENVIRONMENTALLY BENIGN, MILD AND EFFICIENT CATALYST FOR THE SYNTHESIS OF 1,4-DIHYDROPYRIDINES UNDER SOLVENT-FREE CONDITIONS

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A convenient and environmentally benign silica-supported 2,4,6-trichloro-1,3,5-triazine (Silica-TCT) catalyzed Hantzsch multicomponent reaction has been shown between aldehydes, 1,3-dicarbonyl compounds and ammonium acetate in combination with stirring at room temperature under solvent-free condition to yield 1,4-dihydropyridines. Use of Silica-TCT catalyst gives several advantages in terms of simple reaction procedure, no need of organic solvent, mild reaction conditions giving quantitative yield of desired product.

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Introduction

Solvent-free reaction has captured great current interest towards the development of synthetic organic chemistry.¹⁻³ In views of these observations in recent years environmentally benign synthetic procedure received considerable attention and some solvent-free protocol have been developed.⁴⁻⁵ Solid-state reactions have been reported for some well known reactions such as Grignard reactions,⁶ Reformatsky reactions,⁴ Aldol condensations,⁷ Dieckmann condensations,⁵ Knoevenagel condensations,⁸ reductions⁹ and others.¹⁰ Most of these reactions are carried out at room temperature in absence of solvent-free environment.

Arthur Hantzsch was the first to discover and utilize 1,3-dicarbonyl derivatives as potential multi-component substrate for the synthesis of dihydropyridines and pyridines with symmetrical substitution patterns.¹¹ Hantzsch one-pot three component condensation reactions provides certainly the most efficient access to 1,4-dihydropyridines (DHP) derivatives due to its atom economy feature and the availability and diversity of the building blocks engaged in this reaction. 1,4-Dihydropyridines are class of nitrogen containing heterocycles having a 6-membered ring. 1,4-DHPs, which are the most potent calcium antagonists or calcium channel blockers, have received much attention due to their wide range of pharmaceutical and biological properties such as inhibition of human cytochrome P450 enzyme,¹² angiotensin-converting enzyme inhibition, and blood pressure control on chronic, nondiabetic nephropathies.¹³ The classical Hantzsch reaction involves the cyclocondensation of β -keto esters, an aldehyde with

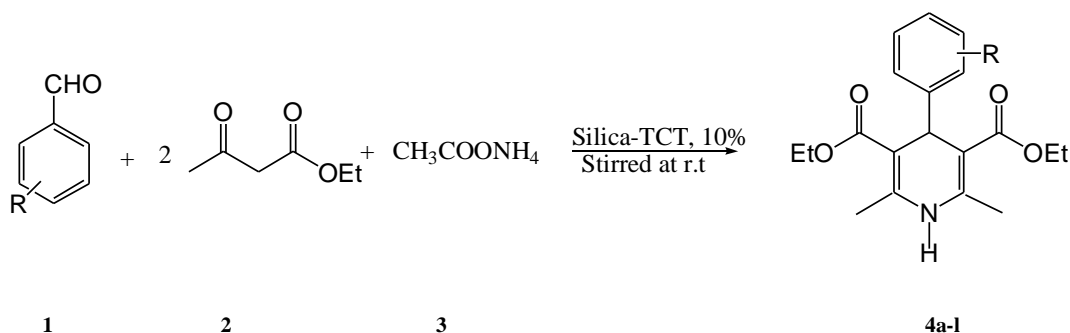
ammonia to give 1,4-dihydropyridines. There are many modification and verification of the Hantzsch synthesis have been made which include use of molecular sieves and pyridine,¹⁴ Yb(OTf)₃,¹⁵ Me₃SiI,¹⁶ p-TSA,¹⁷ TBAHS,¹⁸ ionic liquid¹⁹ and microwave technique.²⁰ The combination of solvents, costly chemicals/expensive reagents, stoichiometric amount of catalyst, strongly acidic conditions and high temperature makes these methods environmentally hazardous. Therefore, there is scope for further work towards mild conditions, increased variation of the substituent in the product and better yields. In views of these observations it was thought worthily to synthesize 1,4-dihydropyridines by the condensation of aldehydes, 1,3-dicarbonyl compounds with ammonium acetate in combination with stirring at room temperature under solvent-free condition using environmentally benign silica-supported 2,4,6-trichloro-1,3,5-triazine (Silica-TCT).

Materials and Methods

Melting points were determined in an open capillary tube and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer spectrometer. ¹H NMR spectra were recorded on a Gemini 400-MHZ instrument in CDCl₃ as solvent and TMS as an internal standard. The mass spectra were recorded on EISHIMADZU-GC-MS spectrometer.

General procedure for the synthesis of 1,4-dihydropyrazolines

To a mixture of different substituted aromatic aldehydes (5 mmol), ethyl acetoacetate (10 mmol), ammonium acetate (5.5 mmol) was added. To this silica supported 2,4,6-trichloro-1,3,5-triazine (Silica-TCT) (250 mg, 10 mol% equivalent). The resulting reaction mixture was stirred at room temperature for 2-2.5 hr. The progress of the reaction mixture was monitored by TLC. After completion of



Scheme 1

reaction as on TLC, reaction mixture was poured into crushed ice and the solid product was filtered and crystallized from ethanol to give pure yellow crystalline 1,4-dihydropyridines derivatives **4a-l**.

Preparation and determination of Silica-TCT catalyst

The desired silica supported 2,4,6-trichloro-1,3,5-triazine (Silica-TCT) was prepared in our laboratory by simple approach. The mixture of silica and TCT in appropriate ratio was mixed together and heated in dry dichloromethane (dry DCM) followed by filtration, washing with cold dry DCM drying in air. The exact loading of the TCT in terms of free chloride groups was determined by titrating the HCl generated from supported TCT on silica against standard NaOH using phenolphthalein indicator. The loading of chlorine equivalent was found to be 2.75 mmol/gm of silica which is correspond to 1.0 mmol of TCT. The catalyst so prepared was then used for further catalytic study.

Spectral analysis of 1,4-dihydropyridines derivatives 4a-l.

4a: 2,6-Dimethyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester: Yellow colored crystalline solid, IR (KBr, cm^{-1}): 3423, 3026, 2983, 1735, 1685, 1556, 1234, 1043, 862, 754, 700. ^1H NMR (CDCl_3 , δ ppm): 1.21 (t, $J = 7.08$ Hz, 6H, two CH_3), 2.32 (s, 6H, two CH_3), 4.08 (q, $J = 7.04$ Hz, 4H, two OCH_2), 4.98 (s, 1H, broad NH), 7.09-7.13 (m, 1H, Ar-H), 7.20 (t, $J = 8.52$ Hz, 2H, ArH), 7.26-7.28 (m, 2H, ArH). MS m/z : 328 (M^+). Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{O}_4\text{N}$: C, 69.15; H, 6.70. Found: C, 69.28; H, 6.63.

4b: 4-(4-Methoxy-phenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester: Yellow colored crystalline solid, IR (KBr, cm^{-1}): 3420, 2986, 1732, 1670, 1548, 1230, 1051, 853, 750, 700. ^1H NMR (CDCl_3 , δ ppm): 1.23 (t, $J = 7.10$ Hz, 6H, two CH_3), 2.28 (s, 6H, two CH_3), 3.72 (s, 3H, OCH_3), 4.12 (q, $J = 7.06$ Hz, 4H, two OCH_2), 4.95 (s, 1H, broad NH), 7.20 (d, $J = 8.50$ Hz, 2H, ArH), 7.18 (d, $J = 8.50$ Hz, 2H, ArH). MS m/z : 358 (M^+). Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{O}_5\text{N}$: C, 67.03; H, 6.70. Found: C, 67.18; H, 6.67.

4c: 4-(3,4-Dimethoxy-phenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester: Yellow colored crystalline solid, IR (KBr, cm^{-1}): 3428, 2974, 1730, 1655, 1553, 1233, 1051, 850, 755, 730. ^1H NMR (CDCl_3 , δ ppm): 1.27 (t, $J = 7.13$ Hz, 6H, two CH_3), 2.26 (s, 6H, two CH_3), 3.75 (s, 6H, two OCH_3), 4.14 (q, $J = 7.10$ Hz, 4H, two

OCH_2), 4.92 (s, 1H, broad NH), 6.80 (s, 1H, ArH), 6.72 (d, $J = 8.28$ Hz, 1H, ArH), 6.79 (d, $J = 8.28$ Hz, 1H, ArH). MS m/z : 388 (M^+). Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{O}_6\text{N}$: C, 67.27; H, 6.93. Found: C, 67.35; H, 6.88.

4d: 4-(4-Hydroxy-phenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester: Yellow colored crystalline solid, IR (KBr, cm^{-1}): 3436, 2970, 1732, 1662, 1580, 1226, 1047, 855, 750. ^1H NMR (CDCl_3 , δ ppm): 1.26 (t, $J = 7.13$ Hz, 6H, two CH_3), 2.26 (s, 6H, two CH_3), 4.13 (q, $J = 7.10$ Hz, 4H, two OCH_2), 4.94 (s, 1H, broad NH), 5.72 (s, 1H, OH), 7.18 (d, $J = 8.48$ Hz, 2H, ArH), 7.20 (d, $J = 8.48$ Hz, 2H, ArH). MS m/z : 388 (M^+). Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{O}_6\text{N}$: C, 64.94; H, 6.70. Found: C, 64.83; H, 6.74.

4e: 4-(4-Hydroxy-3-methoxy-phenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester: Yellow colored crystalline solid, IR (KBr, cm^{-1}): 3432, 2978, 1736, 1680, 1575, 1220, 1043, 852, 758. ^1H NMR (CDCl_3 , δ ppm): 1.26 (t, $J = 7.12$ Hz, 6H, two CH_3), 2.26 (s, 6H, two CH_3), 3.71 (s, 3H, OCH_3), 4.15 (q, $J = 7.11$ Hz, 4H, two OCH_2), 4.90 (s, 1H, broad NH), 5.78 (s, 1H, OH), 6.83 (s, 1H, ArH), 6.75 (d, $J = 8.30$ Hz, 1H, ArH), 6.82 (d, $J = 8.30$ Hz, 1H, ArH). MS m/z : 374 (M^+). Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{O}_6\text{N}$: C, 64.17; H, 6.41. Found: C, 64.28; H, 6.45.

4f: 4-(4-Dimethylamino-phenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester: Yellow colored crystalline solid, IR (KBr, cm^{-1}): 3435, 2972, 1732, 1689, 1572, 1217, 1047, 858, 751. ^1H NMR (CDCl_3 , δ ppm): 1.24 (t, $J = 7.12$ Hz, 6H, two CH_3), 2.28 (s, 6H, two CH_3), 2.85 (s, 6H, $\text{N}(\text{CH}_3)_2$), 4.13 (q, $J = 7.10$ Hz, 4H, two OCH_2), 4.93 (s, 1H, broad NH), 7.24 (d, $J = 8.51$ Hz, 2H, ArH), 7.18 (d, $J = 8.51$ Hz, 2H, ArH). MS m/z : 370 (M^+). Anal. Calcd for $\text{C}_{21}\text{H}_{27}\text{O}_4\text{N}_2$: C, 68.10; H, 7.29. Found: C, 68.17; H, 7.36.

4g: 4-(4-Chloro-phenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester: Yellow colored crystalline solid, IR (KBr, cm^{-1}): 3432, 2958, 1726, 1680, 1535, 1224, 1038, 852, 746. ^1H NMR (CDCl_3 , δ ppm): 1.28 (t, $J = 7.14$ Hz, 6H, two CH_3), 2.29 (s, 6H, two CH_3), 4.15 (q, $J = 7.12$ Hz, 4H, two OCH_2), 4.91 (s, 1H, broad NH), 7.16 (d, $J = 8.48$ Hz, 2H, ArH), 7.21 (d, $J = 8.48$ Hz, 2H, ArH). MS m/z : 362 (M^+). Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{O}_4\text{NCl}$: C, 62.98; H, 5.80; Cl, 10.23. Found: C, 63.08; H, 5.83; 9.74.

4h: 4-(4-Bromo-phenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester: Yellow colored crystalline solid, IR (KBr, cm^{-1}): 3436, 2952, 1730,

1683, 1531, 1218, 1042, 848, 755. ¹HNMR (CDCl₃, δ ppm): 1.27 (t, *J* = 7.14 Hz, 6H, two CH₃), 2.26 (s, 6H, two CH₃), 4.12 (q, *J* = 7.11 Hz, 4H, two OCH₂), 4.90 (s, 1H, broad NH), 7.18 (d, *J* = 8.48 Hz, 2H, ArH), 7.20 (d, *J* = 8.48 Hz, 2H, ArH). MS *m/z*: 407 (M⁺). Anal. Calcd for C₁₉H₂₁O₄NBr: C, 56.01; H, 5.15; Br, 19.65. Found: C, 56.13; H, 5.19; Br, 19.74.

4i: 2,6-Dimethyl-4-p-tolyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester: Yellow colored crystalline solid, IR (KBr, cm⁻¹): 3430, 2963, 1734, 1683, 1546, 1224, 1040, 842, 747. ¹HNMR (CDCl₃, δ ppm): 1.28 (t, *J* = 7.15 Hz, 6H, two CH₃), 2.23 (s, 3H, ArCH₃), 2.29 (s, 6H, two CH₃), 4.14 (q, *J* = 7.13 Hz, 4H, two OCH₂), 4.92 (s, 1H, broad NH), 7.23 (d, *J* = 8.51 Hz, 2H, ArH), 7.20 (d, *J* = 8.51 Hz, 2H, ArH). MS *m/z*: 342 (M⁺). Anal. Calcd for C₂₀H₂₄O₄N: C, 70.17; H, 7.01. Found: C, 70.25; H, 7.13.

4j: 2,6-Dimethyl-4-(4-nitro-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester: Yellow colored crystalline solid, IR (KBr, cm⁻¹): 3435, 2972, 1729, 1672, 1538, 1229, 1022, 846, 742. ¹HNMR (CDCl₃, δ ppm): 1.26 (t, *J* = 7.14 Hz, 6H, two CH₃), 2.27 (s, 6H, two CH₃), 4.15 (q, *J* = 7.13 Hz, 4H, two OCH₂), 4.94 (s, 1H, broad NH), 7.18 (d, *J* = 8.48 Hz, 2H, ArH), 7.20 (d, *J* = 8.48 Hz, 2H, ArH). MS *m/z*: 372 (M⁺). Anal. Calcd for C₁₉H₂₁O₆N₂: C, 61.29; H, 5.64. Found: C, 61.34; H, 5.71.

4k: 2,6-Dimethyl-4-(3-nitro-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester: Yellow colored crystalline solid, IR (KBr, cm⁻¹): 3435, 3084, 2985, 1734, 1601, 1558, 1215, 1082, 916, 860, 792. ¹HNMR (CDCl₃, δ ppm): 1.22 (t, *J* = 7.08 Hz, 6H, two CH₃), 2.36 (s, 6H, two CH₃), 4.10 (q, *J* = 7.12 Hz, 4H, two OCH₂), 4.97 (s, 1H, broad NH), 7.37 (t, *J* = 7.92 Hz, 1H, ArH), 7.64 (d, *J* = 8.96 Hz, 1H, ArH), 8.01 (d, *J* = 9.4 Hz, 1H, ArH), 8.12 (s, 1H, ArH). MS *m/z*: 372 (M⁺). Anal. Calcd for C₁₉H₂₁O₆N₂: C, 61.29; H, 5.64. Found: C, 61.24; H, 5.70.

4l: 2,6-Dimethyl-4-(2-nitro-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester: Yellow colored crystalline solid, IR (KBr, cm⁻¹): 3438, 3089, 2970, 1732, 1606, 1552, 1217, 1087, 912, 858, 790. ¹HNMR (CDCl₃, δ ppm): 1.23 (t, *J* = 7.08 Hz, 6H, two CH₃), 2.36 (s, 6H, two CH₃), 4.11 (q, *J* = 7.12 Hz, 4H, two OCH₂), 4.95 (s, 1H, broad NH), 7.37-8.15 (m, 4H, ArH). MS *m/z*: 372 (M⁺). Anal. Calcd for C₁₉H₂₁O₆N₂: C, 61.29; H, 5.64. Found: C, 61.27; H, 5.71.

Results and Discussion

With increasing economical concerns and regulatory faced by pharmaceutical and chemical industries, development of environmentally benign organic reactions has become the crucial and demanding area in modern organic chemical research. Therefore, in present work we decided to look closely at the reactivity of various aromatic aldehydes towards Hantzsch condensation reaction in the presence of Silica-TCT as catalyst. In typical experimental procedure, a mixture of ethyl acetoacetate (**4** mmol), benzaldehydes (**2** mmol) and ammonium acetate (**3** mmol) using varying amount of Silica-TCT was stirred at room temperature (Scheme 1). The reaction was much sluggish in the absence of catalyst and gave unacceptable yields of product. In order to optimize the use of Silica-TCT catalyst, the 3-

nitrobenzaldehyde, ethyl acetate and ammonium acetate was subjected to stirred at room temperature using 2.5 mol %, 5 mol %, 7.5 mol % and 10 mol % of catalyst, the reaction resulted in the formation of 2,6-Dimethyl-4-(3-nitro-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester **4k** in 45, 59, 77 and 84 % yields respectively (Table 1). Promoted by these results, various aromatic aldehydes were subjected to Hantzsch condensation with ethyl acetoacetate and ammonium acetate using our optimized reaction conditions to yield 1,4-dihydropyridine derivatives (Scheme 1). The product was isolated in high purity by simple aqueous work-up followed by recrystallisation from ethanol. The structures of the products were confirmed on the basis of physical constant and spectroscopic data²¹. It follows from Table 2 that the yields of all the products are good to excellent and a variety of functionalities such as nitro, halide, alkoxy and hydroxyl, etc. can be accommodated in 1,4-dihydropyridine derivatives. Aromatic aldehydes carrying electron withdrawing substituent reacted in shorter reaction time to give excellent yields of corresponding 1,4-dihydropyridine compared to electron releasing substituent.

Table 1. 2,6-Dimethyl-4-(3-nitro-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester.

Entry	Silica-TCT, mol %	Time, min ^a	Yield, % ^b
1	2.5	85	45
2	5	70	59
3	7.5	58	77
4	10	28	88

^aTime required to convert reactant into product; ^bIsolated yields

Table 2. Silica-TCT catalyzed synthesis of 1,4-dihydropyridines derivatives through Hantzsch reaction under solvent-free condition

Compound	Ar	Time, min	Yield, %	M.P., °C
4a	C ₆ H ₅	55	84	156-157
4b	4-MeOC ₆ H ₄	47	77	80-82
4c	3,4-(MeO) ₂ C ₆ H ₃	46	71	85-87
4d	4-OHC ₆ H ₄	53	79	120-122
4e	4-OH-3-MeOC ₆ H ₃	45	81	134-136
4f	4-Me ₂ NC ₆ H ₄	48	84	95-97
4g	4-ClC ₆ H ₄	39	70	144-146
4h	4-BrC ₆ H ₄	40	83	112-115
4i	4-CH ₃ C ₆ H ₄	42	78	127-129
4j	4-NO ₂ C ₆ H ₄	34	80	150-152
4k	3-NO ₂ C ₆ H ₄	28	88	162-164
4l	2-NO ₂ C ₆ H ₄	37	81	155-157

Conclusion

In summary we have successfully exploited the Silica-TCT as an inexpensive and readily available catalyst for synthesis of 1,4-dihydropyridines. The present protocol has several advantages including simple reaction procedure, shorter reaction time compared to classical Hantzsch condensation reaction, solvent-free conditions and high yields of product.

References

- ¹Lancaster, M. In: *Handbook of Green Chemistry and Technology*; Clark TH, Macquarrie DJ, Eds.; Blackwell: Abingdon, **2002**.
- ²Sanchez, L. M., Sathicq, A. G., Jios, J. L., Baronetti, G. T., Thomas, H. J. *Tetrahedron Lett.*, **2011**, *52*, 4412-4416.
- ³Rothenberg, G., Dowine, A. P., Raston, C. L., Scott, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 8701-8708.
- ⁴Tanaka, K., Kishigami, S., Toda, F. *J. Org. Chem.* **1991**, *56*, 4333-4334.
- ⁵Zangade, S. B., Mokle, S. S., Shinde, A. T., Vibhute, Y. B., *Green Chem. Lett. Rev.* **2013**, *6*, 123-127.
- ⁶Toda, F., Suzuki, T., Higa, S. *J. Chem. Soc. Perkin Trans I.* **1998**, *1*, 3521-3522.
- ⁷Miles, W.H., Rivera, S. L., Rosario, J. D. *Tetrahedron Lett.* **1992**, *33*, 305-308.
- ⁸Toda, F., Tanaka, K., Hamai, K. *J. Chem. Soc. Perkin Trans I.* **1990**, *1*, 3207-3209.
- ⁹Ren, Z., Cao, W., Tong, W. *Synth. Commun.* **2002**, *32*, 3475-3479.
- ¹⁰Toda, F., Kiyoshige, K., Yagi, M., *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 320-321.
- ¹¹Zangade S, Mokle S, Vibhute Y, Vibhute, Y., *Chem. Sci. J.*, **2011**, *Article ID:CSJ-13*, 1-6.
- ¹¹Hantzsch, A., *Lieb. Ann. Chem.* **1882**, *215*, 1.
- ¹²Katoh, M., Nakajima, M., Shimada, N., Yamazaki, H., Yokoi, T. *Eur. J. Clin. Pharmacol.* **2000**, *55*, 843-852.
- ¹³Ruggenenti, P., Perna, A., Benini, R., Remuzzi, G., *J. Am. Soc. Nephrol.* **1998**, *9*, 2096-2101.
- ¹⁴Gordeev, M. F., Patel, D. V., Gordan, E. M., *J. Org. Chem.* **1996**, *61*, 924-928.
- ¹⁵Wang, L. M., Sheng, J., Zhang, J. W., Han, J. W., Fan, Z. Y., Yian, H., Qian, C. T., *Tetrahedron* **2005**, *61*, 1539-1543.
- ¹⁶Sabitha, G., Kiran kumar Reddy, G. S., Reddy, C. S., Yadav, J. S., *Tetrahedron Lett.* **2003**, *44*, 4129-4131.
- ¹⁷Cherkupally, S. R., Mekala, R., *Chem. Pharm. Bull.* **2008**, *56*, 1002-1004.
- ¹⁸Tewari, N., Namrata, D., Tripathi, R. P., *Tetrahedron Lett.* **2004**, *45*, 9011-9014.
- ¹⁹Sridhar, R., Perumal, P. T., *Tetrahedron*, **2005**, *61*, 2465-2470.
- ²⁰Yadav, J. S., Subba Reddy, B. V., Nagaraju, A., Sarma, J. A. R. P., *Synth. Commun.*, **2002**, *32*, 893-896.
- ²¹Cotterill, I. C., Usyatinsky, A. Y., Arnold, J. M., Clark, D. S., Dordick, J. S., *Tetrahedron Lett.*, **1998**, *39*, 1117-1120.

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