Tetrahedron Letters 52 (2011) 1265–1268

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient one-pot synthesis of novel polysubstituted 4-amino-2,3-dihydropyridines

Nitu Mahajan [a], Ambika Sambyal [a], Ajay P. S. Pannu [b], T. K. Razdan [a,*]

[a] Department of Chemistry, University of Jammu, Ambedkar Road, Jammu 180 006, India
[b] Department of Chemistry, G.N.D. University, Amritsar, Punjab 154 003, India

ARTICLE INFO

Article history:
Received 19 November 2010
Revised 23 December 2010
Accepted 7 January 2011
Available online 20 January 2011

Keywords:
Aldehydes
2,3-Dihydropyridines
Indium triflate
Ketones
Malononitrile
Multi-component reaction

ABSTRACT

A convenient and efficient one-pot multi-component synthesis of novel polysubstituted 4-amino-2,3-dihydropyridines from carbonyl compounds, malononitrile and acetonitrile, using indium triflate is reported. Acetonitrile acts both as a solvent as well as a substrate.

Dihydropyridines constitute an important class of bioactive heterocycles.[1–5] Among these, 4-substituted 1,4-dihydropyridines are established calcium channel regulators and their synthesis has been the subject of extensive study.[6–12] On the other hand, the synthesis of 2,3-dihydropyridines,which are useful intermediates in the formation of biologically active substances, has not received adequate attention. This may be due to their tendency to undergo facile disproportionation to pyridine derivatives.[13] The known methods for the synthesis of 2,3-dihydropyridines include the oxidative dehydrogenation of tetrahydropyridine,[14] thermal cyclization of allene amidines,[15] acid catalyzed cyclization of some 2,4-dinitrophenyl hydrazones,[16] Ritter reaction of saturated and unsaturated diols[17] and the reduction of pyridinium salts.[18] Trialkyl 2,3-dihydropyridinium salts have been prepared by the Lewis acid catalyzed condensation–cyclization of acyclic aldehydes and benzyl ammonium chloride.[19] These reactions also afforded the corresponding pyridinium salts in the ratio of 3:1. Despite their attractiveness, most of the known methodologies are associated with the limitations of stringent reaction conditions, formation of multitude of products, and poor yield. Therefore, a simple and efficient synthetic methodology for the preparation of usefully functionalized 2,3-dihydropyridines is still desirable.

Since, multi-component reactions are flexible, atom-economic, and eco-friendly they have gained great importance in synthetic organic chemistry.[20–22] Our aim to establish a synthetic methodology for the one-pot preparation of stable polysubstituted 2,3-dihydropyridines, from the readily accessible substrates, led us to explore the reaction of alkyl and aryl ketones with malononitrile and acetonitrile in the presence of Lewis acids. Herein, we wish to report a simple and efficient one-pot synthesis of novel polysubstituted 2,3-dihydropyridines, under ambient reaction conditions, and their subsequent semi-synthetic transformation to carboxylic acid and amino derivatives.

Acetonitrile has been used as a solvent in many Lewis acid catalyzed reactions. We assumed that in the presence of Lewis acids, acetonitrile, by virtue of the presence of a triple bond, may participate actively in chemical reactions and behave as a substrate as well. Initially, we studied the reaction of acetone, malononitrile, and acetonitrile, in the presence of Lewis acids, at room temperature, as a model for our methodology. After trying several Lewis acids viz $ZnCl_2$, $BiCl_3$, $TiCl_4$ and their triflates it was observed that indium triflate and triethylamine catalyzed the multi-component reaction, at room temperature, to afford the 2,3-dihydropyridine (**3a**), albeit in low yield (40%).

In order to improve the yield, we set out to modify the catalyst system and found that the addition of a catalytic amount of triflic acid to the catalyst mixture of $In(OTf)_3$ and triethylamine enhanced the catalytic activity of the mixture and carried forward the reaction efficiently, at room temperature.

Optimization of the reaction conditions revealed that for the best performance the concentration of $In(OTf)_3$, Et_3N, and triflic

* Corresponding author.
E-mail address: tk_razdan@rediffmail.com (T.K. Razdan).

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doi:10.1016/j.tetlet.2011.01.017

acid in the catalyst mixture was 20 mol %, 1 mol equivalent of acetone, and 0.1 mol %, respectively. Moreover, acetonitrile was needed in slight excess. With optimized conditions in hand, a mixture of acetone, acetonitrile, and malononitrile (1:5:2 mol) were stirred, at room temperature, in the presence of the catalyst mixture.[23] The reaction was complete within 8 h and the product **3a** separated out as a colorless crystalline solid in 89% yield (Table 1). Its IR spectrum displayed characteristic absorption bands at ν_{max} 3333 (NH_2), 2210, 2215 (C≡N), 1645 (C=N), 1580 (C=N). The ^{1}H NMR spectrum[24] was quite simple and displayed resonance signals at δ 1.35, 1.39, 1.93 (s, 3H each), and 7.04 (s br, exch. D_2O, 2H, and NH_2). ^{13}C NMR spectrum confirmed the presence of three nitrile groups, δ_C 112.0, 113.4, and 114.4. The structure of compound **3a** was finally confirmed by XRD (CCDC No. 66716).[25]

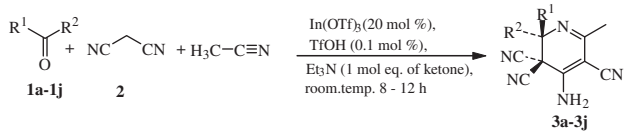
In order to determine the scope and limitations of the indium triflate promoted multicomponent reaction, the reaction was extended to higher homologs of acetone and various methyl aryl ketones (Scheme 1). Under optimized reaction conditions, these reactions afforded the corresponding 4-amino-2,3-dihydropyridine-3,3,5-tricarbonitrile derivatives **3b–3j**, as the major products and in high yield (Table 1). The reaction was also carried out with different aldehydes. Acetaldehyde did not afford the required 2,3-dihydropyridine derivative. This may be due to its tendency to polymerize. However, the reaction of aromatic aldehydes afforded complex mixtures of compounds, which were not further investigated.

Mechanistically, the reaction leading to the formation of 4-amino-2,3-dihydropyridine-3,3,5-tricarbonitriles seems to proceed by a condensation-addition reaction (Scheme 2). Acetonitrile functions both as a substrate as well as a solvent. It may be pertinent to mention here that with the current methodology, we were able to prepare multigram quantities of the compounds **3a–3j**.

The structural features of compounds **3a–3j** prompted us to study their chemical behavior. The compounds did not respond to hydrolysis with methanolic HCl and NaOH, at room temperature. However, on heating the compounds with 1 M HCl in 90% MeOH on a water bath (temp. 99.5 °C) for 36–48 h,[25] compounds **3a–3h** afforded the corresponding 3,5-dicarboxylic acids **4a–4h**[26,27] in 60–65% yield (Scheme 3 and Table 2). The reaction of compounds **3i** and **3j** afforded a mixture of products, which were separated by column chromatography on silica gel and were characterized as pyridine derivatives, **4i**, **4j** and **5i**, **5j** (Scheme 4). Similar results, with improved yield (70–75%) (Table 2), were obtained by refluxing the methanolic solutions of **3a–3j** in the presence of

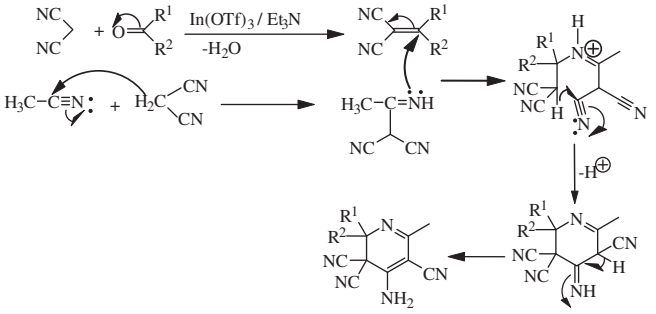
Table 1
Yield of Products **3a–3j**

Compd	Reaction time (h)	% Yield	Compd	Reaction time (h)	% Yield
3a	8	89	**3f**	10	90
3b	10	84	**3g**	12	80
3c	10	86	**3h**	9	81
3d	12	88	**3i**	8	80
3e	12	84	**3j**	8	82



1a/3a: $R^1 = R^2 = CH_3$
1b/3b: $R^1 = CH_3$; $R^2 = C_2H_5$
1c/3c: $R^1 = CH_3$; $R^2 = C_3H_7$
1d/3d: $R^1 = CH_3$; $R^2 = C_3H_7$
1e/3e: $R^1 = CH_3$; $R^2 = C_6H_5$
1f/3f: $R^1 = CH_3$; $R^2 = 4\text{-}CH_3OC_6H_5$
1g/3g: $R^1 = CH_3$; $R^2 = 4\text{-}NO_2C_6H_5$
1h/3h: $R^1 = CH_3$; $R^2 = 2\text{-}ClC_6H_5$
1i/3i: $R^1 = H$; $R^2 = C_2H_5$
1j/3j: $R^1 = H$; $R^2 = C_3H_7$

Scheme 1. Preparation of polysubstituted 2,3-dihydropyridines.

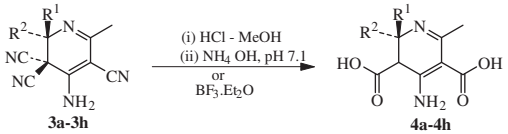


Scheme 2. Rationalization of the formation of polysubstituted 2,3-dihydropyridines.

BF_3–Et_2O. These results substantiate that for the stability of these products the presence of a quaternary carbon at position 2 of 2,3-dihydropyridines is essential.

Next, compounds **3a–3j** were subjected to metal hydride reduction. The reduction of **3a–3j** with sodium borohydride did not give satisfactory results. However, reduction with lithium aluminum hydride proceeded smoothly, at room temperature,[28] and afforded the corresponding compounds **6a–6j** in 80–96% yield (Table 3 and Scheme 5). On spectral analysis,[29] the products **6a–6j** were found to result from the regiospecific decyanation and reduction of **3a–3j**. These products were characterized as 4-amino-2,3-dihydropyridine-3,3-dimethyl amine derivatives. While the present study substantiates that in the presence of metal hydrides α-aminonitriles undergo decyanation[30] it also suggests that in the compounds possessing several nitrile groups at the α-position the group, which is conjugated to an amino group via a double bond is decyanated preferentially than the non-conjugated nitrile groups.

In summary, we have developed a convenient and efficient three component synthesis of novel polysubstituted 4-amino-2,3-dihydropyridines, which may be further elaborated to useful products by simple chemical manipulation. The advantages of the aforementioned methodologies are that the reactions are operationally simple, efficient, cost-effective, and eco-friendly. The mul-

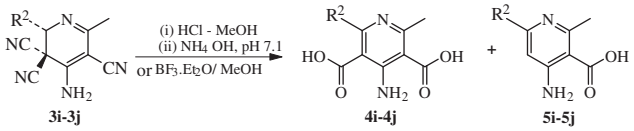


3a/4a: $R^1 = R^2 = CH_3$
3b/4b: $R^1 = CH_3$; $R^2 = C_2H_5$
3c/4c: $R^1 = CH_3$; $R^2 = C_3H_7$
3d/4d: $R^1 = CH_3$; $R^2 = C_3H_7$
3e/4e: $R^1 = CH_3$; $R^2 = C_6H_5$
3f/4f: $R^1 = CH_3$; $R^2 = 4\text{-}CH_3OC_6H_5$
3g/4g: $R^1 = CH_3$; $R^2 = 4\text{-}NO_2C_6H_5$
3h/4h: $R^1 = CH_3$; $R^2 = 2\text{-}ClC_6H_5$

Scheme 3. Hydrolysis of 4-amino-2,3-dihydropyridine-3,3,5-tricarbonitrile derivatives.

Table 2
Yield of hydrolyzed products **4a–4j** and **5i**, **5j**

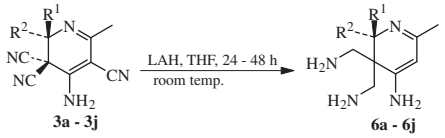
Compd	Reaction time (h)	% Yield (HCl–MeOH)	% Yield (BF_3·Et_2O)	Compd	Reaction time (h)	% Yield (HCl–MeOH)	% Yield (BF_3·Et_2O)
4a	48	60	75	**4g**	36	60	73
4b	36	62	71	**4h**	34	61	70
4c	36	64	74	**4i**	24	32	24
4d	24	62	73	**4j**	24	31	25
4e	28	60	71	**5i**	24	28	75
4f	26	65	72	**5j**	24	27	73



Scheme 4. Hydrolysis of **3i** and **3j**.

Table 3
Yield of reduced products **6a–6j**

Compd	Reaction time (h)	% Yield	Compd	Reaction time (h)	% Yield
6a	24	94	**6f**	36	90
6b	36	91	**6g**	48	80
6c	36	92	**6h**	36	94
6d	48	90	**6i**	24	96
6e	40	93	**6j**	38	94



3a/6a: $R^1 = R^2 = CH_3$
3b/6b: $R^1 = CH_3$; $R^2 = C_2H_5$
3c/6c: $R^1 = CH_3$; $R^2 = C_3H_7$
3d/6d: $R^1 = CH_3$; $R^2 = C_3H_7$
3e/6e: $R^1 = CH_3$; $R^2 = C_6H_5$
3f/6f: $R^1 = CH_3$; $R^2 = 4\text{-}CH_3OC_6H_5$
3g/6g: $R^1 = CH_3$; $R^2 = 4\text{-}NO_2C_6H_5$
3h/6h: $R^1 = CH_3$; $R^2 = 2\text{-}ClC_6H_5$
3i/6i: $R^1 = H$; $R^2 = C_2H_5$
3j/6j: $R^1 = H$; $R^2 = C_3H_7$

Scheme 5. Lithium aluminum hydride reduction of 4-amino-2,3-dihydropyridine-3,3,5-tricarbonitrile derivatives.

ticomponent reaction of ketones, malononitrile, and acetonitrile can be scaled up easily. Moreover, the synthesized compounds may also find significant use for the preparation of complex nitrogen heterocycles, with useful pharmacological properties. The scope of the reaction and further synthetic applications of these products are currently under investigation in our laboratory.

Acknowledgments

The authors are thankful to Dr. S.K. Koul (Indian Institute of Integrative Medicine; formerly Regional Research Laboratory, Jammu), Prof. T.S. Banipal and Prof. M.P.S. Isher of Guru Nanak Dev University, Amritsar (India), for providing spectral facilities. We are also grateful to Prof. M.S. Hundal, Department of Chemistry, Guru Nanak Dev University, Amritsar (India), for XRD.

Supplementary data

Supplementary data (experimental procedures, characterization data of compounds, crystallographic data, and ORTEP diagram for compound **3a**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.017.

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23. *General experimental procedure for the preparation of polysubstituted dihydropyridines*: see Supplementary data.
24. *Spectral data of selected polysubstituted dihydropyridines* (**3a**): colorless crystals, mp 137 °C. IR: ν_{max} cm^{-1} 3321, 2986, 2218, 2210, 2209, 1654, 1578, 1400, 1380, 1257, 1156, 994, 874. ^1H NMR $(CD_3)_2CO$: δ 1.35 (s, 3H), 1.39 (s, 3H), 1.93 (s, 3H), 7.04 (s br, exch. D_2O, 2H). ^{13}C NMR $(CD_3)_2CO$: δ_C 19.2, 22.3 (2C), 40.8, 49.1, 69.5, 112.0, 113.4, 114.4, 161.4, 166.9. HRMS: *m*/*z* (rel. int.) 213.1020 (100) (M^+), (calcd for $C_{11}H_{11}N_5$, 213.1014), 187 (58), 172 (72), 107 (34), 106 (28), 66 (35), 41 (42). Anal. Calad for CHN: C, 61.96; H, 5.20; N, 32.84. Found: C, 61.99; H, 5.25; N, 32.86. *Compound* **3f**: colorless crystals, mp 144 °C. IR: ν_{max} cm^{-1} 3325, 2984, 2210, 2209, 1648, 1562, 1465, 1450, 1375, 1350, 1270, 1145, 986, 876. ^1H NMR $(CD_3)_2CO$: δ 1.20 (s, 3H), 1.89 (s, 3H), 2.62 (s br, exch. D_2O, 2H), 3.76 (s, 3H), 7.02 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H). ^{13}C NMR $(CD_3)_2CO$: δ_C 19.6, 26.1, 48.1, 51.3, 57.1, 69.5, 112.2, 114.6, 114.8, 125.4 (2C), 128.6 (2C), 151.2, 158.0, 161.2, 166.7. HRMS: *m*/*z* (rel. int.) 305.1282 (100) (M^+), (calcd for $C_{17}H_{15}N_5O$, 305.1277), 279 (59), 264 (73), 198 (26), 107 (38), 66 (33), 41 (45). Anal. Calad for CHN: C, 66.87; H, 4.95; N, 22.94. Found: C, 66.86; H, 4.99; N, 22.91.
25. For XRD studies, single crystals were obtained by slow evaporation of the acetone–chloroform solution of the compound. The compound crystallized in triclinic form (Table 1 of Supplementary data). The ORTEP diagram of the compound **3a** is given in the Supplementary data for this Letter.
26. *General procedure for hydrolysis of* **3a–3j**: see Supplementary data.
27. *Spectral data of selected hydrolysis products* (**4a**): colorless crystals, mp 171 °C. IR: ν_{max} cm^{-1} 3448, 3116, 2925, 2851, 2670, 1691 (COOH), 1607, 1542, 1430, 1351, 1200, 1110, 1014, 932. ^1H NMR (CD_3OD): δ 1.20 (s, 6H), 1.86 (s, 3H), 2.60 (s br, exch. D_2O, 2H), 3.10 (s, 1H), 11.46 (s br, exch. D_2O, 1H), 12.51 (s br, exch. D_2O, 1H). ^{13}C NMR (CD_3OD): δ_C 22.7, 27.5, 28.3, 43.3, 69.5, 113.9, 167.3, 168.2, 170.0, 178.1. HRMS: *m*/*z* (rel. int.) 226.0959 (100) (M^+), (calcd for $C_{10}H_{14}N_2O_4$, 226.0954), 182 (45), 166 (60), 138 (65), 122 (72), 85 (77). Anal. Calad for CHN: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.12; H, 6.26; N, 12.32. *Compound* **4i**: colorless crystals, mp 210 °C. IR: ν_{max} cm^{-1} 3452, 3224, 3181, 2673, 1692, 1605, 1572, 1547, 1530, 1410, 1350, 1210, 985. ^1H NMR (CD_3OD): δ 1.24 (t, J = 6.9 Hz, 3H), 2.56 (s, 3H), 2.36 (q, J = 6.9 Hz, 2H), 4.56 (s br, exch. D_2O, 2H), 11.45 (s br, exch. D_2O, 2H). ^{13}C NMR (CD_3OD): δ_C 16.8, 22.4, 30.5, 109.5, 109.7, 110.4, 158.1, 166.1, 169.4, 169.6. HRMS: *m*/*z* (rel. int.) 224.0790 (100) (M^+), (calcd for $C_{10}H_{12}N_2O_4$, 224.0797), 183 (42), 180 (45), 139 (43), 136 (72), 107 (50), 85 (31). Anal. Calad for CHN: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.59; H, 5.36; N, 12.48. *Compound* **5i**: colorless crystals, mp 187 °C. IR: ν_{max} cm^{-1} 3455, 3220, 3184, 2675, 1692, 1606, 1576, 1544, 1533, 1410, 1352, 1210, 986. ^1H NMR (CD_3OD): δ 1.27 (t, J = 6.7 Hz, 3H), 2.48 (q, J = 6.7 Hz, 2H), 2.55 (s, 3H), 3.85 (s br, exch. D_2O, 2H), 6.73 (s, 1H), 11.20 (s br, exch. D_2O, 1H). ^{13}C NMR (CD_3OD): δ_C 16.0, 22.5, 31.2, 107.3, 108.8, 160.0, 163.6, 164.1, 169.8. HRMS: *m*/*z* (rel. int.) 180.0895 (100) (M^+), (calcd for $C_9H_{12}N_2O_2$, 180.0899), 139 (42), 136 (72b), 107 (49), 85 (31). Anal. Calad for CHN: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.96; H, 6.78; N, 15.56.
28. *General procedure for lithium–aluminum hydride reduction of* **3a–3j**: see Supplementary data.
29. *Spectral data of selected reduced products* (**6a**): colorless crystals, mp 192 °C. IR: ν_{max} cm^{-1} 3240, 3231, 2977, 1640, 1469, 1373, 1350, 1238, 1145, 927. ^1H NMR $(CDCl_3)$: δ 1.14 (s, 3H), 1.27 (s, 6H), 1.78 (s br, exch. D_2O, 4H), 2.0 (s br, exch. D_2O, 2H), 3.62 (t, J = 3.2 Hz, 4H), 4.77 (s, 1H). ^{13}C NMR $(CDCl_3)$: δ_C 16.9, 22.1 (2C), 38.5 (2C, 2x CH_2), 45.2, 60.9, 79.5, 162.6, 168.3. HRMS: *m*/*z* (rel. int.) 196.1694 (100) (M^+), (calcd for $C_{10}H_{20}N_4$, 196.1688), 151 (44), 122 (78), 114 (39), 85 (45), 84 (50), 56 (64), 43 (36). Anal. Calad for CHN: C, 61.19; H, 10.27; N, 28.54. Found: C, 61.16; H, 10.25; N, 28.50. *Compound* **6f**: colorless crystals, mp 167 °C. IR: ν_{max} cm^{-1} 3230, 2980, 1650, 1641, 1560, 1465, 1456, 1450, 1380, 1350, 1275, 1240, 1210, 1180, 1040, 860, 970. ^1H NMR $(CDCl_3)$: δ 1.13 (s, 3H), 1.25 (s, 3H), 1.80 (s br, exch. D_2O, 4H), 2.10 (s br, exch. D_2O, 2H), 3.61 (t,

J = 3.2 Hz, 4H), 3.73 (s, 3H), 4.70 (s, 1H), 6.69 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ_C 16.5, 23.2, 36.1 (2C), 55.7, 57.4, 61.3, 84.9, 114.6 (2C), 129.9 (2C), 134.6, 157.8, 162.3, 168.5. HRMS: *m*/*z* (rel. int.) 288.1956 (100) (M^+), (calcd for $C_{16}H_{24}N_4O$, 288.1950), 243 (40), 214 (78), 182 (40), 177 (45), 148 (65), 84 (51), 43 (33). Anal. Calad for CHN: C, 66.64; H, 8.39; N, 19.43. Found: C, 66.68; H, 8.36; N, 19.48.

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