Tetrahedron Letters 50 (2009) 7096–7098

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Multicomponent one-pot solvent-free synthesis of functionalized unsymmetrical dihydro-1*H*-indeno[1,2-*b*]pyridines

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ARTICLE INFO

Article history:
Received 12 September 2009
Revised 29 September 2009
Accepted 3 October 2009
Available online 8 October 2009

Keywords:
Multicomponent reaction
One-pot synthesis
Indenopyridine
Hantzsch reaction
Solvent-free

ABSTRACT

A simple and efficient synthesis of 4-aryl-4,5-dihydro-1*H*-indeno[1,2-*b*]pyridine derivatives has been achieved via a four-component cyclocondensation of 1,3-indanedione, aromatic aldehydes, β-ketoesters and ammonium acetate in one-pot in the absence of catalyst and solvent at room temperature on grinding. The present approach offers several advantages such as shorter reaction times, higher yields, low cost, simple work-up and easy purification.

The developing of new multicomponent reactions (MCRs) and improving the known MCRs are an area of considerable current interest. However, if the one-pot MCRs could be carried out under solvent- and catalyst-free conditions, it would be most efficient synthetic methods of organic synthesis. As opposed to the classical way to synthesize complex molecules by sequential synthesis, MCRs allow the assembly of complex molecules in one-pot and show a facile execution, high atom-economy and high selectivity.[1] As a one-pot reaction, MCRs generally afford good yields and are fundamentally different from two-component and stepwise reactions in several aspects[2] and permitted a rapid access to combinatorial libraries of complex organic molecules for an efficient lead structure identification and optimization in drug discovery.

Dihydropyridine derivatives possess a variety of biological activities[3] and drugs such as nifedipine, nicardipine and amlodipine are effective cardiovascular agents for the treatment of hypertension.[3d,e] In particular, indenopyridines (azafluorenes) are one of the most important privileged medicinal scaffolds, which were developed initially as antihistamines[4a] but shown inadvertently to cause antispermatogenic effects[4b,c] in various species and are useful inhibitors of spermatogenesis in animals,[5] and showed a fungicidal activity.[6] Compounds with this motif show a wide range of pharmacological activities. Hydrogenated indenopyridines have valuable therapeutic uses.[7] They lower serum lipids, in particular the triglycerides, and are used for the therapy of primary hyperlipidemias and certain other hyperlipidemias. They also have potential antidepressant activity.[8]

Indeno[1,2-*b*]pyridines have been synthesized in good yields by two-component (under reflux in high boiling solvents such as toluene, xylene and dioxane in the presence of acid or base catalysts),[9–11] three-component (at 70 °C)[12a] and four-component reactions (under solvent-free MW irradiation).[12b,c] 5-Oxo-1*H*-4,5-dihydroindeno[1,2-*b*]pyridines have been synthesized by the condensation of 2-arylideneindane-1,3-diones with β-aminocrotonates in refluxing acetic acid.[13] 4-Aryl-2-oxo-2,5-dihydro-1*H*-indeno[1,2-*b*]pyridines were synthesized by three-component reaction in the presence of sodium hydroxide under solvent-free condition.[14] A green method for the synthesis of indeno[2,1-*c*]pyridines in ionic liquid catalyzed by malononitrile has been developed.[15] Recently, a MCR of indane-1,3-dione, an aldehyde and an amine-containing aromatic compound leading to the formation of indenopyridine-based heterocyclic medicinal scaffolds has been investigated.[16] However, the use of high temperatures, expensive catalysts and longer reaction times limits the use of these methods. Therefore, the search for a better method for the synthesis of dihydroindenopyridines is of prime importance.

In recent days the progress of solvent- and catalyst-free synthesis has attracted the attention of chemists as they are environmentally benign processes. There are many reactions (Grignard,[17] Aldol condensation,[18] Reformatsky reaction,[19] Dieckmann condensation,[20] Knoevenagel condensation[21] and polyhydroquinoline synthesis[22]), which have been reported under solvent-free condition at room temperature on grinding. As part of our continued interest[23] in the development of facile multi-

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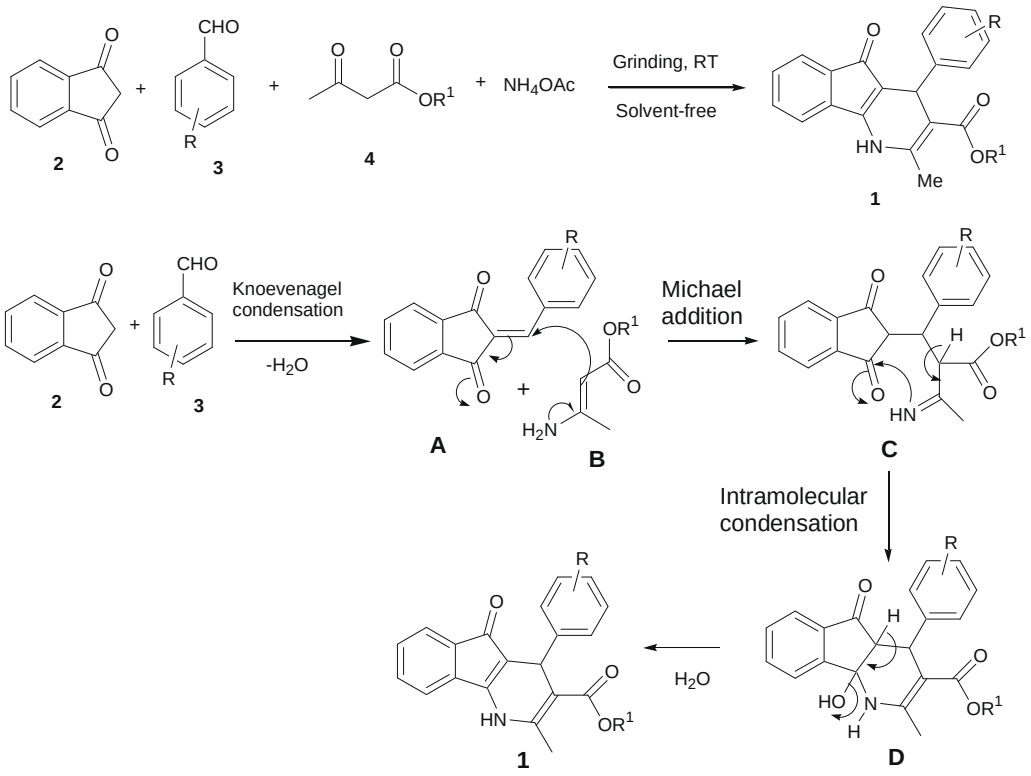
doi:10.1016/j.tetlet.2009.10.022



Scheme 1. Synthesis of 4-aryl-5-oxo-4,5-dihydro-1*H*-indeno[1,2-*b*]pyridines.

component reaction, herein we report a very simple and highly efficient one-pot method for the synthesis of unsymmetrical dihydro-1*H*-indeno[1,2-*b*]pyridine derivatives via a multicomponent process under solvent- and catalyst-free conditions (Scheme 1).

4-Aryl-4,5-dihydro-1*H*-indeno[1,2-*b*]pyridines have been synthesized via four-component cyclocondensation of 1,3-indanedione (1.0 mmol), aldehyde (1.0 mmol), β-ketoester (1.0 mmol) and ammonium acetate (1.5 mmol) in a mortar at room temperature on grinding.[24] From a mechanistic point of view, the first step is the formation of Knoevenagel product **A**. The second key intermediate is ester enamine **B**, produced by the condensation of β-ketoester with ammonia. Condensation of these two fragments gives the acyclic Michael adduct intermediate **C**, which undergoes intramolecular cyclization with participation of the amino function and one of the indanedione carbonyl group to form the dihydroindenopyridine **1**. A mechanistic rationale portraying the probable sequence of events for the formation of 4-aryl-4,5-dihydro-1*H*-indeno[1,2-*b*]pyridines is given in Scheme 1. All the synthesized compounds have been characterized by elemental and spectral (IR, ^{1}H, ^{13}C NMR and mass) studies (Table 1).

Investigations of the reaction scope revealed that various aromatic aldehydes (bearing electron-withdrawing and electron-donating groups) and esters can be utilized in this protocol (Table 1). It has been observed that better yields are obtained with substrates having electron-withdrawing groups. In the case of *ortho*-substituted aldehydes the yields are slightly lower (probably due to steric hindrance) than *para*-substituted ones. A possible explanation for the better yield in solvent-free conditions is that the eutectic mixture having uniform distribution of the reactants brings the reacting species in close proximity to react than in solvent. It may be considered that the environment of the reaction system without solvent is different from that in the solutions, resulting in a higher concentration of local reaction sites, and improving the global efficiency.

Table 1
Synthesis of indeno[1,2-*b*]pyridines (**1a**–**o**)

Entry	R	R^1	Product	Time (min)	Yield[a] (%)
1	H	Et	**1a**	12	79
2	*p*-NO_2	Et	**1b**	5	87
3	*p*-Cl	Et	**1c**	15	86
4	*p*-OH	Et	**1d**	17	73
5	*o*-OMe	Et	**1e**	20	67
6	*p*-OMe	Et	**1f**	20	71
7	*p*-CH_3	Et	**1g**	18	71
8	2,4-Cl_2	Et	**1h**	15	74
9	*o*-Cl	Et	**1i**	20	72
10	*o*-NO_2	Et	**1j**	12	75
11	*m*-NO_2	Et	**1k**	20	69
12	H	Me	**1l**	10	77
13	*p*-NO_2	Me	**1m**	7	85
14	*p*-Cl	Me	**1n**	12	83
15	*p*- CH_3	Me	**1o**	15	73

[a] Isolated yield.

In conclusion, we have developed a facile and efficient one-pot, four-component synthesis of 1*H*-indeno[1,2-*b*]-pyridines under solvent- and catalyst-free conditions at room temperature in high yields. The key step in our synthetic sequence is the intramolecular condensation with participation of the amino function and one of the indanedione carbonyl group in the acyclic intermediate resulting in ring closure to form the 1*H*-indeno[1,2-*b*]pyridines. The milder conditions, shorter reaction times, low costs, easy work-up and high yields make this process attractive over the other available methods.

Acknowledgement

S.S. and G.C.N. are thankful to the Council for Scientific and Industrial Research (CSIR), New Delhi, for financial assistance in the form of Senior Research Fellowship.

References and notes

1. (a) Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 734; (b) Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187. and references cited therein; (c)For a monograph, see: *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; (d) Domling, A. *Chem. Rev.* **2006**, *106*, 17; (e) D'Souza, D. M.; Mueller, T. J. *Chem. Soc. Rev.* **2007**, *36*, 3169; (f) Cariou, C. C. A.; Clarkson, G. J.; Shipman, M. *J. Org. Chem.* **2008**, *73*, 9762; (g) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (h) Weber, L.; Illegen, K.; Almstetter, M. *Synlett* **1999**, 366; (i) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831; (j) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471; (k) da Silva, E. N., Jr. *Res. J. Chem. Environ.* **2007**, *11*, 90.
2. (a) Weber, L. *Drug Discovery Today* **2002**, *7*, 143; (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51; (c) Tempest, P. A. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 776; (d) Kalinski, C.; Lemoine, H.; Schmidt, J.; Burdack, C.; Kolb, J.; Umkehrer, M.; Ross, G. *Synlett* **2008**, 4007; (e) Emelen, K. V.; Wit, T. D.; Hoornaert, G. J.; Compernolle, F. *Tetrahedron* **2002**, *58*, 4225.
3. (a) Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 279; (b) Mager, P. P.; Coburn, R. A.; Solo, A. J.; Trigle, D. J.; Rothe, H. *Drug Des. Discov.* **1992**, *8*, 273; (c) Mannhold, R.; Jablonka, B.; Voigdt, W.; Schoenafinger, K.; Schravan, K. *Eur. J. Med. Chem.* **1992**, *27*, 229; (d) Buhler, F. R.; Kiowski, W. *J. Hypertens.* **1987**, *5*, S3; (e) Reid, J. L.; Meridith, P. A.; Pasanisi, F. *J. Cardiovasc. Pharmacol.* **1985**, *7*, S18; (f) Debache, A.; Ghalem, W.; Boulcina, R.; Belfaitah, A.; Rhouati, S.; Carboni, B. *Tetrahedron Lett.* **2009**, *50*, 5248; (g) Wang, S.-X.; Li, Z.-Y.; Zhang, J.-C.; Li, J.-T. *Ultrason. Sonochem.* **2008**, *15*, 677.
4. (a) Augstein, J.; Ham, A. L.; Leeming, P. R. *J. Med. Chem.* **1972**, *15*, 466; (b) Hild, S. A.; Attardi, B. J.; Reel, J. *Biol. Reprod.* **2004**, *71*, 348; (c) Cook, C. E.; Wani, M. C.; Jump, J. M.; Lee, Y.-W.; Fail, P. A.; Anderson, S. A.; Gu, Y.-Q.; Petrow, V. *J. Med. Chem.* **1995**, *38*, 753.
5. Cook, C. E.; Lee, Y. W.; Wani, M. C.; Fail, P. A.; Jump, J. M. U.S. Patent 5,319,084, 1993; *Chem. Abstr.* **1995**, *122*, 265250a.
6. Umeda, N.; Saito, K.; Hosokowa, H.; Hashimoto, S. Jpn patent 303,771, 1991; *Chem. Abstr.* **1993**, *119*, 203428u.
7. a Kunstmann, R.; Granzer, E. U.S. Patent 3,980,656, 1976.; (b) Meyer, M. D.; DeBernardis, J. F.; Hancock, A. A. *J. Med. Chem.* **1994**, *37*, 105.
8. Kunstmann, R.; Fischer, G. *J. Med. Chem.* **1984**, *27*, 1312.
9. Kurihara, T.; Nakamura, K.; Hirano, H. *Chem. Pharm. Bull.* **1974**, *22*, 1839.
10. (a) El-Ossaily, Y. A. *Phosphorus, Sulfur Silicon* **2007**, *182*, 1109; (b) Abd, A. J.; Hassanein, E. B. *Synth. Commun.* **2000**, *30*, 3883.
11. Rong, L.; Han, H. X.; Jiang, H.; Zhang, Q.; Tu, S. *Synth. Commun.* **2009**, *39*, 1027.
12. (a) Petrow, V.; Saper, J.; Sturgeon, B. *J. Chem. Soc.* **1949**, 2134; (b) Hatamjafari, F. *Synth. Commun.* **2006**, *36*, 3563; (c) Zhou, J.-F.; Song, Y.-Z.; Lv, J.-S.; Gong, G.-X.; Tu, S. *Synth. Commun.* **2009**, *39*, 1443.
13. Muceniece, D.; Popelis, J.; Lusis, V. *Chemistry of Heterocyclic Compounds* **2008**, *44*, 35.
14. Rong, L.; Han, H.; Jiang, H.; Tu, S. *J. Heterocycl. Chem.* **2009**, *46*, 465.
15. Wang, X. S.; Wu, J. R.; Li, Q.; Yao, C. S.; Tu, S. J. *Synlett* **2008**, 1185.
16. Manpadi, M.; Uglinskii, P. Y.; Rastogi, S. K.; Cotter, K. M.; Wong, Y. S.; Anderson, L. A.; Ortega, A. J.; Van Slambrouck, S.; Steelant, W. F. A.; Rogelj, S.; Tongwa, P.; Antipin, M. Y.; Magedov, I. V.; Kornienko, A. *Org. Biomol. Chem.* **2007**, *5*, 3865.
17. Toda, F.; Takumi, H.; Yamaguchi, H. *Chem. Exp.* **1989**, *4*, 507.
18. Toda, F.; Tanaka, K.; Hamai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3207.
19. Tanaka, K.; Kishigami, S.; Toda, F. *J. Org. Chem.* **1991**, *56*, 4333.
20. Toda, F.; Suzuki, T.; Higa, S. *J. Chem. Soc.* **1998**, 3521.
21. Ren, Z.-J.; Cao, W.-G.; Tong, W.-Q. *Synth. Commun.* **2002**, *32*, 3475.
22. Kumar, S.; Sharma, P.; Kapoor, K. K.; Hundal, M. S. *Tetrahedron* **2008**, *64*, 536.
23. Nandi, G. C.; Samai, S.; Kumar, R.; Singh, M. S. *Tetrahedron* **2009**, *65*, 7129.
24. In a typical reaction procedure 1,3-indanedione (1.0 mmol), aldehyde (1.0 mmol), ethyl acetoacetate or methyl acetoacetate (1.0 mmol) and ammonium acetate (1.5 mmol) were thoroughly mixed in a mortar followed by grinding till the completion of reaction (monitored by TLC). The resultant solid material was washed thoroughly with water to remove any unreacted ammonium acetate and was air-dried overnight, which was purified by silica gel column chromatography using ethyl acetate and *n*-hexane as eluent.
2-Methyl-4-(4-nitrophenyl)-5-oxo-4,5-dihydro-1H-indeno-[1,2-b]pyridine-3-carboxylic acid ethyl ester (**1b**): mp 216–217 °C; FT-IR (KBr, cm^{-1}): 3294, 1702, 1653, 1599; ^1H NMR (300 MHz, $CDCl_3$): δ 8.13 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 6.9 Hz, 2H), 7.39–7.29 (m, 2H), 7.29 (d, J = 7.2 Hz, 1H), 7.09 (d, J = 7.2 Hz, 1H), 6.52 (s, 1H, NH, D_2O exchangeable), 5.13 (s, 1H), 4.07 (q, J = 7.5 Hz, 2H), 2.57 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.8, 166.7, 153.1, 152.9, 146.5, 144.6, 135.6, 133.5, 131.5, 130.5, 128.7, 123.6, 121.7, 117.2, 109.3, 106.8, 60.3, 37.7, 20.0, 14.0; ESI MS (m/z): 390.12 (M^++1). Anal. Calcd for $C_{22}H_{18}N_2O_5$: C, 67.69; H, 4.65; N, 7.18. Found: C, 67.58; H, 4.53; N, 7.32.
4-(4-Chlorophenyl)-2-methyl-5-oxo-4,5-dihydro-1H-indeno-[1,2-b]pyridine-3-carboxylic acid methyl ester (**1n**): mp 228–229 °C; FT-IR (KBr, cm^{-1}): 3275, 1707, 1639; ^1H NMR (300 MHz, DMSO-d_6): δ 10.22 (s, 1H, NH, D_2O exchangeable), 7.59–7.20 (m, 8H), 4.78 (s, 1H), 3.15 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 190.8, 167.1, 153.8, 145.5, 145.3, 136.0, 133.3, 131.7, 130.7, 130.1, 129.3, 128.1, 120.5, 119.3, 108.1, 105.7, 50.9, 36.5, 18.6; ESI MS (m/z): 366.16 (M^++1). Anal. Calcd for $C_{21}H_{16}NO_3Cl$: C, 68.95; H, 4.41; N, 3.83. Found: C, 68.90; H, 4.38; N, 3.72.