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A Practical and One-Pot Procedure for the Synthesis of 3-Amino-2-cyclohexen-1-one from 3-Aminophenol

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Abstract:

A simple, totally catalytic, and environmentally benign process for the synthesis of 3-amino-2-cyclohexen-1-one using 10% Pd/C-catalyzed hydrogenation has been developed.

3-Amino-2-cyclohexen-1-one (**1**), a cyclic enaminone, is a useful intermediate in organic synthesis as a synthon for the construction of biologically active compounds (such as dopamine autoreceptor agonists,[1] acetylcholinesterase inhibitors,[2] oxytocin antagonists,[3] anticonvulsants,[4] and K_{ATP} channel openers[5]) and functionally interesting heterocyclic compounds (such as pyridines or quinolines,[6−13] azaazulenes,[14] sesquiterpenes,[15] tetrahydro-1,3-oxazines,[16] and angucyclinone 5-aza-analogues[17]). The generally and industrially employed synthetic methods for the preparation of 1,3-amino-2-cyclohexen-1-one (**1**) are classified into three categories (Scheme 1). The first type of applicable methods is condensation of relatively expensive 1,3-cyclohexandione (**2**) with ammonia or ammonium acetate under refluxing conditions with azeotropic removal of water using hazardous solvents such as benzene.[6,17−24] These procedures usually require a large excess of ammonia or ammonium acetate. The second type of methods entails two-step procedures, viz., the Pd/C-catalyzed hydrogenation of 1,3-phenylenediamine (**3**) and subsequent hydrolysis of the resulting 3-amino-2-cyclohexen-1-imine (**4**) under strong basic conditions.[25] The third type of methods is the intramolocular cyclization of 5-oxohexanenitrile (**5**) under drastic (high heat and strong basic) conditions;[26] however, these methods involve some problems such as the relatively low selectivity of the cyclization and the cost of the substrate (**5**). Since environmentally benign synthetic procedures have been the focus of attention in recent years, development of an entirely catalytic, selective, mild, inexpensive, and new synthetic method of **1** to overcome all the problems of conventional methods[6,17−26] is an important goal.

We have recently developed a selective and reductive mono-*N*-alkylation method of amines using nitriles as an alkylating reagent under Pd/C- or Rh/C-catalysed hydrogenation conditions (Scheme 2).[27] During our efforts to extend the applicability of the mono-*N*-alkylation,[27] we observed that an unexpected reduction of an aromatic ring was proceeded by the use of 3-aminophenol (**6**) as a substrate, and the expected 3-ethylaminophenol (**7**) and unexpected 3-ethylamino-2-cyclohexen-1-one (**8**) and **1** were obtained as a mixture (Scheme 3). This led us to test whether the hydrogenation conditions without MeCN can produce only the reduced products, 3-amino-2-cyclohexen-1-one (**1**). We now disclose that the 10% Pd/C-catalyzed hydrogenation of 3-aminophenol (**6**) in MeOH is quite efficient in the synthesis of **1**.

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(1) Caprathe, B. W.; Jaen, J. C.; Wise, L. D.; Heffner, T. G.; Pugsley, T. A.; Meltzer, L. T.; Parvez, M. *J. Med. Chem.* **1991**, *34*, 2736−2746.
(2) Gatta, F.; Del Giudice, M. R.; Pomponi, M.; Marta, M. *Heterocycles* **1992**, *34*, 991−1004.
(3) Bell, I. M.; Erb, J. M.; Freidinger, R. M.; Gallicchio, S. N.; Guare, J. P.; Guidotti, M. T.; Halpin, R. A.; Hobbs, D. W.; Homnick, C. F.; Kuo, M. S.; Lis, E. V.; Mathre, D. J.; Michelson, S. R.; Pawluczyk, J. M.; Pettibone, D. J.; Reiss, D. R.; Vickers, S.; Williams, P. D.; Woyden, C. J. *J. Med. Chem.* **1998**, *41*, 2146−2163.
(4) Foster, J. E.; Nicholson, J. M.; Butcher, R.; Stables, J. P.; Edafiogho, I. O.; Goodwin, A. M.; Henson, M. C.; Smith, C. A.; Scott, K. R. *Bioorg. Med. Chem.* **1999**, *7*, 2415−2425.
(5) (a) Carrol, W. A.; Altenbach, R. J.; Bai, H.; Brioni, J. D.; Brune, M. E.; Buckner, S. A.; Cassidy, C.; Chen, Y.; Coghlan, M. J.; Daza, A. V.; Drizin, I.; Fey, T. A.; Fitzgerald, M.; Gopalakrishnan, M.; Gregg, R. J.; Henry, R. F.; Holladay, M. W.; King, L. L.; Kort, M. E.; Kym, P. R.; Milicic, I.; Tang, R.; Turner, S. C.; Whiteaker, K. L.; Yi, L.; Zhang, H.; Sullivan, J. P. *J. Med. Chem.* **2004**, *47*, 3163−3179. (b) Carroll, W. A.; Agrios, K. A.; Altenbach, R. J.; Buckner, S. A.; Chen, Y.; Coghlan, M. J.; Daza, A. V.; Drizin, I.; Gopalakrishnan, M.; Henry, R. F.; Kort, M. E.; Kym, P. R.; Milicic, I.; Smith, J. C.; Tang, R.; Turner, S. C.; Whiteaker, K. L.; Zhang, H.; Sullivan, J. P. *J. Med. Chem.* **2004**, *47*, 3180−3192.
(6) Zymalkowski, F.; Rimek, J. *Naturwissenschaften* **1960**, *47*, 83.
(7) Nitta, M.; Soeda, H.; Iino, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 932−934.
(8) Fernández, M.; Cuesta, E.; Avendaño, C. *Heterocycles* **1994**, *38*, 2615−2620.
(9) Mulamba, T.; Boukili-Garré, R. E.; Séraphin, D.; Noé, E.; Charlet-Fagnère, C.; Hénin, J.; Laronze, J.; Sapi, J.; Barret, R.; Laronze, J.-Y.; Lévy, J. *Heterocycles* **1995**, *41*, 29−36.
(10) Singh, K.; Singh, J.; Singh, H. *Tetrahedron* **1998**, *54*, 935−942.
(11) Pyrko, A. N. *Chem. Heterocycl. Compd.* **1999**, *35*, 688−694.
(12) (a) Miyabara, H.; Takayasu, T.; Nitta, M. *Heterocycles* **1999**, *51*, 983−987. (b) Miyabara, H.; Takayasu, T.; Nitta, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3199−3205.
(13) Albright, J. D.; Du, X. *J. Heterocycl. Chem.* **2000**, *37*, 41−46.
(14) Nitta, M.; Mori, S.; Iino, Y. *Heterocycles* **1991**, *32*, 23−28.
(15) Amougay, A.; Pete, J.-P.; Piva, O. *Tetrahedron Lett.* **1992**, *33*, 7347−7350.
(16) Bartoli, G.; Cimarelli, C.; Palmieri, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 537−543.
(17) Collet, S. C.; Rémi, J.-F.; Cariou, C.; Laib, S.; Guingant, A. Y.; Vu, N. Q.; Dujardin, G. *Tetrahedron Lett.* **2004**, *45*, 4911−4915.
(18) Dubas-Sluyter, M. A. T.; Speckamp, W. N.; Huisman, H. O. *Recueil* **1972**, *91*, 157−160.
(19) Iida, H.; Yuasa, Y.; Kibayashi, C. *Synthesis* **1982**, 471−472.
(20) Baraldi, P. G.; Simoni, D.; Manfredini, S. *Synthesis* **1983**, 902−903.
(21) Montes, I. F.; Burger, U. *Tetrahedron Lett.* **1996**, *37*, 1007−1010.
(22) Huang, Y.; Hartmann, R. W. *Synth. Commun.* **1998**, *28*, 1197−1200.
(23) Lin, Y.-L.; Wu, C.-S.; Lin, S.-W.; Huang, J.-L.; Sun, Y.-S.; Yang, D.-Y. *Bioorg. Med. Chem.* **2002**, *10*, 685−690.
(24) Quite recently, Arcadi et al. reported a mild condensation method of 1,3-cyclohexandione (**2**) with ammonia using $NaAuCl_4$ as a catalyst, although chromatographic purification processes were required to obtain the pure product, see: Arcadi, A.; Bianchi, G.; Giuseppe, S. D.; Marinelli, F. *Green Chem.* **2003**, *5*, 64−67.
(25) (a) Jacobson, S. E. U.S. Patent 5,149,874, 1992. (b) Iimuro, S. Pat. Appl. No. JP 1987-135451, 1987.
(26) (a) Kiso, Y.; Saeki, K. Pat. Appl. No. EP 1978-300885, 1978. (b) Cherubim, M.; AboDagga, F. Pat. Appl. No. JP 1973-34859, 1973.
(27) Sajiki, H.; Ikawa, T.; Hirota, K. *Org. Lett.* **2004**, *6*, 4977−4980.

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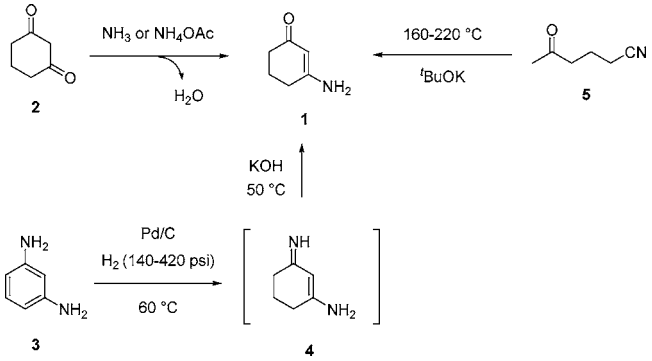
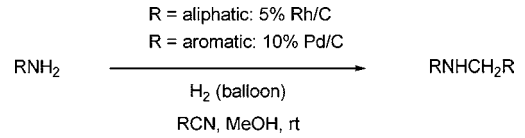
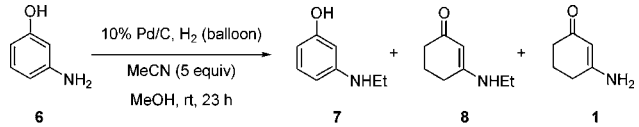
Scheme 1



Scheme 2

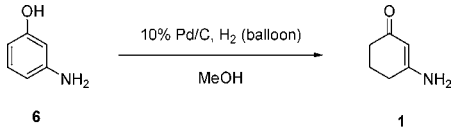


Scheme 3



7 : **8** : **1** = 30 : 60 : 10

Scheme 4



Temp.	Time (h)	**6** : **1**
rt	32	44 : 56
60 °C	14	0 : 100 (94)[a]

[a]Isolated Yield

Our protocol (Scheme 4) consists of stirring **6** with commercial 10% Pd/C (Aldrich, 10% of the weight of **1**) in MeOH under hydrogen atmosphere. Within 11 h stirring at 60 °C the hydrogenation was complete by TLC and GC-FID, while the hydrogenation at room temperature was incomplete even after 32 h stirring. After the reaction mixture was cooled to room temperature, the catalyst was filtered through a Celite cake or a membrane filter (Millipore Dimex-13, 0.22 μm), and the product (**1**) was isolated by simple solvent evaporation. As shown in Scheme 4, the desired 3-amino-2-cyclohexen-1-one (**1**) was prepared in 94% isolated yield from commercially available **6**. Over-reduction was not a problem, as the corresponding 3-aminocyclohexane was never observed. The reaction is very clean, and no chromatographic separation is required to obtain spectrally pure **1**.

In summary, a simple and totally catalytic process for the synthesis of 3-amino-2-cyclohexen-1-one (**1**) has been demonstrated. The mild and neutral conditions, quantitative yield of **1**, operational simplicity, easy availability, and low cost of the reagents make this process a more useful and practical alternative to the existing methods for the preparation of **1**.[6,17−26] The waste disposal of the process was greatly diminished compared with those of conventional methods.

Experimental Section

Materials. Reagents and solvents were obtained from commercial suppliers and were used without further purification. The 10% Pd/C was from Aldrich; other reagents were purchased from TCI or Wako. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively, on a JEOL spectrometer. Chemical shifts are expressed in ppm using TMS signal (f = 0.00) as internal reference. Mass spectrometry was performed on a JMS-SX 102A mass spectrometer in electron ionization mode. GC analyses were performed using a SHIMADZU GC-17A gas chromatography (DB-624 column, 60 m × 0.25 mm, df = 1.4 μm) equipped with a flame ionization detector with helium as the carrier gas. The following conditions were used in the GC analysis: injector temperature 260 °C, 200 °C (hold 5 min) to 255 °C (hold 25 min) at 20 °C/min temperature program. Thin-layer chromatography used 0.25 mm thick silica gel 60 F_{254} plates (Art 5715, Merk) using UV light.

10% Pd/C-Catalyzed Hydrogenation of 3-Aminophenol in MeOH in the Presence of MeCN.[27] After two vacuum/H_2 cycles to remove air from the reaction tube, a mixture of the 3-aminophenol (109 mg, 1.00 mmol), MeCN (216 μL, 5 mmol), 10% Pd/C (10.9 mg, 10 wt % of the substrate) in MeOH was stirred at room temperature under ambient pressure of hydrogen (balloon). The reaction was filtered through a membrane filter (Millipore Dimex-13, 0.22 μm), and the filtrate was concentrated under reduced pressure. The ratio of the 3-ethylamino phenol (**7**), 3-(ethylamino)-2-cyclohexen-1-one (**8**), and 3-amino-2-cyclohexen-1-one (**1**) was confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$.

Preparation of 3-Amino-2-cyclohexen-1-one (1). After two vacuum/H_2 cycles to remove air from the reaction tube, a mixture of the 3-aminophenol (5.46 g, 50.0 mmol), 10% Pd/C (546 mg, 10 wt % of the substrate) in MeOH (50 mL) was stirred at 60 °C under ambient pressure of hydrogen (balloon). The reaction was filtered through a Celite cake, and the filtrate was concentrated under reduced pressure to afford analytically pure 3-amino-2-cyclohexene-1-one (**1**) (5.23 g, 94% yield). R_f ($CHCl_3$:MeOH = 5:1) 0.31. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76 (m, 2H), 1.98 (t, J = 6.3 Hz, 2H), 2.25 (t, J = 6.3 Hz, 2H), 4.90 (s, 1H), 6.66 (brs, NH_2). ^{13}C NMR (100 MHzs, DMSO-d_6): δ 194.3, 167.0, 97.5, 35.9, 27.9, 21.5. MS (EI): 111 (34), 84 (84), 83 (55), 66 (100), 55 (23); GC 100.0, AUC, t_R = 16.66 min.

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Supporting Information Available

^{1}H and ^{13}C NMR spectra and GC data and the GC chart for the compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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