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$KAL(SO_4)_2.12H_2O$: AN EFFICIENT CATALYST FOR THE STEREOSELECTIVE SYNTHESIS OF *CIS*-ISOQUINOLONIC ACIDS

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Abstract – $KAl(SO_4)_2.12H_2O$ is found to catalyze efficiently the stereoselective cyclocondensation of homophthlic anhydride with imines under mild conditions to afford the corresponding *cis*-isoquinolonic acids in good yields.

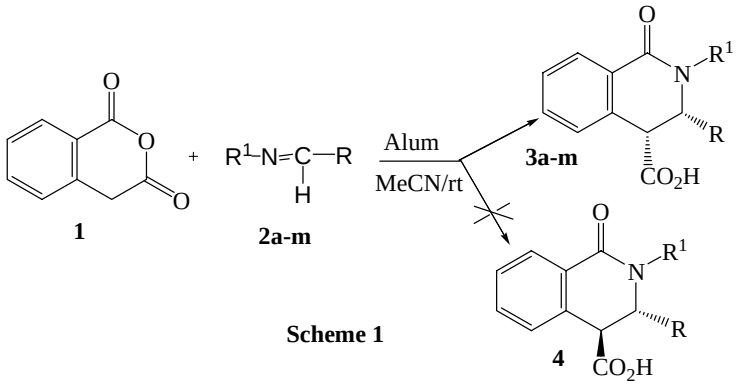
Isoquinolonic acids have been reported as starting materials for the total synthesis of natural compounds such as nitidine chloride,[1] 4-epicorynoline, corynoline, 6-oxocorynoline[2] and decumbenine B.[3] In addition, isoquinolonic acids show some pharmacological and biological activities[4] including anti-inflammatory and psychotropic.

There exist numerous methods for the synthesis of isoquinolonic acids and their derivatives.[5] By various catalysts such as Lewis acids ($ZnCl_2$, $FeCl_3$, $AlCl_3$), protic acids (CH_3COOH, HCl), or bases (TEA, DIEA) etc., a mixture of *cis*- and *trans*- products or complicated mixtures were formed. Recently, BF_3-Et_2O[6] and trimethyl orthoformate[7] have been employed for the preparation of *trans*-isoquinolonic acids, and ionic liquids[8] have been employed for the synthesis of *cis*-isomers.

In view of our general interest in the chemistry of imines,[9] we wish to report the stereoselective synthesis of *cis*-isoquinolonic acids. In this direction, the use of a $KAl(SO_4)_2.12H_2O$ (alum), which is relatively nontoxic and inexpensive, is the center of our study.[10] In the course of our research on application of $KAl(SO_4)_2.12H_2O$ in organic reactions, we have found that alum was an effective promoter in the preparation of *cis*-isoquinolonic acids.

When a mixture of homophthalic anhydride **(1)** and imine[11] **(2a)** in acetonitrile was stirred at rt in the presence of a catalytic amount (0.5 equiv. mol) of alum, the reaction was completed within 8 h. Work-up of the reaction mixture showed that isoquinolonic acid **(3a)** was prepared in 91% yield (Scheme 1).

Interestingly, we have found that this reaction is highly stereoselective in the preparation of *cis*-isoquinolonic acid, since there is no evidence for the formation of *trans*-diasteroisomer **(4)**.



Scheme 1

Promoted by this success, we extended this reaction of homophthalic anhydride with a range of other imines **(2b-i)** under similar conditions, furnishing the respective *cis*-isoquinolonic acids **(3b-i)** in good yields. The optimized results are summarized in Table 1. The all *cis*-stereochemistry of cycloadducts **(3)** was attributed from the two doublets (J=4.6-6.9 Hz) observed close to 4.52-4.99 ppm and 4.96-5.97 ppm, for the H-3 and H-4 hydrogen's, respectively.

The structures of the products were characterized by IR, ^{1}H NMR, ^{13}C NMR spectra, MS spectra, and elemental analyses.

Table 1. Alum-catalyzed reaction of homophthalic anhydride with imines

Product 3	R	R^1	Time (h)	Yield[a] (%)	mp	Lit. mp
A	Ph	Ph	6.5	91	201-203	198[8]
B	Ph	4-ClC_6H_4	6	89	200-201	182[8]
C	Ph	4-MeC_6H_4	6	90	187-188	178[8]
D	Ph	$PhCH_2$	7	87	179-180	-
E	4-ClC_6H_4	$PhCH_2$	8	89	180-181	-
F	Ph	$PhCH_2CH_2$	8	86	168-170	-
G	Ph	2-Benzimidazolyl	8.5	87	222-224 (decomp)	-
H	4-$NO_2C_6H_4$	4-MeC_6H_4	7	86	246-248 (decomp)	-
I	4-BrC_6H_4	4-ClC_6H_4	7.5	85	225-226 (decomp)	-

[a]Yields based on homophthalic anhydride.

In summary, we have described a successful strategy, efficient and convenient green synthesis for the preparation of tetrahydroisoquinolonic acids in cyclocondensation reaction of homophthalic anhydride with imines using the inexpensive, non-toxic, and easily available $KAl(SO_4)_2.12H_2O$ catalyst. The method offers several advantages including high yield of products, recyclable of the catalyst and easy experimental work-up procedure. Surprisingly, this reaction is stereoselective in the preparation of *cis*-isoquinolonic acids, since no detectable amount of *trans*-isomers, which makes it a useful process for the synthesis of *cis*-isoquinolonic acids.

EXPERIMENTAL

Melting points were measured on the Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Shimadzu IR-470 Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were determined on a bruker 500 DRX AVNCE instrument at 500 and 125 MHz, respectively. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

General procedure: A mixture of homophthalic anhydride (162 mg, 1 mmol), imines (1 mmol), alum (0.24 g, 0.5 mmol), and acetonitrile (8-10 mL) in a 25 mL flask was stirred at rt for the time period as indicated in Table 1. After completion of the reaction (monitored by TLC, ethyl acetate/n-hexane 1/1), the solvent was evaporated under reduced pressure, then water (25 mL) was added to the reaction mixture and the resulting solid was separated by filtration. The crude product was washed with chloroform and ether to afford pure *cis*-isoquinolonic acids in 82-94% yields.

General procedure for recovered catalyst: The catalyst in the aqueous phase can be recovered by removing the water under vacuum then washed with acetone and drying at rt.

Spectral data for new product:

***cis*-2-Benzyl-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxlic acid (3d):** White powder, IR (KBr), (ν_{max} /cm^{-1}): 3025, 2910, 1742, 1613. ^{1}H NMR (DMSO-d_6) δ_H: 3.75 (d, 1H, *J*=15.3 Hz, CH_2), 4.69 (d, 1H, *J*=6.0 Hz, H3), 4.96 (d, 1H, *J*=6.0 Hz, H4), 5.31 (d, 1H, *J*=15.3 Hz, CH_2), 6.96-7.57 (m, 13H), 8.08 (d, 1H, *J*=7.5 Hz), 12.99 (br, 1H). ^{13}C NMR (DMSO-d_6) δ_C: 48.55, 48.57, 61.18, 127.69, 127.93, 127.97, 128.03, 128.25, 128.50, 128.75, 129.01, 129.18, 132.52, 134.15, 137.79, 163.59, 170.72. MS (*m/z*, %): 358 (M^++1, 25), 357 (35), 269 (30), 207 (25), 136 (30), 118 (80), 116 (75), 91 (100), 77 (35), 62 (30), 51 (35), 39 (30). Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.20; H, 5.27; N, 3.83.

***cis*-2-Benzyl-3-(4-chlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxlic acid (3e):** White powder, IR (KBr), (ν_{max} /cm^{-1}): 3050, 2905, 1737, 1608. ^{1}H NMR (DMSO-d_6) δ_H: 3.83 (d, 1H, *J*=15.3 Hz, CH_2), 4.70 (d, 1H, *J*=6.2 Hz, H3), 4.99 (d, 1H, *J*=6.2 Hz, H4), 5.24 (d, 1H, *J*=15.3 Hz, CH_2), 6.94-7.55 (m, 13H), 8.07 (d, 1H, *J*=7.5 Hz), 13.02 (br, 1H). ^{13}C NMR (DMSO-d_6) δ_C: 48.52, 48.72, 60.55, 127.69, 128.03, 128.10, 128.49, 128.71, 128.97, 129.03, 130.08, 132.65, 133.39, 133.91, 136.24, 137.67, 163.46, 170.69. MS (*m/z*, %): 391 (M^+, 15), 347 (40), 242 (40), 207 (30), 178 (35), 118 (45), 106 (45), 91 (100), 65 (50), 51 (30), 39(30). Anal. Calcd for $C_{23}H_{18}NO_3Cl$: C, 70.50; H, 4.63; N, 3.57. Found: C, 70.43; H,

4.54; N, 3.514.54; N, 3.51.

***cis*-1-Oxo-2-phenylethyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxlic acid (3f):** White powder, IR (KBr), (ν_{max} /cm^{-1}): 3025, 2910, 1738, 1614. ^{1}H NMR (DMSO-d_6) δ_H: 2.67 (m, 1H, CH_2), 2.86-2.92 (m, 1H, CH_2), 2.98-3.04 (m, 1H, CH_2), 4.01-4.06 (m, 1H, CH_2), 4.52 (d, 1H, *J*=6.2 Hz, H3), 4.98 (d, 1H, *J*=6.2 Hz, H4), 6.97 (d, 2H, *J*=6.2 Hz), 7.16-7.19 (m, 6H), 7.25-7.28 (m, 2H), 7.41-7.44 (m, 1H), 7.49 (m, 2H), 8.02 (d, 1H, *J*=6.8 Hz), 12.91 (br, 1H). ^{13}C NMR (DMSO-d_6) δ_C: 34.05, 48.14, 48.45, 62.00, 126.73, 127.70, 127.84, 128.24, 128.34, 128.63, 128.67, 128.89, 129.08, 129.40, 132.31, 134.06, 137.74, 139.54, 163.13, 170.79. MS (*m/z*, %): 371 (M^+, 10), 353 (15), 327 (25), 280 (35), 236 (80), 221 (30), 207 (60), 174 (40), 146 (25), 118 (40), 91 (100), 92 (30), 65 (30), 51 (30), 44 (30), 39(25). Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.60; H, 5.70; N, 3.77. Found: C, 77.51; H, 5.64; N, 3.67.

***cis*-2-(2-1*H*-Benzoimidazolyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxlic acid (3g):** White powder, IR (KBr), (ν_{max} /cm^{-1}): 3060, 2915, 1700, 1657. ^{1}H NMR (DMSO-d_6) δ_H: 4.61 (d, 1H, *J*=6.5 Hz, H3), 5.96 (d, 1H, *J*=6.5 Hz, H4), 7.29-7.43 (m, 7H), 7.47-7.57 (m, 3H), 7.60 (m, 1H), 7.65 (d, 1H, *J*=7.7 Hz), 8.03 (d, 1H, *J*=7.6 Hz), 12.53 (br, 1H). ^{13}C NMR (DMSO-d_6) δ_C: 49.19, 79.08, 80.35, 124.91, 126.27, 127.28, 128.08, 128.21, 128.72, 128.93, 128.98, 129.02, 129.23, 129.83, 130.22, 134.40, 134.85, 137.26, 137.97, 163.97, 171.58. MS (*m/z*, %): 383 (M^+, 10), 368 (20), 313 (15), 250 (35), 178 (35), 118 (100), 105 (60), 90 (95), 77 (75), 63 (55), 51 (65), 39(45). Anal. Calcd for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96. Found: C, 71.91; H, 4.40; N, 10.87.

***cis*-3-(4-Nitrophenyl)-1-oxo-2-*p*-tolyl-1,2,3,4-tetrahydroisoquinoline-4-carboxlic acid (3h):** White powder, IR (KBr), (ν_{max} /cm^{-1}): 3065, 2915, 1723, 1630, 1598. ^{1}H NMR (DMSO-d_6) δ_H: 2.23 (s, 3H, CH_3), 4.99 (d, 1H, *J*=5.1 Hz, H3), 5.97 (d, 1H, *J*=5.1 Hz, H4), 7.09 (m, 4H), 7.31 (d, 2H, *J*=8.2), 7.49-7.61 (m, 3H), 8.03 (d, 2H, *J*=8.2 Hz), 8.08 (d, 1H, *J*=7.2 Hz), 12.52 (br, 1H). ^{13}C NMR (DMSO-d_6) δ_C: 48.74, 63.40, 123.04, 127.15, 127.43, 127.73, 127.83, 129.10, 129.27, 132.38, 136.01, 138.59, 144.92, 146.95, 162.68, 170.20. MS (m/z, %): 402 (M^+, 10), 383 (15), 356 (50), 295 (40), 252 (25), 240 (50), 193 (30), 165 (20), 118 (70), 106 (100), 90 (60), 77 (30), 63 (35), 51 (30), 39 (50). Anal. Calcd for $C_{23}H_{18}N_2O_5$: C, 68.65; H, 4.51; N, 6.96. Found: C, 68.59; H, 4.47; N, 6.87.

***cis*-3-(4-Bromophenyl)-2-(4-chlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxlic acid (3i):** White powder, IR (KBr), (ν_{max} /cm^{-1}): 3065, 2920, 1723, 1630. ^{1}H NMR (DMSO-d_6) δ_H: 4.86 (d, 1H, *J*=4.9 Hz, H3), 5.54 (d, 1H, *J*=4.9 Hz, H4), 6.94-6.99 (m, 4H), 7.20-7.28 (m, 4H), 7.36-7.59 (m, 5H), 8.05 (d, 1H, *J*=7.5 Hz), 2.43 (br, 1H). ^{13}C NMR (DMSO-d_6) δ_C: 48.87, 63.17, 127.57, 127.68, 127.81, 128.48, 128.57, 128.96, 129.21, 129.99, 130.81, 131.00, 132.45, 134.11, 136.40, 139.38, 162.80, 170.24. MS

(*m/z*, %): 456 (M^++1, 15), 412 (55), 345 (50), 301 (60), 267 (45), 257 (35), 223 (25), 193 (30), 178 (20), 118 (60), 106 (100), 90 (50), 77 (35), 63 (30), 51 (30), 39 (55). Anal. Calcd for $C_{22}H_{15}NO_3BrCl$: C, 57.86; H, 3.31; N, 3.07. Found: C, 57.78; H, 3.22; N, 2.98.

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REFERENCES

1. M. Cushman and L. Cheng, *J. Org. Chem.,* 1978, **43**, 286.
2. M. Cushman, A. Abbaspour, and Y. P. Gupta, *J. Am. Chem. Soc.,* 1983, **105**, 2873.
3. X. Y. Xu, G. W. Qin, R. S. Xu, and X. Z. Zhu, *Tetrahedron,* 1998, **54**, 14179.
4. (a) J. V. Johnson, S. Rauckman, P. D. Baccanari, and B. Roth, *J. Med. Chem.,* 1989, **32**, 1942. (b) E. Stanoeva and M. Haimova, *Khim. Geterotsikl. Soedin.,* 1984, 1587. (c) M. A. Haimova, N. M. Mollov, S. C. Ivanova, A. I. Dimitrova, and V. I. Ognyanov, *Tetrahedron,* 1977, **33**, 331. (d) N. Yamada, S. Kadowaki, K. Takahashi, and K. Umeu, *Biochem. Pharmacol.,* 1992, **44**, 1211.
5. (a) M. Cushman and E. J. Madaj, *J. Org. Chem.,* 1987, **52**, 907. (b) M. Cushman, J. Gentry, and F. W. Dekow, *J. Org. Chem.,* 1977, **42**, 1111. (c) B. Bonnaud, A. Carlessi, and D. C. H. Bigg, *Heterocycl. Chem.,* 1993, **30**, 257. (d) M. A. Haimova, N. M. Mollov, S. C. Ivanova, A. I. Dimitrova, and V. I. Ognyanov, *Tetrahedron,* 1977, **33**, 331. (e) M. P. Stoyanova, I. D. Kozekov, and M. D. Palamareva, *J. Heterocycl. Chem.,* 2003, **40**, 795.
6. N. Yu, L. Bourel, B. Deprez, and J. C. Gesquiere, *Tetrahedron Lett.,* 1998, **39**, 829.
7. N. Yu, R. Poulain, and J. C. Gesquiere, *Synlett,* 2000, 355.
8. J. S. Yadav, B. V. S. Reddy, K. Saritha Raj, and A. R. Prasad, *Tetrahedron,* 2003, **59**, 1805.
9. (a) J. Azizian, A. A. Mohammadi, F. Ardakani, A. R. Karimi, and M. R. Mohammadizadeh, *Heterocycles,* 2004, **63**, 791. (b) J. Azizian, A. Varasteh Morady, S. Soozaangarzadeh, and A. Asadi, *Tetrahedron Lett.,* 2002, **43**, 9721. (c) J. Azizian, A. Asadi, and K. Jadidi, *Synth. Commun.,* 2001, **31**, 2727. (d) J. Azizian, M. Mehrdad, K. Jadidi, and Y. Sarrafi, *Tetrahedron Lett.,* 2000, **41**, 5265.
10. (a) J. Azizian, Ali A. Mohammadi, Ali A. Karimi, and M. R. Mohammadizadeh, *J. Chem. Res.,* in press. (b) 6th International symposium on catalysis applied to fine chemicals. April 6-10, 2003, Delft University of Technology, The Netherlands. (c) 10th Blue Danube symposium on heterocyclic chemistry. September 3-6, 2003, Vienna, Austria.
11. For synthesis of imines see: P. Mangeney, T. Tejero, A. Alexakis, F. Grosjean, and J. Normant, *Synthesis,* 1988, 255.