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A Stereoselective Three-Component Reaction: $KAl(SO_4)_2 \cdot 12H_2O$, an Efficient and Reusable Catalyst for the One-Pot Synthesis of *cis*-Isoquinolonic Acids

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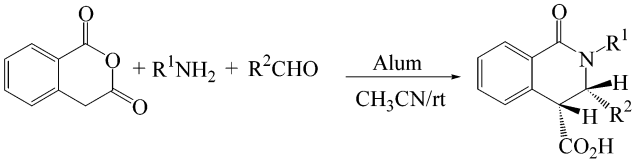
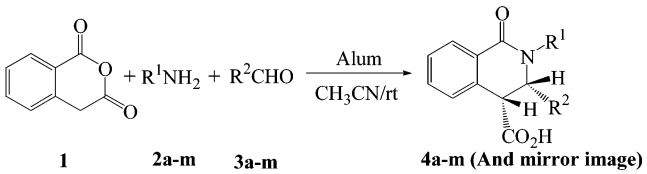


$KAl(SO_4)_2 \cdot 12H_2O$ is found to catalyze efficiently the stereoselective one-pot three-component cyclocondensation of homophthalic anhydride, aldehydes, and amines under mild conditions to afford the corresponding *cis*-isoquinolonic acids in good yields.

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 antiinflammatory 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, $BF_3 \cdot Et_2O$[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.

SCHEME 1. Synthesis of the *cis*-Isoquinolonic Acids 4a−m



Multicomponent condensations (MCCs) constitute an especially attractive synthetic strategy for rapid and efficient library generation due to the fact that the products are formed in a single step and the diversity can be achieved simply by varying the reacting components. Very recently, we have reported the preparation of quinazolinediones,[9a] γ-spiroiminolactones,[9b] and pyrroles[9c] via multicomponent reactions. Along this line, we have designed the stereoselective three-component one-step synthesis of *cis*-isoquinolonic acids. In this direction, the use of a $KAl(SO_4)_2 \cdot 12H_2O$ (alum), which is relatively nontoxic and inexpensive, is the center of our study.[10] In the course of our research on application of $KAl(SO_4)_2 \cdot 12H_2O$ 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**, aniline **2a**, and benzaldehyde **3a** in acetonitrile was stirred at rt in the presence of a catalytic amount of alum, the reaction was completed within 8 h. Workup of the reaction mixture showed that isoquinolonic acid **4a** was prepared in 88% 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 stereoisomers.

After screening a small number of Lewis acids (L.A.), it has been found that alum promotes the reaction of homophthalic anhydride, benzaldehyde, and aniline to afford the *cis*-isoquinolonic acid scaffold in very good results (Table 1).

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

(1) Cushman, M.; Cheng, L. *J. Org. Chem*. **1978**, *43*, 286−288.
(2) Cushman, M.; Abbaspour, A.; Gupta, Y. P. *J. Am. Chem. Soc*. **1983**, *105*, 2873−2879.
(3) Xu, X. Y.; Qin, G. W.; Xu, R. S.; Zhu, X. Z. *Tetrahedron* **1998**, *54*, 14179−14188.
(4) (a) Johnson, J. V.; Rauckman, S.; Baccanari, P. D.; Roth, B. *J. Med. Chem*. **1989**, *32*, 1942−1949. (b) Stanoeva, E.; Haimova, M. *Khim. Geterotsikl. Soedin*. **1984**, 1587−1589. (c) Haimova, M. A.; Mollov, N, M.; Ivanova, S. C.; Dimitrova, A. I.; Ognyanov, V. I. *Tetrahedron* **1977**, *33*, 331−336. (d) Yamada, N.; Kadowaki, S.; Takahashi, K.; Umeu, K. *Biochem. Pharmacol*. **1992**, *44*, 1211−1213.
(5) (a) Cushman, M.; Madaj, E. J. *J. Org. Chem*. **1987**, *52*, 907−915. (b) Cushman, M.; Gentry, J.; Dekow, F. W. *J. Org. Chem*. **1977**, *42*, 1111−1116. (c) Bonnaud, B.; Carlessi, A.; Bigg, D. C. H. *J. Heterocycl. Chem*. **1993**, *30*, 257−265. (d) Haimova, M. A.; Mollov, N. M.; Ivanova, S. C.; Dimitrova, A. I.; Ognyanov, V. I. *Tetrahedron* **1977**, *33*, 331−336. (e) Stoyanova, M. P.; Kozekov, I. D.; Palamareva, M. D. *J. Heterocycl. Chem*. **2003**, *40*, 795−803.
(6) Yu, N.; Bourel, L.; Deprez, B.; Gesquiere, J. C. *Tetrahedron Lett*. **1998**, *39*, 829−832.
(7) Yu, N.; Poulain, R.; Gesquiere, J. C. *Synlett* **2000**, 355−356.
(8) Yadav, J. S.; Reddy, B. V. S.; Saritha Raj, K.; Prasad, A. R. *Tetrahedron* **2003**, *59*, 1805−1809.
(9) (a) Azizian, J.; Mohammadi, A. A.; Karimi, A. R. *Synth. Commun*. **2003**, *33*, 415−420. (b) Azizian, J.; Karimi, A. R.; Mohammadi, A. A. *Synth. Commun*. **2003**, *33*, 387−391. (c) Azizian, J.; Karimi, A. R.; Arefrad, H.; Mohammadi, A. A.; Mohammadizadeh, M. R. *Molecular Diversity* **2003**, *6*, 223−226.
(10) Azizian, J.; Mohammadi, Ali, A.; Karimi, Ali R.; Mohammadizadeh, M. R. *J. Chem. Res*., in press. (c) *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*, Sept 3−6, 2003, Vienna, Austria.

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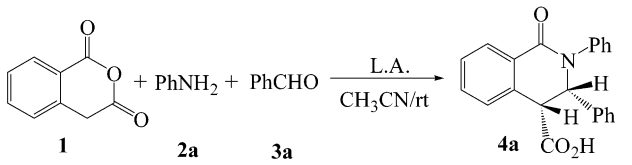
TABLE 1. Screening of Lewis Acids[a]



1 2a 3a 4a

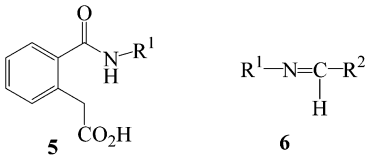
Lewis acid[b]	time (h)	yield[c] (%)
LiCl	30	0
KCl	30	0
LiBr	30	0
KBr	30	0
$NH_4Al(SO_4)_2{\cdot}12H_2O$	30	30
$KAl(SO_4)_2{\cdot}12H_2O$	7	88

[a] Comparison effect of different Lewis acids on the reaction of homophthalic anhydride **1**, aniline **2a**, and benzaldehyd **3a**. [b] For all reactions, 0.5 mmol of Lewis acid was used. [c] Isolated yields based on homophthalic anhydride.

TABLE 2. Reaction of Homophthalic Anhydride, Amines, and Aldehydes[a]

product 4[b]	R^2	R^1	time (h)	yield[c] (%)	mp	lit. mp
a	Ph	Ph	7	88	201−3	198[8]
b	Ph	4-ClC_6H_4	6.5	90	200−1	182[8]
c	Ph	4-MeC_6H_4	6	91	187−8	178[8]
d	Ph	$PhCH_2$	7.5	88	179−80	
e	4-ClC_6H_4	$PhCH_2$	8	87	180−1	
f	Ph	$PhCH_2CH_2$	8.5	84	168−70	
g	Ph	2-benzimid-azolyl	9	85	222−4 dec	
h	4-$NO_2C_6H_4$	4-MeC_6H_4	7.5	86	246−8 dec	
i	4-BrC_6H_4	4-ClC_6H_4	7	89	225−6 dec	
l	3-ClC_6H_4	4-ClC_6H_4	8	87	210−1 dec	
m	2-BrC_6H_4	$PhCH_2$	8.5	81	216−8	

[a] All reactions were run with homophthalic anhydride (162 mg, 1 mmol), 1.2 mmol of aldehydes, 1 mmol of amines, and 0.24 g (0.5 mmol) of alum in (8−10 mL) of acetonitrile at rt. [b] Prepared according to Scheme 1. [c] Yields based on homophthalic anhydride.



5 6

FIGURE 1. Proposed intermediates for the reaction: intermediates **5** were isolated and characterized by IR, ^1H and ^{13}C NMR, and MS spectra and elemental analyses, but imines **6** were not detected.

Although never previously tested, we have found that alum acts as a reusable Lewis acid to catalyze the reaction of homophthalic anhydride, aldehydes, and amines for the synthesis of *cis*-isoquinolonic acids in acetonitrile.

It is noticeable that when the homophthalic anhydride **1**, amines **2a**−**m**, and aldehydes **3a**−**m** in the presence of alum were stirred for within 1.5 h, in all cases the reaction led to the formation of the intermediates **5** which were isolated and characterized by spectroscopic methods (Figure 1). Furthermore, the continuation of reaction for 4 h led to a mixture of **4a**−**m** and intermediates **5** (monitored by TLC and spectroscopic methods), meanwhile after the times indicated in Table 2 just **4a**−**m** were obtained and the intermediates **5** were not detected in the final mixture (Figure 2, Supporting Information).

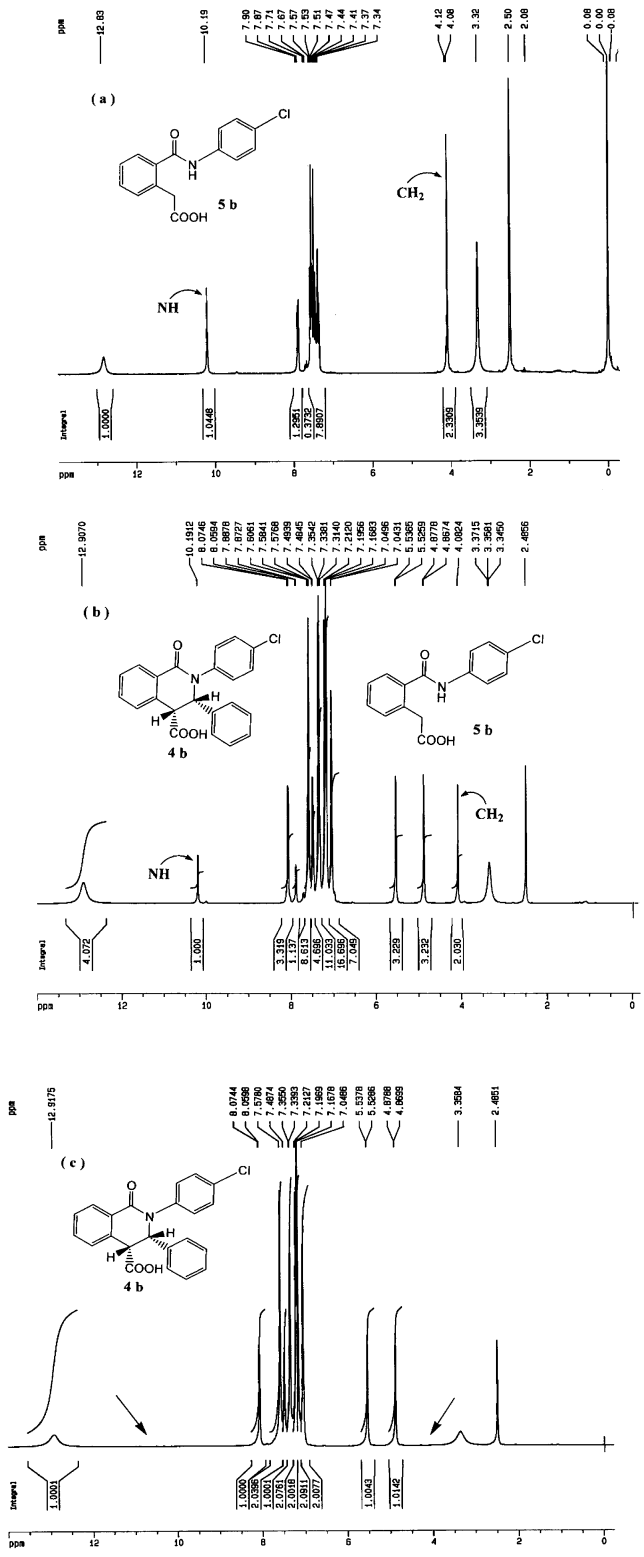
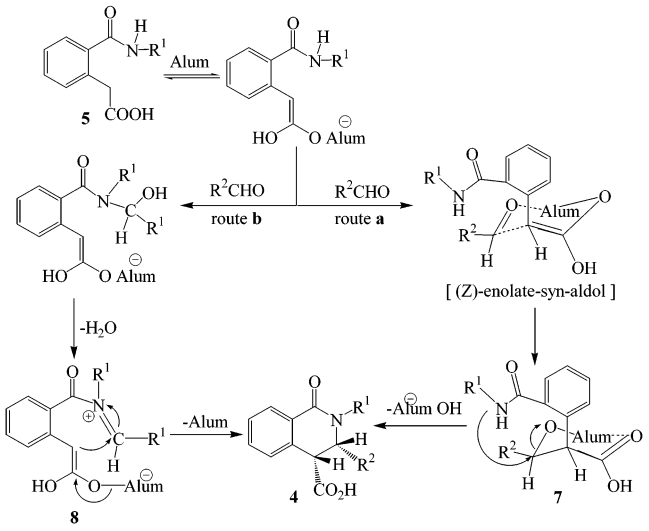


FIGURE 2. Comparison ^1H NMR for **4b** (a) after 1.5 h, (b) after 4 h, and (c) after 6.5 h.

Notably, imines **6** were not detected in the above reaction pathway.

According to the results, the reaction can be mechanistically considered to proceed via the initial formation of the intermediates **5** from homophthalic anhydride and amines, and the noted reaction can be considered through

SCHEME 2. Mechanism of the Alum-Catalyzed Reaction of Homophthalic Anhydride, Amines, and Aldehydes for Preparation of *cis*-Isoquinolonic Acids 4a



[a] Key: (a) by initial reaction of aldehyde with a methylene group; (b) by initial reaction of aldehyde with the amine *N*-atom.

two separate approaches which end in the same result. The former reaction followed by reaction with aldehydes in the presence of alum gives the intermediate **7** via a cyclic transition state (a six-membered, cyclic Zimmerman−Traxler model).[11] Once intermediate **7** is formed, a nucleophilic attack takes place by the nitrogen group in conformity with Baldwin's rules[12] and then elimination of HO−Alum$^-$ and the final product produce (Scheme 2, route a). The later explain that the aldehyde attacks the amine *N*-atom to form an intermediate *N*-acyliminium cation **8**,[13] which then attacks the methylene group to form the final ring (Scheme 2, route b).

(11) (a) Prabhat, A.; Huiping, Q. *Tetrahedron* **2000**, *56*, 917−947. (b) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc*. **1957**, *79*, 1920−1923. (c) Smite, M. B. In *Organic Synthesis*, 2nd ed.; Peterson, K. A., Ed.; McGraw-Hill: New York, 2002; Chapter 9. (d) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; 1993; Part B, Chapter 2.

(12) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun*. **1976**, 734−736. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736−738.

(13) For preparation and reaction of *N*-acyliminium cation, see: Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4416−85.

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

In summary, we have described a successful strategy, an efficient and convenient green synthesis for the preparation of tetrahydroisoquinolonic acids in three-component cyclocondensation reaction of homophthalic anhydride, aldehydes, and amines using the inexpensive, nontoxic, and easily available $KAl(SO_4)_2{\cdot}12H_2O$ catalyst. The method offers several advantages including high yield of products, recyclables of the catalyst, and easy experimental workup procedure. Surprisingly, this reaction is stereoselective in the preparation of *cis*-isoquinolonic acids, since there is no detectable amount of trans stereoisomers, which makes it a useful process for the synthesis of *cis*-isoquinolonic acids.

Experimental Section

Representative Procedure: Compound 4a. A mixture of homophthalic anhydride (162 mg, 1 mmol), benzaldehyde (0.12 mL, 1.2 mmol), aniline (0.09 mL 1 mmol), and alum (0.24 g, 0.5 mmol) in acetonitrile (8−10 mL) in a 25 mL flask was stirred at rt for about 7 h. After completion of the reaction (monitored by TLC, ethyl acetate/*n*-hexane 1/1), the solvent was evaporated under reduced pressure, water (25 mL) was added to the reaction mixture, and the resulting solid was separated by filtration. The crude product was washed with chloroform (2 × 3 mL) and diethyl ether (2 × 5 mL) to afford the product: white powder; yield 88% (302 mg); mp 201−3 °C; IR (KBr), (ν_{max}/cm^{-1}) 3020, 2915, 1723, 1633; ^{1}H NMR (CD_3SOCD_3) δ_H 4.94 (d, 1H, J = 6.9 Hz, H_3), 5.49 (d, 1H, J = 6.9 Hz, H_4), 7.01−7.30 (m, 10H), 7.57−7.60 (m, 3H), 8.07 (d, 1H, J = 8.7 Hz), 12.04 (broad, 1H); ^{13}C NMR (CD_3SOCD_3) δ_C 49.5, 65.1, 126.6, 128.1, 128.2, 128.3, 128.4, 128.4, 128.6, 129.4, 129.6, 132.6, 135.9, 136.1, 137.3, 139.5, 163.2, 171.1; MS (*m/z*) 343 (M$^+$, 75), 298 (30), 207 (25), 181 (100), 134 (45), 118 (35), 105 (35), 90 (25), 77 (80), 63 (35), 51 (50), 39 (35). Anal. Calcd for $C_{22}H_{17}NO_3$: C, 76.95; H, 4.99; N, 4.08. Found: C, 76.78; H, 4.90; N, 4.00.

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Supporting Information Available: General experimental procedures, IR, ^{1}H and ^{13}C NMR, and MS data, and elemental analysis for compounds **4a**−**m**, **5a**,**b**, and a mixture of **4b** and **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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