A Highly Convenient, Efficient, and Selective Process for Preparation of Esters and Amides from Carboxylic Acids Using Fe^{3+}-K-10 Montmorillonite Clay[1]

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Abstract: In the presence of Fe^{3+}-K-10 montmorillonite clay as a catalyst, aliphatic carboxylic acids selectively produced the corresponding esters in the presence of aromatic carboxylic acids by treatment with alcohols. Both the aliphatic and aromatic carboxylic acids formed the amides by reacting with the aliphatic amines, but only the aliphatic carboxylic acids yielded the anilides by treatment with aromatic amines. The catalyst is recoverable and recyclable.

Esterification is an important method for the protection of a carboxylic acid group. The selective esterification of an aliphatic carboxylic acid in the presence of an aromatic carboxylic acid is a useful procedure in organic synthesis. Different methods are known[2] for selective esterification of aliphatic carboxylic acids. All of these methods have some degree of general applicability, but most of them are associated with several drawbacks such as complex, expensive, and hazardous reagents; tedious experimental procedures; harsh reaction conditions; long conversion times; and incompatibility with other functions in the molecules. The catalyst, $NiCl_2 \cdot 6H_2O$, has recently been applied[2f] for selective esterification, but it is applicable to aliphatic nonconjugated carboxylic acids. 2,2-Dimethylpropane, MeOH, and a catalytic amount of HCl have been employed[2g] only for the preparation of the methyl esters of aliphatic carboxylic acids. We have also introduced[2h] the catalyst, sodium hydrogen sulfate, adsorbed on silica gel ($NaHSO_4 \cdot SiO_2$) for the selective esterification of aliphatic carboxylic acids, but the catalyst has to be prepared at the time of use. Moreover, the recovery of the catalyst in the reported methods is also a problem.

In a continuation of our work on the development of useful synthetic methodologies,[2h,3] we have recently observed that Fe^{3+}-K-10 montmorillonite clay is a highly efficient catalyst for the esterification of aliphatic carboxylic acids in the presence of aromatic carboxylic acids. Different aliphatic carboxylic acids, both conjugated and nonconjugated, were treated with various alcohols in the presence of the catalyst under reflux to obtain the corresponding esters in high yields (Table 1). The aromatic carboxylic acids underwent no conversion under similar conditions. The selectivity of the esterification of aliphatic carboxylic acids has been demonstrated by taking molecules with both types of carboxylic groups as well as by competition experiments (Table 1). The products were characterized from their analytical and spectral (IR, ^1H NMR, and MS) data.

The catalyst used here can easily be prepared[4] from the readily available and inexpensive $FeCl_3$ and K-10 montmorillonite clay. It can be safely handled. It can also be recovered and reused. When K-10 montmorillonite clay was used alone, the yields of the products were somewhat lower (10−20%).

The catalyst, Fe^{3+}-K-10 montmorillonite clay, is also efficient for the preparation of amides from carboxylic acids. There are some reagents that can be applied for the one-step conversion of carboxylic acids into amides;[2d,5] however, many of these reagents are not easily available and expensive. Their preparations are also hard tasks. Selectivity of the amide formation by using these reagents has been studied only in a few cases.[2d] Moreover, complex experimental procedures, long reaction times, and unsatisfactory yields are also certain drawbacks in applying some of these reagents. Recovery of the catalyst also creates a problem. However, Fe^{3+}-K-10 montmorillonite clay can conveniently be used for the preparation of amides from carboxylic acids. Various aliphatic and aromatic carboxylic acids were treated with aliphatic amines in the presence of the catalyst to prepare different amides (Table 2). The same catalyst also catalyzed the reaction of aliphatic carboxylic acids and aniline (and its derivatives) to form anilides. However, the aromatic carboxylic acids did not form anilides by reacting with aromatic amines under similar experimental conditions, and they remained unchanged. Under the activity of the catalyst for amide formation at least one of either the acid or the amine should be aliphatic, but if both are aromatic, the reaction will not occur. The selectivity of the amide formation was readily observed by performing reactions with compounds containing both types of carboxylic groups and also by competition experiments (Table 2). The selectivity is summarized in Chart 1. Also, in this case, the yields of the amides were found to be somewhat lower (10−20%) when K-10 montmorillonite clay was used alone instead of Fe^{3+}-K-10 clay.

In conclusion, a simple, highly efficient, and selective method has been developed for the preparation of esters

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[2] (a) Bertin, J.; Kagan, H. B.; Luche, J. L.; Setton, R. *J. Am. Chem. Soc.* **1974**, *96*, 8113. (b) Rehn, D.; Ugi, I. *J. Chem. Res., Synop.* **1977**, 119. (c) Banerjee, A.; Sengupta, S.; Adak, M. M.; Banerjee, G. C. *J. Org. Chem.* **1983**, *48*, 3106. (d) Ogaura, T.; Hikasa, T.; Ikegami, T.; Ono, N.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3473. (e) Sharma, A.; Chattopadhyay, S.; Mamdapur, V. R. *Biotechnol. Lett.* **1995**, *17*, 939. (f) Ram, R. N.; Charles, I. *Tetrahedron* **1997**, *53*, 7335. (g) Rodriguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett.* **1998**, *39*, 8563. (h) Das, B.; Venkataiah, B.; Madhusudhan, P. *Synlett* **2000**, 59.

[3] (a) Das, B.; Madhusudhan, P.; Venkataiah, B. *Synlett* **1999**, 1569. (b) Das, B.; Venkataiah, B. *Synthesis* **2000**, 1671. (c) Ravindranath, N.; Ramesh, C.; Das, B. *Synlett* **2001**, 1777. (d) Srinivas, K. V. N. S.; Reddy, E. B.; Das, B. *Synlett* **2002**, 625.

[4] Laszlo, P.; Mathy, A. *Helv. Chim. Acta* **1987**, *70*, 557.

[5] (a) Barstow, L. E.; Hruby, V. J. *J. Org. Chem.* **1971**, *36*, 1305. (b) Gorecka, A.; Leplawy, M.; Zabrocki, J.; Zwierzak, A. *Synthesis* **1978**, 474. (c) Kubota, T.; Miyashita, S.; Kitazume, T.; Ishikawa, N. *J. Org. Chem.* **1980**, *45*, 5052. (d) Kunieda, T.; Abe, Y.; Higuchi, T.; Hirobe, M. *Tetrahedron Lett.* **1981**, *22*, 1257. (e) Trapani, G.; Reho, A.; Latrofa, A. *Synthesis* **1983**, 1013.

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TABLE 1. Preparation of Esters Using Fe^{3+}-K-10 Montmorillonite Clay as the Catalyst

entry	acid	alcohol	time (h)	yield (%)[a] A	yield (%)[a] B	ref
1	$C_6H_5CH_2CO_2H$	CH_3OH	7	96		6a,b
2	$C_6H_5CH_2CO_2H$	CH_3CH_2OH	7	93		6a,b
3	4-(OH)$C_6H_4CH_2CO_2H$	CH_3OH	7.5	94		6a,c
4	4-(OH)$C_6H_4CH_2CO_2H$	CH_3CH_2OH	7.5	91		6a,c
5	4-(OH)$C_6H_4CH_2CO_2H$	$(CH_3)_2CHOH$	8	90		6a
6	3,4-$(CH_3O)_2C_6H_3CH_2CO_2H$	CH_3OH	7	94		6d
7	3,4-$(CH_3O)_2C_6H_3CH_2CO_2H$	CH_3CH_2OH	7.5	92		6c,d
8	$C_6H_5CO_2H$	CH_3OH	8		0	
9	4-(OH)$C_6H_4CO_2H$	CH_3OH	8.5		0	
10	3-(Cl)$C_6H_4CO_2H$	CH_3OH	8		0	
11	$C_6H_5CH_2CO_2H$	$C_6H_5CH_2OH$	9	84		6a
12	CH_3COCO_2H	$C_6H_5CH_2OH$	7	86		6a
13	$CH_3(CH_2)_{16}CO_2H$	CH_3OH	7.5	94		6a,b
14	$CH_3(CH_2)_{16}CO_2H$	CH_3CH_2OH	8	92		6a,b
15	$CH_3(CH_2)_{16}CO_2H$	$(CH_3)_2CHOH$	8.5	89		6e
16	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	CH_3OH	8	92		6b,e
17	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	CH_3CH_2OH	8.5	87		6b
18	$C_6H_5CH{=}CHCO_2H$	CH_3OH	9	76		6a,b
19	$C_6H_5CH{=}CHCO_2H$	CH_3CH_2OH	9.5	72		6a,b
20	2-$(CO_2H)C_6H_4CH_2CO_2H$	CH_3OH	7	94	0	6a
21	2-$(CO_2H)C_6H_4CH_2CO_2H$	CH_3CH_2OH	8	93	0	6a
22	2-$(CO_2H)C_6H_4CH_2CH_2CO_2H$	CH_3OH	7.5	95	0	6a
23	2-$(CO_2H)C_6H_4CH_2CH_2CO_2H$	CH_3CH_2OH	8	93	0	6a
24	$C_6H_5CH_2CO_2H$ and $C_6H_5CO_2H$	CH_3OH	7	94	0	6a,b
25	$C_6H_5CH_2CO_2H$ and 3-(Cl)$C_6H_4CO_2H$	CH_3OH	7.5	92	0	6a,b
26	3,4-$(CH_3O)_2C_6H_3CH_2CO_2H$ and $C_6H_5CO_2H$	CH_3CH_2OH	8	91	0	6c,d

[a] Calculated on the basis of the amount of the isolated product. A: Ester derived from an aliphatic carboxylic acid group. B: Ester derived from an aromatic carboxylic acid group.

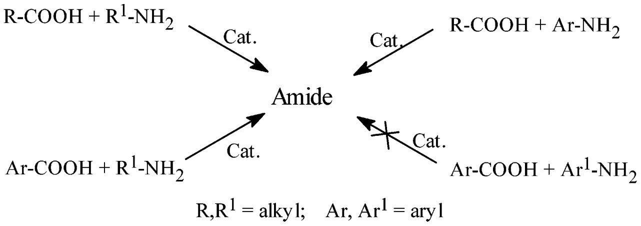
TABLE 2. Preparation of Amides Using Fe^{3+}-K-10 Montmorillonite Clay as the Catalyst

entry	acid	amine	time (h)	yield (%)[a] A	yield (%)[a] B	ref
1	$C_6H_5CH_2CO_2H$	$C_6H_5NH_2$	7	97		7a
2	$C_6H_5CH_2CO_2H$	4-$(CH_3O)C_6H_4NH_2$	7.5	95		7b
3	$C_6H_5CH_2CO_2H$	4-(Cl)$C_6H_4NH_2$	7.0	92		7c
4	4-(OH)$C_6H_4CH_2CO_2H$	$C_6H_5NH_2$	8	93		7d
5	4-(OH)$C_6H_4CH_2CO_2H$	4-$(CH_3O)C_6H_4NH_2$	7.5	91		
6	3,4-$(CH_3O)_2C_6H_3CH_2CO_2H$	4-$(CH_3O)C_6H_4NH_2$	8	95		7e
7	$C_6H_5CH_2CO_2H$	$C_6H_5NHCH_3$	8.5	93		7f
8	3,4-$(CH_3O)_2C_6H_3CH_2CO_2H$	$C_6H_5NHCH_3$	9	92		7e
9	$C_6H_5CO_2H$	$C_6H_5NH_2$	8		0	
10	4-(OH)$C_6H_4CO_2H$	$C_6H_5NH_2$	8.5		0	
11	$C_6H_5CO_2H$	$C_6H_5CH_2NH_2$	7	95		7a,g
12	$C_6H_5CO_2H$	4-$(CH_3O)C_6H_4CH_2NH_2$	7.5	93		7h
13	$C_6H_5CO_2H$	$C_6H_5CH_2CH_2NH_2$	8	92		7a,i
14	$CH_3CH_2CO_2H$	$C_6H_5CH_2NH_2$	8	87		7a
15	$C_6H_5CH{=}CHCO_2H$	$C_6H_5NH_2$	9	78		7a
16	$C_6H_5CH_2CO_2H$ and $C_6H_5CO_2H$	$C_6H_5NH_2$	8	95	0	7a
17	4-(OH)$C_6H_5CH_2CO_2H$ and $C_6H_5CO_2H$	4-$(CH_3O)C_6H_4NH_2$	8.5	89	0	
18	3,4-$(CH_3O)_2C_6H_3CH_2CO_2H$ and $C_6H_5CO_2H$	4-$(CH_3O)C_6H_4NH_2$	8	92	0	7e
19	$C_6H_5CO_2H$	$C_6H_5NH_2$ and $C_6H_5CH_2NH_2$	8	93	0	7a,g
20	$C_6H_5CO_2H$	$C_6H_5NH_2$ and 4-$(CH_3O)C_6H_4CH_2NH_2$	8	91	0	7h
21	3,4-$(CH_3O)_2C_6H_3CH_2CO_2H$	$C_6H_5NH_2$ and $C_6H_5CH_2CH_2NH_2$	8.5	90		7j,k
22	2-$(CO_2H)C_6H_4CH_2CH_2CO_2H$	$C_6H_5NH_2$	9	88	0	
23	$C_6H_5CH_2CO_2H$	$C_6H_5CH_2NH_2$	7	95		7a,l
24	$C_6H_5CH_2CO_2H$	4-$(CH_3O)C_6H_4CH_2NH_2$	7	93		7m
25	$C_6H_5CH_2CO_2H$	$C_6H_5CH_2CH_2NH_2$	8.5	93		7a,l
26	3,4-$(CH_3O)_2C_6H_3CH_2CO_2H$	$C_6H_5CH_2NH_2$	7	94		7n
27	3,4-$(CH_3O)_2C_6H_3CH_2CO_2H$	$C_6H_5CH_2CH_2NH_2$	7.5	92		7k
28	3,4-$(CH_3O)_2C_6H_3CH_2CO_2H$	4-$(CH_3O)C_6H_4CH_2NH_2$	8	93		7e

[a] Calculated on the basis of the amount of the isolated product. A: Amide derived from an aliphatic or aromatic carboxylic acid group and an aliphatic amine or from an aliphatic carboxylic acid group and an aromatic amine. B: Amide derived from an aromatic carboxylic acid group and an aromatic amine.

and amides by using an inexpensive, nonhazardous, and easily available catalyst. Both conjugated and nonconjugated aliphatic carboxylic acids formed the esters in the presence of aromatic carboxylic acids. The catalyst was successfully applied for the one-step conversion of the aliphatic as well as aromatic acids into the corresponding amides by treatment with aliphatic amines. However, only the aliphatic carboxylic acids (and not the

CHART 1. Selectivity of Amide Formation



aromatic carboxylic acids) yielded the anilides by reacting with aniline and its derivatives. The yields of the esters and amides are high. For the preparation of the esters both the primary and secondary alcohols and for preparation of the amides both the primary and secondary amines can be used. All the prepared esters are known compounds,[6] while among the amides two compounds (Table 2, entries 5, 17, and 22) are new.[7] The experimental procedure of the present method is very simple. The greatest advantage is that the catalyst can be recovered and reused. The developed method can be applied for the separation of aromatic carboxylic acids from a mixture containing aliphatic carboxylic acids and of aromatic amines from a mixture containing aliphatic amines. We feel the present process will find important applications in synthetic organic chemistry.

Experimental Section

General Remarks. All the acids and amines were available commercially. K-10 montmorillonite clay was obtained from Fluka Chemicals.

Typical Experimental Procedure. (A) Preparation of Ester. To a solution of 2-carboxyphenyl propanoic acid (194 mg, 1 mmol) in EtOH (10 mL) was added Fe^{3+}-K-10 montmorillonite clay (100 mg, prepared by reported method[4]). The mixture was refluxed for 8 h and cooled. After filtration, the filtrate was concentrated and purified by column chromatography over silica gel using hexane−EtOAc (4:1) as the eluent to afford pure ethyl-2-carboxyphenyl propionate (178 mg, 92%; Table 1, entry 23). IR (KBr): 3080, 1720, 1692, 1598 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 8.10 (1H, d, J = 8.0 Hz), 7.52−7.26 (3H, m), 4.11 (2H, q, J = 7.0 Hz), 3.35 (2H, t, J = 7.0 Hz), 2.68 (2H, t, J = 7.0 Hz), 1.22 (3H, t, J = 7.0 Hz). MS (m/z): 204 (M$^{\bullet+}$ − H$_2$O). Anal. Calcd for C$_{12}$H$_{14}$O$_4$: C, 64.86; H, 6.30. Found: C, 64.94; H, 6.28.

The spectral and analytical data of the other two representative esters are given below.

Isopropyl-4-hydroxyphenylacetate (Table 1, Entry 5). IR (KBr): 3458, 1726, 1684, 1592 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 7.12 (2H, d, J = 8.0 Hz), 6.75 (2H, d, J = 8.0 Hz), 6.25 (1H, brs), 5.10 (1H, m), 3.55 (2H, s), 1.32 (6H, d, J = 7.0 Hz). MS (m/z): 194 (M$^{\bullet+}$). Anal. Calcd for C$_{11}$H$_{14}$O$_3$: C, 68.04; H, 7.22. Found: C, 68.22; H, 7.36.

Benzyl Pyruvate (Table 1, Entry 12). IR (neat): 1736, 1652, 1543 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 7.42−7.26 (5H, m), 5.24 (2H, s), 2.45 (3H, s). MS (m/z): 178 (M$^{\bullet+}$). Anal. Calcd for C$_{10}$H$_{10}$O$_3$: C, 67.41; H, 5.62. Found: C, 67.64; H, 5.84.

(B) Preparation of Amide. To a solution of phenylacetic acid (136 mg, 1 mmol) and aniline (93 mg, 1 mmol) in CHCl$_3$ (10 mL) was added Fe^{3+}-K-10 montmorillonite clay (100 mg). The mixture was refluxed for 7 h under an N$_2$ atmosphere, cooled, and filtered. The concentrated filtrate was subjected to column chromatography over silica gel using hexane−EtOAc (3:2) as the eluent to obtain pure phenyl acetanilide (N,2-diphenylacetamide; 204 mg, 97%; Table 2, entry 1). IR (KBr): 3447, 3031, 1645, 1600, 1547, 1496 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 7.18−7.28 (5H, m), 6.98−7.04 (2H, m), 6.48−6.62 (3H, m), 6.78 (1H, brs), 3.52 (2H, s). MS (m/z): 211 (M$^{\bullet+}$). Anal. Calcd for C$_{14}$H$_{13}$NO: C, 79.62; H, 6.16; N, 6.63. Found: C, 79.84; H, 6.18; N, 6.72.

The spectral and analytical data of the unknown amides (Table 2, entries 5, 17, and 22) and the other two representative amides are given below.

***N*-(4-Methoxyphenyl)-2-(4-hydroxyphenyl)acetamide (Table 2, Entries 5 and 17).** IR (KBr): 3291, 1651, 1596, 1514, 1468 cm^{-1}. ^{1}H NMR (CDCl$_3$ + DMSO-d_6): δ 7.20 (2H, d, J = 8.0 Hz), 6.82 (2H, d, J = 8.0 Hz), 6.64 (2H, d, J = 8.0 Hz), 6.56 (2H, d, J = 8.0 Hz), 6.12 (1H, brs), 3.78 (3H, s), 3.46 (2H, s). MS (m/z): 257 (M$^{\bullet+}$). Anal. Calcd for C$_{15}$H$_{15}$NO$_3$: C, 70.04; H, 5.84; N, 5.45. Found: C, 70.12; H, 5.78; N, 5.41.

***N*-Benzylbenzamide (Table 2, Entry 11).** IR (KBr): 3412, 3032, 1631, 1523, 1456 cm^{-1}. ^{1}H NMR (CDCl$_3$ + DMSO-d_6): δ 7.82−7.96 (2H, m), 7.18−7.42 (8H, m), 6.44 (1H, brs), 3.98 (2H, s). MS (m/z): 211 (M$^{\bullet+}$). Anal. Calcd for C$_{14}$H$_{13}$NO: C, 79.62; H, 6.16; N, 6.63. Found: C, 79.88; H, 6.22; N, 6.77.

***N*-Phenyl-3-(2-carboxyphenyl)propionamide (Table 2, Entry 22).** IR (KBr): 3375, 3222, 1724, 1631, 1543, 1440 cm^{-1}. ^{1}H NMR (CDCl$_3$ + DMSO-d_6): δ 7.98 (1H, d, J = 8.0 Hz), 7.40−6.74 (8H, m), 5.87 (1H, brs), 2.98 (2H, t, J = 7.0 Hz), 2.64 (2H, t, J = 7.0 Hz). MS (m/z): 269 (M$^{\bullet+}$). Anal. Calcd for C$_{16}$H$_{15}$NO$_3$: C, 71.37; H, 5.57; N, 5.20. Found: C, 71.42; H, 5.51; N, 5.24.

***N*-Benzyl-2-(3,4-dimethoxyphenyl)acetamide (Table 2, Entry 26).** IR (KBr): 3398, 1638, 1513, 1452, 1230, 1150 cm^{-1}. ^{1}H NMR (CDCl$_3$ + DMSO-d_6): δ 7.30 (5H, s), 6.79 (1H, s), 6.69 (2H, s), 6.54 (1H, brs), 3.78 (6H, s), 3.69 (2H, s), 3.29 (2H, s). MS (m/z): 285 (M$^{\bullet+}$). Anal. Calcd for C$_{17}$H$_{19}$NO$_3$: C, 71.57; H, 6.66; N, 4.91. Found: C, 7.64; H, 6.82; N, 4.87.

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(6) (a) Das, B.; Venkataiah, B.; Madhusudhan, P. *Synlett* **2000**, 59. (b) Commercially available, Aldrich Chemicals. (c) Commercially available, Lancaster Chemicals. (d) Desmaele, D. *Tetrahedron Lett.* **1996**, *37*, 1233. (e) Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Tetrahedron Lett.* **2002**, *43*, 879.

(7) (a) Buch Staller, H.-P.; Ebert, H. M.; Anlauf, U. *Synth. Commun.* **2001**, *31*, 1001. (b) Gazit, A.; App, H.; McMahon, G.; Chen, J.; Lavitzki, A.; Bohner, F. D. *J. Med. Chem.* **1996**, *39*, 2170. (c) Vidya, J.; Sarma, R. K. *J. Indian Chem. Soc.* **1988**, *65*, 564. (d) Ramanarayan, S. R.; Mona, A. M.; Ahmed, S. M.; Abraham, D. J. *J. Med. Chem.* **1991**, *34*, 752. (e) Commercially available, Exploratory Laboratories. (f) Wakita, Y.; Kobayashi, T.; Maeda, M.; Kojima, M. *Chem. Pharm. Bull.* **1982**, *30*, 3395. (g) Commercially available, Aldrich Chemicals. (h) Sampath Kumar, H. M.; Subba Reddy, B. V.; Anjaneyulu, S.; Jagan Reddy, E.; Yadav, J. S. *New. J. Chem.* **1999**, *23*, 955. (i) Laurence, P.; Andre, L.; Francois, V. *Tetrahedron* **2002**, *58*, 2155. (j) Nagarajan, K.; Talwalker, P. K.; Kulkarni, C. L.; Shah, R. K.; Shenoy, S. J.; Prabhu, S. S. *Indian J. Chem.* **1985**, *24B*, 83. (k) Pridgen, L. N.; Killmer, L. B.; Leewebb, R. *J. Org. Chem.* **1982**, *47*, 1985. (l) Thomas, J. B.; Fall, M. J.; Cooper, J. B.; Burgess, J. P.; Carroll, I. F. *Tetrahedron Lett.* **1997**, *38*, 5099. (m) Cabaret, D.; Gonzalez, G. M.; Walkselmen, M.; Adediran, S. A.; Pratt, R. F. *Eur. J. Org. Chem.* **2001**, 141. (n) Vazquez-Tato, P. M. *Synlett* **1993**, 506.