Pergamon

Tetrahedron Letters 41 (2000) 1495–1500

TETRAHEDRON LETTERS

A novel dealkylation affording 3-aminoimidazo[1,2-*a*]pyridines: access to new substitution patterns by solid-phase synthesis†

Christopher Blackburn * and Bing Guan

Drug Discovery, Millennium Pharmaceuticals, 75 Sidney Street, Cambridge, MA 02139, USA

Received 2 November 1999; revised 16 December 1999; accepted 20 December 1999

Abstract

The three-component synthesis of 3-aminoimidazo[1,2-*a*]pyridine derivatives has been extended by a novel acid-induced dealkyation reaction that removes the 1,1,3,3-tetramethylbutyl group derived from the isonitrile input. This reaction was conducted on the solid-phase using the HMBA linker and the resulting products subjected to reductive alkylation using several aldehydes, thereby accessing novel substitution patterns at the 3-position. © 2000 Elsevier Science Ltd. All rights reserved.

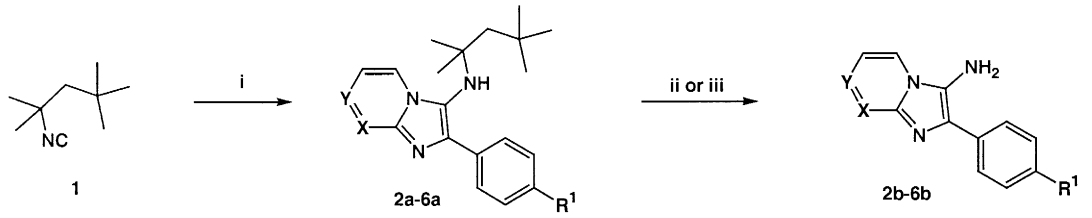
Multiple component condensations (MCCs)[1] have received renewed attention as a consequence of their application to the combinatorial parallel synthesis of large arrays of compounds with diverse substitution patterns. The number of products accessible in one step is given by the product of the number of available inputs, and thus very large virtual libraries are possible. There is particular interest in MCCs involving isonitrile inputs, such as the Passerini[1b] and Ugi[2,3] reactions; post-condensation reactions leading to constrained scaffolds are particularly notable.[4] Recently, we[5,6] and others[7] described a new three component condensation (3CC) involving 2-aminopyridine, an aldehyde and an isonitrile, e.g. **1**, leading to drug-like[8–11] 3-aminoimidazo[1,2-*a*]pyridines (Scheme 1). Access to a large and diverse series of compounds based on this scaffold is limited by the commercial availability of the isonitrile component, and by the low reactivity of the 3-amino group of these compounds when substituted by aryl or hindered alkyl groups.[5,6] We report here a new route to primary amines **2b**–**6b** that improves on established methods[8–11] and is amenable to parallel synthesis. These primary amines proved to be more reactive towards electrophiles than related secondary amines; in particular, reductive alkylation can be performed using a variety of aldehydes on the solid-phase to give products that could not be accessed directly by 3CC because the appropriate isonitrile is not readily available.

In principle, substitution of cyanide ion for the isonitrile component in the 3CC reaction would lead to the desired primary amines directly.[12] A condensation reaction between 2-aminopyridine, methyl-4-formylbenzoate and KCN in MeOH–H_2O followed by purification on a cation exchange resin led directly

* Corresponding author. E-mail: blackburn@mpi.com (C. Blackburn)

† Dedicated to the memory of Ray Blackburn, 1933–1999.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00003-4



Cpd.	R^1	X	Y	Yield (%)	Cpd.	R^1	X	Y	Yield (%)
2a	H	CH	CH	75	**2b**	H	CH	CH	76
3a	OMe	CH	CH	74	**3b**	OMe	CH	CH	85
4a	COOMe	CH	CH	85	**4b**	COOMe	CH	CH	75
5a	COOMe	N	CH	35	**5b**	COOMe	N	CH	55
6a	COOMe	CH	N	82	**6b**	COOMe	CH	N	75

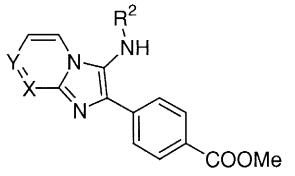
Scheme 1. Reagents and conditions. (i) 2-Aminoazine, ArCHO, $Sc(OTf)_3$, CH_2Cl_2, MeOH, 25°C, 48 h; (ii) a. 12N HCl:MeOH (1:1), b. Dowex-500 cation exchange resin, c. 2N NH_3, MeOH; (iii) TFA:CH_2Cl_2 (1:1), 25°C, 10 min

to primary amine **4b** but in low yield (25%) and moderate purity (60%). We noted that 3CC products derived from 1,1,3,3-tetramethylbutylisonitrile (**1**) were unstable towards acid treatment affording the corresponding primary amines. To investigate this reaction further, compounds **2a**–**6a** were prepared as shown in Scheme 1; high yields were obtained with the exception of the condensation involving 2-aminopyrimidine. Treatment of **2a**–**6a** with 5N HCl in MeOH at ambient temperature for 0.5 h resulted in clean dealkylation, giving primary amines **2b**–**6b** which were conveniently isolated, in good to high yields and high purities, by capture on Dowex cation exchange resin, washing with MeOH until acid-free, and elution from the resin using methanolic ammonia. Presumably, this novel reaction is a reflection of the ability of the 3-aminoimidazopyridine system to function as a leaving group, and the stability of a carbocation or its elimination product. Isonitrile **1** thus serves as a cyanide ion equivalent in the 3CC reaction, affording two-step access to the primary amino compounds. These reaction conditions are more compatible with library synthesis than hydrogenolysis of *N*-benzyl compounds[5] or the well established method involving the condensation of α-halocarbonyl compounds with the appropriate 2-aminoazine and subsequent nitrosation and reduction.[8–11]

In order to apply this synthesis to the solid-phase, we sought dealkylation conditions more compatible with the swelling characteristics of polystyrene-based resins. Using the methyl ester **4a** to mimic the resin anchoring point, we compared the kinetics of dealkylation induced by TFA–CH_2Cl_2 with those of the *t*-butyl analogue **4c** (Table 1).[13] Compound **4a** exhibited clean first order kinetics and a half life of 100 s whereas the *t*-butyl analogue **4c**, which would also be expected to afford a stable carbocation, underwent much slower dealkylation ($t_{1/2}$>20 h), during which time trifluoroacetylation of the amino group also took place. These observations led us to apply the 3CC reaction involving isonitrile **1** to the solid-phase, employing the base-labile linker 4-hydroxymethylbenzoic acid (HMBA). Esters derived from this resin are more stable than those obtained from Merrifield resin[14] towards the acidic conditions used in the dealkylation step, and can be cleaved by base under milder conditions.[15] 4-Carboxybenzaldehyde was anchored to HMBA-AM resin in the presence of DIC and DIEA, and the resulting resin-bound aldehyde subjected to a 3CC reaction with 2-aminopyridine and isonitrile **1** (Scheme 2) to give resin **7a**. Cleavage of **7a** by treatment with sodium methoxide in MeOH:THF (1:1) afforded **4a** in high yield and purity. Treatment of **7a** with TFA:CH_2Cl_2 (1:1) for 10 min, gave resin **7b** which could be cleaved to give primary

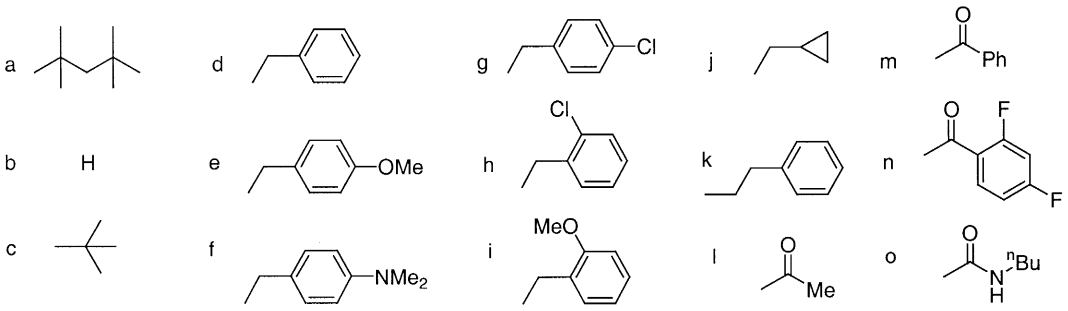
amine **4b** in good yield and high purity (Table 1, entries 1 and 2). In order to prepare 3-alkyl derivatives not accessible from commercially available isonitriles, we investigated the reductive alkylation of resin-bound amine **7b** by treatment with aldehydes in the presence of $NaBH_3CN$. After cleavages induced by treatment with sodium methoxide, monobenzylated derivatives were obtained from aryl aldehydes in high yields and purities (entries 3–5, and 7), although yields were lowered by steric hindrance at the *ortho* position of the aldehyde (entry 6). Cyclopropanecarboxyaldehyde and phenylacetaldehyde afforded mixtures of mono and dialkylated derivatives (entries 8 and 9).

Table 1
Solid-phase synthesis of aminoimidazol[1, 2-*a*]pyridine and pyrimidine derivatives



	X	Y
4	CH	CH
5	N	CH
6	CH	N

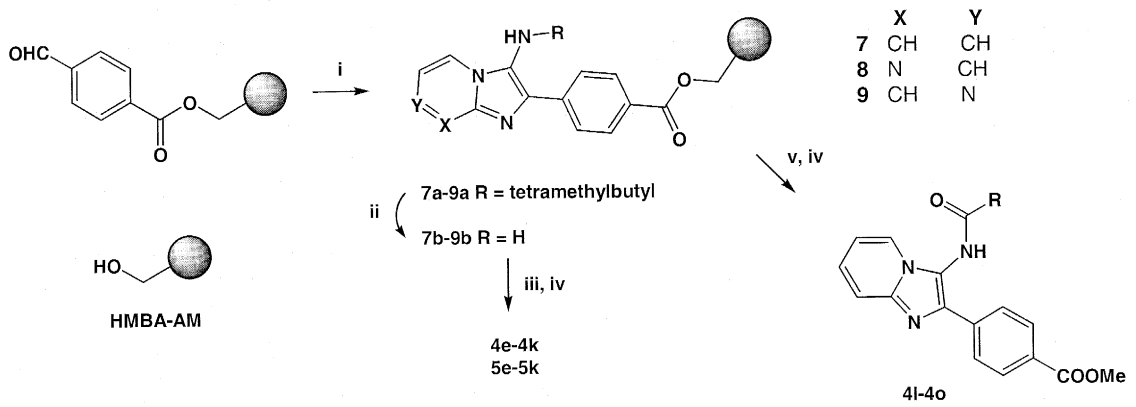
R^2 Substituents



Entry	Compd.	Area %[a]	Yield %[b]	Entry	Compd.	Area %[a]	Yield %[b]	Entry	Compd.	Area %[a]	Yield %[b]
1	**4a**	>95	98	9	**4k**	70[d] 3[e]	50[d] 2[e]	17	**5h**	65	50
2	**4b**	95	95	10	**5a**	85	80	18	**5i**	60	50
3	**4e**	90	95	11	**5b**	75	70	19	**5j**	85[e]	90[e]
4	**4f**	90	95	12	**6a**	95	95	20	**5k**	5[d], 5[e]	5[d], 5[e]
5	**4g**	95	90	13	**6b**	90	90	21	**4l**	>95	90
6	**4h**	35, 40[c]	30	14	**5e**	70	60	22	**4m**	25	20
7	**4i**	90	95	15	**5f**	<5, 60[c]	0	23	**4n**	90	95
8	**4j**	35[d] 60[e]	32[d] 55[e]	16	**5g**	60	45	24	**4o**	>95	75

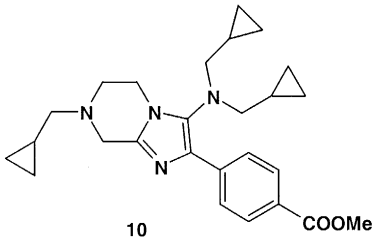
a. Relative peak area in diode array trace with detector recording from 210-300 nm.
b. Yields of cleavage products were calculated from an HPLC standard curve of peak area vs concentration constructed using an appropriate standard. All products were analysed by LC-MS recorded on a Micromass Platform LC in positive ion ESI mode and gave the expected molecular ions. LC conditions: C-18 column, linear gradient from 90% A 10% B to 100% B over 10 min. where A was 5mM NH_4OAc in H_2O and B was 5mM NH_4OAc in MeCN. Pure **4d**[5] was used as the calibrant for compounds **e, f, g, h, i, j, k.** Pure **4m**, prepared by solution-phase synthesis and fully characterised, was used as the calibrant for compounds **4l-4o.** Yield = loading capacity/theoretical loading capacity.[18]
c. Recovered starting material
d. Monoalkylated product. e. Dialkylated product.

2-Aminopyrimidine and aminopyrazine afforded resin-bound primary amines **8b** and **9b**, respectively, by solid-phase 3CC followed by dealkylation (Scheme 2). Cleavage of these resins by treatment with sodium methoxide afforded **5b** and **6b**, respectively, albeit in lower purities than **4b** (Table 1 entries 2, 11

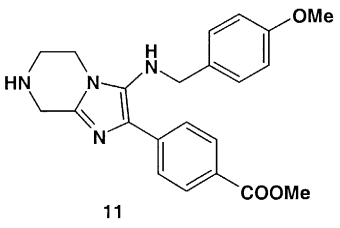


Scheme 2. Reagents and conditions. (i) 2-aminoazine, isonitrile **1**, $Sc(OTf)_3$, CH_2Cl_2, MeOH, 25°C, 60 h; (ii) TFA:CH_2Cl_2 (1:1), 25°C, 10 min; (iii) RCHO, $NaBH_3CN$, DMF–HOAc, 25°C, 50 h; (iv) 0.25 M NaOMe in MeOH:THF (1:1), 25°C, 1 h; (v) RCOCl, DMF-pyridine (4:1), 25°C, 24 h, or RNCO, DMF, 25°C, 24 h

and 13). Solid-phase reductive alkylations of **8b** (entries 14–20) gave products in lower yields and purities than those derived from resin **7b**. In marked contrast, treatment of resin **9b**, derived from aminopyrazine, with the same series of aldehydes under identical reducing conditions, gave rise to mixtures in which the expected product was a minor component. LC-MS data indicated that reduction of the pyrazine ring[16] was taking place, together with further reductive alkylation reactions. Thus, for example, the major product from the reductive alkylation of resin **9b** with cyclopropanecarboxaldehyde was shown to be compound **10** (ca. 50% purity by LC-MS diode array trace), in which the pyrazine ring had been reduced and the secondary amine alkylated. Reductive alkylation of **9b** by 4-methoxybenzaldehyde afforded a reduced and monoalkylated derivative as the major product (ca. 35% purity by LC-MS diode array trace). To investigate the latter reaction further, **6b** was subjected to reductive alkylation with 4-methoxybenzaldehyde in DMF solution. The major product, isolated in 24% yield after HPLC, was shown (see experimental) to be compound **11**. Reductions of the imidazo[1,2-*a*]pyrazine heterocycle on-resin is of interest for accessing a new scaffold for combinatorial synthesis and is under further investigation.



10



11

Primary amines **2b**–**6b** were found to be more reactive towards acid chlorides and isocyanates than related secondary amines and could be functionalised in solution followed by polymer-supported quenching.[5,17] Derivatives of **4b** were more conveniently prepared on the solid-phase by treatment with excess acid chloride or isocyanate prior to cleavage using sodium methoxide (Table 1 entries 21–24).

1. Experimental

The following procedure is typical for the solution-phase synthesis of primary amines **2b**–**6b**. A 0.5 M solution of 2-aminopyridine (1.5 mL) in MeOH:CH_2Cl_2 (1:3) was treated with methyl-4-formylbenzoate (1 equiv.) and scandium triflate (0.1 equiv.). After 0.5 h, isonitrile **1** (1 equiv.) was added and the solution was stirred for 48 h at ambient temperature. The solvent was evaporated and the crude product purified by chromatography on neutral alumina eluting with ethyl acetate–hexane to give **4a** (85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (1H, d, J=7Hz), 8.12 (2H, d, J=9 Hz), 7.98 (2H, d, J=9 Hz), 7.55 (1H, d, J=7 Hz), 7.16 (1H, dd), 6.78 (1H, dd), 3.94 (3H, s), 1.60 (2H, s), 1.04 (9H, s), 0.95 (6H, s). Dealkylation as described in the text gave primary amine **4b** (75%) ^{1}H NMR (CD_3OD, 300 MHz) δ 8.22 (1H, d, J=7Hz), 8.08 (4H, s), 7.44 (1H, d, J=7 Hz), 7.20 (1H, dd), 6.94, (1H, dd), 3.94 (3H, s).

Solid-phase syntheses: HMBA-AM resin 1.15 mmol/g loading (from Novabiochem) (1.6 g, 1.84 mmol) was allowed to swell in DMF (12 mL) and CH_2Cl_2 (12 mL) and treated with 4-carboxybenzaldehyde (1.11g, 7.4 mmol), diisopropylcarbodiimide (1.15 mL, 7.4 mmol), and 4-dimethylaminopyridine (0.225 g, 1.86 mmol). The mixture was shaken at ambient temperature for 24 h then filtered and the resin washed successively with DMF, CH_2Cl_2, MeOH, CH_2Cl_2 and dried under vacuo. The loading of the aldehyde resin was found to be 1.0 mmol/g (quantitative) determined by cleavage of an aliquot of resin using 0.25 M NaOMe in MeOH:THF (1:1) for 1 h at ambient temperature and quantification of the released methyl-4-formylbenzoate by LC-MS using authentic material as calibrant. Theoretical loading capacity[18] is given by 1.15 mmol/[1g+(1.15 mmol×MW added to resin)].

The resin-bound aldehyde (0.4 g, 0.4 mmol) was treated with a solution of 2-aminopyridine (0.38 g, 4 mmol) and $Sc(OTf)_3$ (200 mg, 0.4 mmol) in CH_2Cl_2 (5 mL) and MeOH (1.6 mL). After shaking for 30 min at ambient temperature, isonitrile **1** (0.56 g, 4 mmol) was added and the mixture shaken for 60 h at ambient temperature. Resin **7a** was washed successively with CH_2Cl_2, MeOH, H_2O, MeOH, DMF and CH_2Cl_2 and dried under vacuo. Dealkylation of resin **7a** was effected by treatment with TFA:CH_2Cl_2 (1:1) for 10 min at ambient temperature (longer reaction times resulted in trifluoroacetylation of the primary amine). The loadings of resins **7a** and **7b** were determined by cleavage of an aliquot of resin by treatment with 0.25 M NaOMe in MeOH:THF (1:1) for 1 h at ambient temperature and quantification of the released esters by HPLC (see Table 1). Resins **8b** and **9b** were prepared similarly. Reductive alkylations of resins **7b**–**9b** were carried out by treatment with the appropriate aldehyde (8 equiv.) and $NaBH_3CN$ (24 equiv.) in DMF:HOAc (7:1) for 50 h; product resins were washed successively with DMF, MeOH, H_2O, MeOH, DMF and CH_2Cl_2 and cleaved as described above. Yields and purities were calculated as described in Table 1.

Compound **11** was prepared in the solution phase by treatment of **6b** (40 mg, 0.15 mmol) with 4-methoxybenzaldehyde (2.5 equiv.) in 2.5 ml of DMF:HOAc (15:1) in the presence of $NaBH_3CN$ (10 equiv.) for 72 h at ambient temperature. The crude product was subjected to prep. HPLC on a C-18 column eluting with a H_2O–MeCN gradient and the major product of mass 392 was isolated (14 mg, 24%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.98 (2H, d, J=9 Hz), 7.84 (2H, d, J=9 Hz), 7.06 (2H, d, J=9 Hz), 6.78 (2H, d, J=9 Hz), 4.20 (1H, d, J=17Hz), 4.05 (1H, d, J=14Hz), 3.98 (1H, d, J=14Hz), 3.96 (1H, m), 3.74 (3H, s), 3.54 (1H, m), 3.10 (1H, m). The benzylic protons resonating at 4.05 and 3.98 ppm showed NOEs with the aromatic protons at 7.84 and 7.06 but no correlations with the protons of the tetrahydropyrazine ring system indicating that the primary amino group was the site of alkylation.

Acknowledgements

We thank Ian Parsons, Izumi Takagi, ZhiSong Ji and Zhi-Dong Jiang for analytical support and Lee Herman for proof reading the manuscript.

References

1. (a) Armstrong, R. W.; Brown, D. S.; Keating, T. A.; Tempest, P. A. In *Combinatorial Chemistry Synthesis and Applications*; Wilson, S. R.; Czarnik, A. W., Eds.; John Wiley & Sons: New York, 1997; p. 153. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123–131. Strocker, A. M.; Keating, T. A.; Tempest, P. A.; Armstrong, R. W. *Tetrahedron Lett.* **1996**, *37*, 1149–1152.
2. (a) Ugi, I. *Isonitrile Chemistry*; Academic Press: London, 1971. (b) Ugi, I.; Domling, A.; Horl, W. *Endeavour* **1994**, *18*, 115–122.
3. (a) Cao, X.; Moran, E. J.; Siev, D.; Lio, A.; Ohasi, C.; Mjalli, A. M. M. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 2953–2958. (b) Short, K. M.; Ching, B. W.; Mjalli, A. M. M. *Tetrahedron* **1997**, *53*, 6653–6679.
4. Hulme, C.; Cherrier, M.-P. *Tetrahedron Lett*. **1999**, *40*, 5295–5299.
5. Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. *Tetrahedron Lett*. **1998**, *39*, 3635–3638.
6. Blackburn, C. *Tetrahedron Lett*. **1998**, *39*, 5469–5472.
7. (a) Groebke, K.; Weber, L.; Fridolin, M. *Synlett* **1998**, 661–663. (b) Bienayme, H.; Bouzid, K. *Angew. Chem., Int. Ed. Engl.* **1998**, 37, 2234–2237.
8. Starrett, J. E.; Montzka, T. A.; Crosswell, A. R.; Cavanagh, R. L. *J. Med. Chem*., **1989**, *32*, 2204–2210.
9. Sabalayrolles, C.; Cros, G. H.; Milhavet, J. C.; Rechenq, E.; Chapat, J. P.; Boucard, M.; Serrano, J. J.; McNeill, J. H. *J. Med. Chem.* **1984**, *27*, 206–212.
10. Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170–1176.
11. (a) Fisher, M. H.; Lusi, A. *J. Med. Chem*. **1972**, *15*, 982–985. (b) Trapani, G.; Franco, M.; Ricciardi, L.; Latrofa, A.; Genchi, G.; Sanna, E.; Tuveri, F.; Cagetti, E.; Biggio, G.; Liso, G. *J. Med. Chem.*, **1997**, *40*, 3109–3118.
12. For related reactions, see: (a) Bristow, N. W.; Charlton, P. T.; Peak, D. A.; Short, W. F. *J. Chem. Soc.* **1954**, 616–629. (b) Tadeka, K.; Shudo, K.; Okamoto, T.; Kousuge, T. *Chem. Pharm. Bull.* **1978**, *26*, 2924. (c) Knott, E. B. *J. Chem. Soc*. **1956**, 1360. (d) Saint–Ruf, G.; Loukakou, B.; N'Zousi, C. *J. Heterocyclic Chem*. **1981**, *18*, 1565–1570.
13. The compounds were dissolved in TFA–CH_2Cl_2 at a concentration of 50 mM and dealkylations were allowed to proceed at ambient temperature. Aliquots were removed at time intervals, quenched by treatment with methanolic ammonia and subjected to HPLC analysis.
14. Syntheses were less successful when Merrifield chloromethyl-PS resin was used in place of HMBA-AM because of partial cleavages from the resin during the acid-induced dealkylation step.
15. (a) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett*. **1996**, *37*, 4869–4872. (b) Cheng, Y.; Chapman, K. T. *Tetrahedron Lett*. **1997**, *38*, 1497–1500.
16. For examples of the reduction of related heterocylcles, see: (a) Chavignon, O.; Teulade, J. C.; Madesclaire, M.; Geueiffier, A.; Blache, Y. *J. Heterocyclic Chem.* **1992**, 29, 691–697. (b) Bonnet, P. A.; Sablayrolles, C.; Chapat, J. P. *J. Chem. Res. (M)* **1984**, 468–480.
17. (a) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett*. **1996**, *37*, 7193–7196. (b) Booth, R. J.; Hodge, J. C. *J. Am. Chem. Soc*. **1997**, *119*, 4882–4886. (c) Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. *J. Am. Chem. Soc*. **1997**, *119*, 4874–4881.
18. Metcalf, C. A.; Vu, C. B.; Sundaramoorthi, R.; Jacobsen, V. A.; Laborde, E. A.; Green, J.; Green, Y.; Macek, K. J.; Merry, T. J.; Pradeepan, S. G.; Uesugi, M.; Varkhedkar, V. M.; Holt, D. A. *Tetrahedron Lett.* **1998**, 39, 3435–3438.