Pergamon

Tetrahedron Letters 42 (2001) 6097–6100

TETRAHEDRON LETTERS

Grafted ionic liquid-phase-supported synthesis of small organic molecules

Joan Fraga-Dubreuil and Jean Pierre Bazureau*

Université Rennes 1, Institut de Chimie, Synthèse & Electrosynthèse Organiques 3, UMR 6510, Bât. 10A, Campus de Beaulieu, Avenue du Général Leclerc, CS 74205, 35042 Rennes Cedex, France

Received 8 June 2001; accepted 29 June 2001

Abstract—The preparation and applications in the Knoevenagel and 1,3-dipolar cycloaddition reactions of new grafted soluble liquid phases derived from imidazolium ionic liquids are described. Good yields and high regioselectivity are the features observed with these unconventional liquid phases.

Molecular diversity based on combinatorial organic synthesis[1] is now being used for rapid lead generation in both drug discovery and the development of biologically active compounds with potential therapeutic value. This demand for large numbers of new compounds has in turn, caused chemists to look for ways to simplify, expedite, and automate the process of small organic molecule synthesis. Synthetic approaches that utilise solid phases exhibits several shortcomings owing to the nature of heterogeneous reaction conditions.[2] Reaction kinetics can be non-linear, slow reactions and degradation of the polymer support after long reaction time were mentioned. The transfer of traditional solid-phase synthesis is often complicated. The soluble polymers[3] such as poly(ethylene)glycol (PEG), poly(styrenes), polyethylenes couple the advantages of homogeneous solution chemistry (reaction kinetics, lack of diffusion phenomena) with those of solid-phase methods (the ability to use an excess of reagents to drive a reaction to completion, ease of analysis and including ease of product isolation). The fact that they can, in certain cases, be recycled for repeated use is also interesting.

Previous work[4] from our group has demonstrated that room-temperature ionic liquids (IL) gave significant rate enhancements and improved yields in solvent-free 1,3-dipolar cycloaddition when the dipolarophile was covalently grafted on the ionic liquid. ILs[5] have gained increasing attention for performing all types of reaction. By modification of the cation and anion, their properties can be turned in many ways. There are basically three modes of operation: use of the ionic liquid as a co-solvent, as a pure solvent or in a biphasic system.[6]

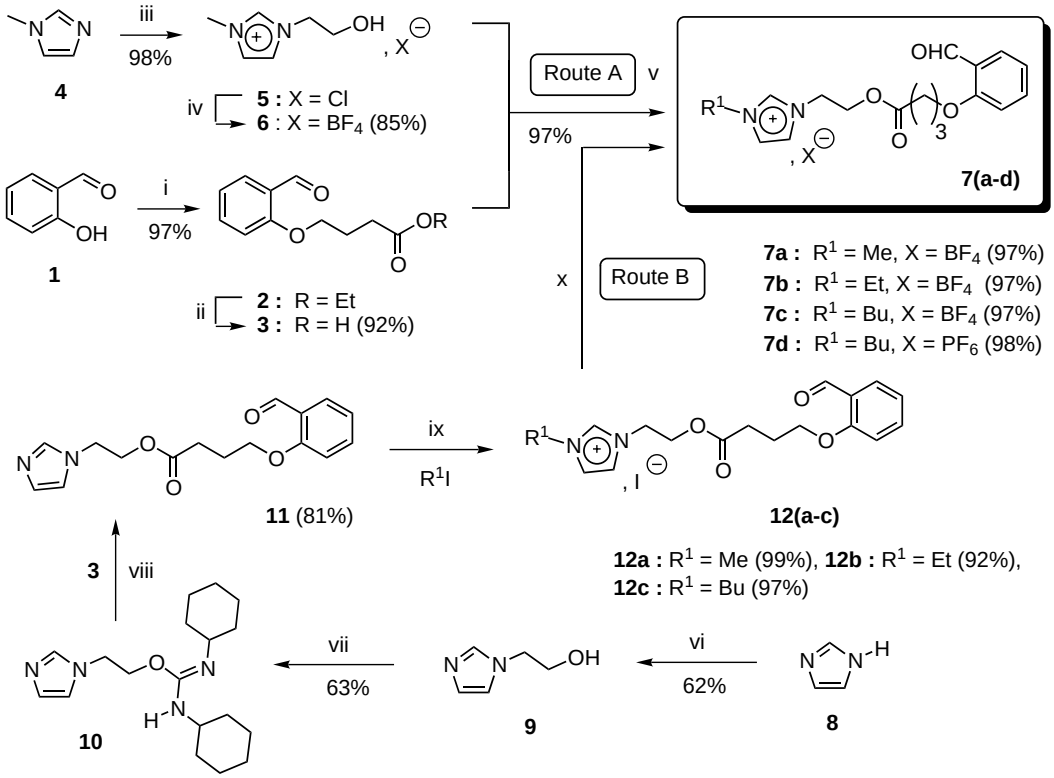
In this paper, we report our results about the first application of ILs for liquid-phase synthesis into the field of supported reagent. We have chosen the ILs as liquid phase because: (1) they are soluble in a wide range of both inorganic and organic materials, (2) they are immiscible with a number of organic solvents and provide a non-aqueous alternative for two-phase systems, and (3) ionic liquid phases are simple to prepare and are potentially compatible with a broad spectrum of reactions.[7]

Usual polymers for liquid-phase synthesis must also provide a reasonable compromise between loading capacity and solubilising power. With ILs as liquid phases, the loading capacity was easily evaluated using ^{1}H or ^{13}C spectroscopy and after cleavage the starting IL phase was recovered and reused for a further cycle.

As a suitable model reaction for ionic liquid-phase-supported organic synthesis, we have chosen to use benzaldehyde bound to the ionic liquid moiety. The synthesis of the corresponding grafted ionic liquid phases **7**(**a**–**d**) is shown in Scheme 1. For the preparation of the starting 4-(2-formylphenoxy)butyric acid[8] **3**, salicylaldehyde **1** was reacted in a *Williamson* ether synthesis with ethyl bromobutyrate (EBB) to give ester **2** in 97% yield followed by saponification with KOH in refluxing MeOH (**3**: 92% yield).

* Corresponding author. Fax: +(33) 02 99 28 63 74; e-mail: jean-pierre.bazureau@univ-rennes1.fr

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01190-X

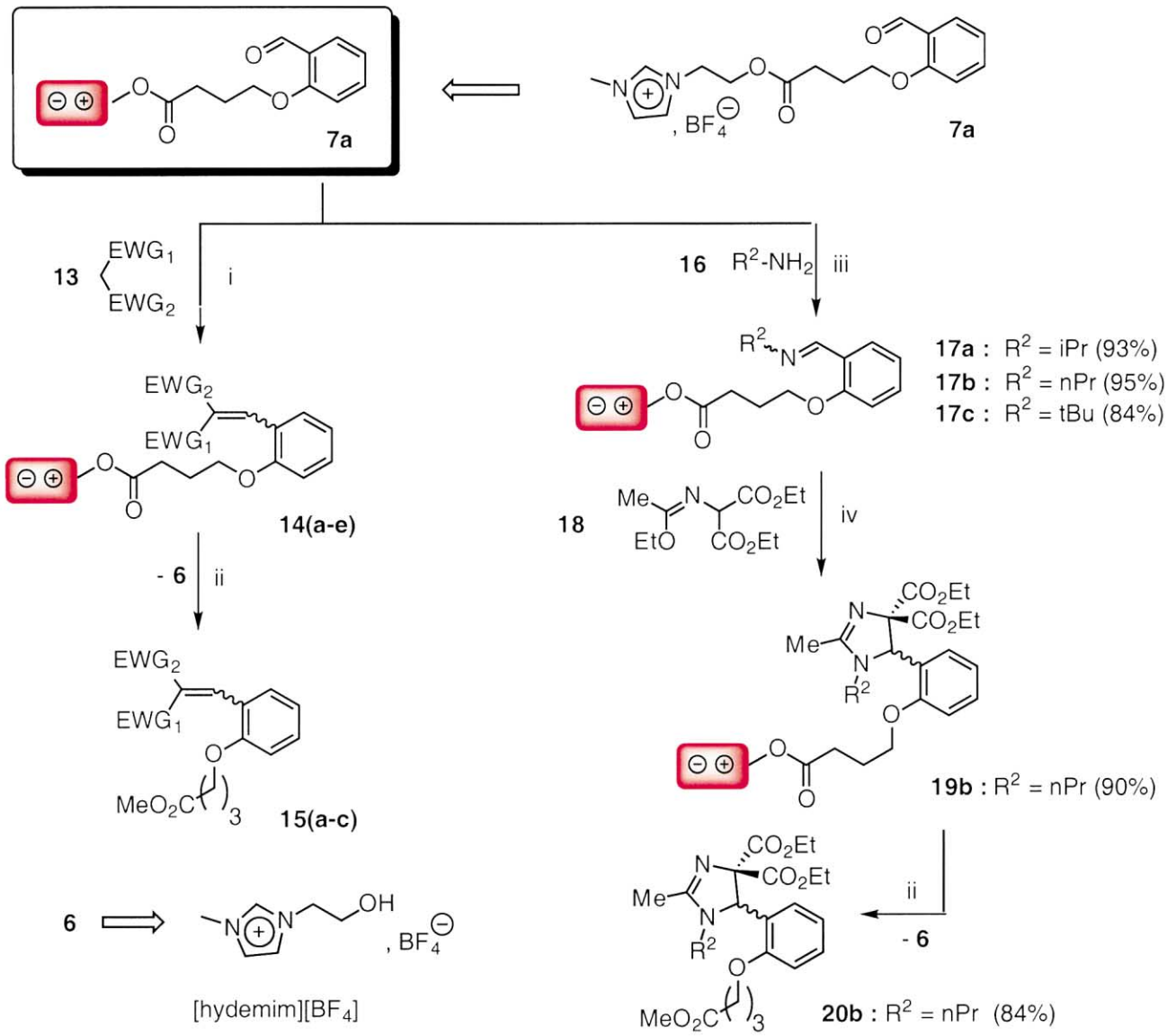


Scheme 1. *Reagents and conditions*: (i) EBB, K_2CO_3 (2 equiv.), MeCN, reflux, 24 h; (ii) KOH 2N, MeOH, reflux, 1.5 h, HCl 5N; (iii) chloroethanol (1 equiv.), 80°C, N_2, 96 h; (iv) NH_4BF_4 (3 equiv.), MeCN, 60°C, 20 h; (v) DCC (1 equiv.), DMAP (5%), MeCN, rt, 18 h; (vi) chloroethanol (1 equiv.), EtONa (1.1 equiv.), EtOH, reflux, 12 h.; (vii) DCC (1 equiv.), CuCl (0.1 equiv.), 70°C, 24 h; (viii) **3** (1 equiv.), MeCN, reflux, 20 h, satd $NaHCO_3$; (ix) for **12a**: MeI (1.5 equiv.), DCM, reflux, 72 h; for **12b**: EtI (1.5 equiv.), $CHCl_3$, reflux, 96 h; for **12c**: BuI (1 equiv.), MeCN, reflux, 72 h; (x) for **7**(**a**–**c**): NH_4BF_4 (2 equiv.), MeCN, reflux, 48 h; for **7d**: KPF_6 (1.1 equiv.), THF, rt, 24 h.

Two synthetic strategies were developed for the preparation of the ionic liquid phases **7**(**a**–**d**). In the direct route A, the novel 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate ([hydemim][BF_4]) **6** was easily prepared in two steps using standard procedures (83% yield). Then esterification of **3** (1.01 equiv.) with the IL **6** in dry MeCN in the presence of dicyclohexylcarbodiimide[9] (DCC) produced the new ionic liquid phase **7a** in more than 97% yield as pale yellow oil after repeated washings of the crude residue with benzene. The conversion was almost quantitative as judged by acquisition of clean ^1H and ^{13}C NMR as well as by FAB-MS. In route B, we directed our efforts toward a simple and general route to imidazolium iodides **12** with various lipophilic side chains of the cation. The available *N*,*N*′-dicyclohexyl isourea[10] **10** (63% yield) from 2-imidazol-1-yl ethanol[11] **9** (62% yield from **8**) reacted with **3** in refluxed MeCN for 20 h. After repeated washings with saturated $NaHCO_3$, ester **11** was obtained in 81% yield and undergoes quantitative quaternisation with alkyl iodides (**12**(**a**–**c**): 92–99%). Subsequent anion metathesis of iodide salts **12**(**a**–**c**) with NH_4BF_4 (2 equiv.) or KPF_6 (1.1 equiv.) respectively in MeCN (60°C, 2 days) and in THF (25°C, 24 h) leads to the desired grafted ionic liquid phases **7**(**a**–**d**). These ionic liquid phases (ILPs) **7** are isolated in high yield (~98%) as straw-coloured liquids after filtration to remove NH_4I or KI followed by vacuum evaporation of the solvent. At room temperature the ILPs **7** are viscous oils and became fully liquid at 60°C without decomposition.[12]

In order to define the ability of the ILPs **7a**[13] in liquid-phase combinatorial synthesis, we have checked the reactivity of the formyl group covalently grafted on the IL phase for Knoevenagel reactions[14] and dipolar cycloadditions. As shown in Scheme 2, we obtained successfully catalysed (2% of piperidine) Knoevenagel reactions with malonate derivatives **13** (1 equiv.) using solvent-free conditions associated with focused microwave irradiations[15] (μω: Synthewave® 402 oven[16]) after a short reaction time (15–60 min) at 80°C. Following AcOEt or Et_2O washings of the IL phase, the bound products **14**(**a**–**c**) were subjected to a very efficient cleavage from the IL phase with NaOMe in methanol.[17] Reaction progress was conveniently monitored by ^1H and ^{13}C NMR spectroscopy. After removal of solvent in vacuo, the expected compounds **15**(**a**–**c**) were extracted with CH_2Cl_2 in 87% yield without the need for silica gel chromatography (Table 1) and, finally, it was possible to reuse the insoluble [hydemim][BF_4] **6** in another cycle of synthesis.[18]

By utilising this IL-phase methodology, reaction of **7a** with various alkylamines **16** (1 equiv.) gave the desired bound aldimines **17**(**a**–**c**) in short reaction times (20



Scheme 2. *Reagents and reaction conditions*: (i) **13** (1 equiv.), piperidine (2%), μω, 80°C; (ii) MeONa (0.1 equiv.), MeOH, rt, 18 h; (iii) **16** (1 equiv.), μω, 80°C, 20 min; (iv) **18** (1 equiv.), 70°C, 15 h.

min). The successful regioselective addition of amines onto the IL-phase **7a** will allow diversity introduction at this step, i.e. R = *i*Pr (**17a**, 93%), *n*Pr (**17b**, 95%), *t*Bu (**17c**, 84%). Next, the IL-phase dipolarophile **17b** was submitted to a regioselective 1,3-dipolar cycloaddition[19] reaction with the imidate **18** derived from dimethyl aminomalonate (1 equiv.). Finally, treatment of bound cycloadduct **19b** with 10% NaOMe in MeOH resulted also in a practical cleavage from the Il phase to provide only the diethyl 2-imidazoline-4,4-dicarboxylate **20b** in 84% yield and the structure was confirmed by ^{1}H, ^{13}C NMR and FAB-MS.

In summary, we have shown that benzaldehyde bound to IL can be readily prepared and used in Knoevenagel reactions and 1,3-dipolar cycloadditions using solvent-free conditions assisted by focused microwave irradia-

Table 1. Compounds **14** and **15** generated via Scheme 2

Compound	EWG[1]	EWG[2]	Reaction time	Yield (%)[c]
14a	CO_2Me	CN	15 min[a]	98
14b	CO_2Me	CO_2Me	1 h[a]	98
14c	CO_2Et	CO_2Et	1 h[a]	98
14d	CN	CN	15 min[a]	98
14e	COMe	COMe	2 h[a]	98
15a	CO_2Me	CN	18 h[b]	87
15b	CO_2Me	CO_2Me	18 h[b]	87
15c	CN	CN	18 h[b]	87

[a] The reaction was monitored by ^{1}H NMR spectroscopy in $CDCl_3$ as solvent with TMS as internal reference.
[b] The reaction was considered complete when no starting compound **13** was detected by TLC.
[c] Yields are based on the conversion of **13** to **14**, **14** to **15** and are isolated yields.

tions. Product isolation is routine and the reactions are high yielding. The use of this novel IL phase in liquid-phase organic synthesis (LPOS) offers considerable advantages because the side product is removed by simple extraction and washings from the cleaved IL phase, so no chromatography is necessary. In contrast to the various restrictions of reaction development in solid-phase synthesis, IL phases allow standard analytical methods (NMR, TLC) to monitor reaction progress. This work has highlighted a novel soluble-phase approach to LPOS. Perhaps one of the exciting features of the IL phases is their generality, with potential applications to many other chemistries. Finally the IL-phase methodology should be compatible with high-throughput organic synthesis and automation technology. We are currently exploring the scope and the potential of microwave assisted liquid-phase synthesis[20] by extending this approach to other IL-phase transformations.

Acknowledgements

J. Fraga-Dubreuil wishes to thank the Ministère de la Recherche et de l'Enseignement Supérieur for a research fellowship. We also thank Professor Jack Hamelin for fruitful discussions.

References

1. Ley, S. V.; Baxendale, J. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, *23*, 3815 and references cited therein.
2. Yan, B. *Acc. Chem. Res.* **1998**, *31*, 621 and references cited therein.
3. (a) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546; (b) Wentworth, Jr., P.; Janda, K. D. *Chem. Commun.* **1999**, 1917; (c) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489.
4. Fraga-Dubreuil, J.; Bazureau, J. P. *Tetrahedron Lett.* **2000**, *41*, 7351.
5. (a) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772; (b) Hagiwara, R.; Ito, Y. *J. Fluorine Chem.* **2000**, *105*, 221; (c) Welton, T. *Chem. Rev.* **1999**, *99*, 2071; (d) Seddon, K. R. *J. Chem. Tech. Biotechnol.* **1997**, *38*, 351; (e) Seddon, K. R. *Kinet. Catal. Engl. Transl.* **1996**, *37*, 693.
6. Olivier, H. *J. Mol. Catal. A* **1999**, *146*, 285.
7. (a) Sundermeyer, W. *Angew. Chem.* **1965**, *77*, 241; *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 222; (b) Sundermeyer, W. *Chem. Unserer Z.* **1967**, *1*, 150; (c) Volkov, S. V. *Chem. Soc. Rev.* **1990**, *19*, 21.
8. Benson, D. R.; Valentekovich, R.; Tam, S. W.; Diederich, F. *Helv. Chim. Acta* **1993**, *76*, 2034.
9. Mathias, L. J. *Synthesis* **1979**, 561.
10. Vowinkel, E.; Wolff, C. *Chem. Ber.* **1974**, *107*, 496.
11. Giesemann, H. *J. Prakt. Chem.* **1957**, *4*, 169.
12. Ngo, H. L.; LeCompte, K.; Hargens, L.; McEwen, A. B. *Thermochem. Acta* **2000**, *357–358*, 97.
13. Typical procedure for the preparation of *1-{2-[4-(2-formylphenoxy)butyryloxy]ethyl}-3-methyl-3*H*-imidazol-1-ium tetrafluoroborate (**7a**)* (route A): To a mixture of dicyclohexylcarbodiimide (2.97 g, 14.42 mmol) and dimethylaminopyridine 5% (88 mg, 0.7 mmol) in dry acetonitrile (75 ml) were added successively [hydemim][BF_4] **6** (3.08 g, 14.42 mmol) in one portion, then 4-(2-formylphenoxy)butyric acid **3** (3 g, 14.42 mmol). After vigorous stirring at rt for 18 h, the insoluble *N,N′*-dicyclohexylurea was eliminated by filtration. The filtrate was concentrated under reduced pressure and the resulting crude reaction mixture was washed three times with benzene (20 ml). Removal of the solvent in vacuo lead to a pale yellow viscous oil in 97% yield. The ionic liquid phase **7a** was stored under an inert atmosphere at 4°C. ^{1}H NMR δ_H [$(CD_3)_2CO$, 300 MHz] 2.15 (quint., 2H), 2.66 (t, 2H), 4.02 (s, 1H), 4.20 (t, 2H), 4.52 (t, 2H), 4.66 (t, 2H), 7.06 (t, 1H), 7.20 (d, 1H), 7.63 (ddd, 1H), 7.67 (t, 1H), 7.73 (dd, 1H), 7.78 (t, 1H), 9.02 (s, 1H), 10.44 (s, 1H); ^{13}C NMR δ_C [$(CD_3)_2CO$, 75 MHz] 24.9, 30.8, 36.6, 49.5, 63.1, 68.3, 114.0, 121.4, 123.9, 124.7, 125.7, 128.4, 137.0, 138.1, 162.1, 173.2, 189.8; HRMS, *m/z*: 317.1497 found (calcd for $C_{17}H_{21}N_2O_4$, M^+ requires: 317.1501)
14. (a) Chérouvrier, J. R.; Boissel, J.; Carreaux, F.; Bazureau, J. P. *Green Chem.* **2001**, in press; (b) Vanelle, P.; Meuche, J.; Maldonado, J.; Crozet, M. P.; Delmas, F.; Timon-David, P. *Eur. J. Org. Chem.* **2000**, 157; (c) Bourmendjel, A.; Nuzillard, J. M.; Massiot, G. *Tetrahedron Lett.* **1999**, *40*, 9033; (d) Chamontin, K.; Lokskin, V.; Rossollin, V.; Samat, A.; Guglielmetti, R. *Tetrahedron* **1999**, *55*, 5821; (e) Michaud, D.; Ayoubi, S. A.; Dozias, M. J.; Toupet, L.; Texier-Boullet, F.; Hamelin, J. *Chem. Commun.* **1997**, 1613.
15. (a) Varma, R. S. *Green Chem.* **1999**, *1*, 43; (b) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213; (c) Caddick, S. *Tetrahedron* **1995**, *51*, 10403.
16. Commarmot, R.; Didenot, R.; Gardais, J. F. *Fr. Demande* 25 560 529, 1985; *Chem. Abstr.* **1986**, *105*, 17442.
17. (a) Chi, Y. C.; Sun, C. M. *Synthesis* **2000**, 591; (b) Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **2000**, 1217; (c) Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis* **2000**, 1035.
18. Before using [hydemim][BF_4] **6** in the second run, the IL-phase **6** was washed twice with methylene chloride (15 ml). After addition of acetone and filtration, the filtrate was concentrated in vacuo. Then, the grafted IL-phase **7a** was synthesised also in high yield (97%) with the same reaction time (18 h) from [hydemim][BF_4]) **6** according to the experimental procedure describe in Ref. 13.
19. (a) de La Hoz, A.; Diaz-Ortis, A.; Morenos, A.; Langa, F. *Eur. J. Org. Chem.* **2000**, 3659; (b) Fraga-Dubreuil, J.; Cherouvrier, J. R.; Bazureau, J. P. *Green Chem.* **2000**, *2*, 226.
20. Stadler, A.; Kappe, C. O. *Eur. J. Org. Chem.* **2001**, 919.