Special Issue

Journal of Physical Organic Chemistry

Received: 4 October 2007, Revised: 7 February 2008, Accepted: 8 February 2008, Published online in Wiley InterScience: 23 May 2008

(www.interscience.wiley.com) DOI 10.1002/poc.1356

Formylation of activated arenes by phenyl formate: implications for the mechanism of the Fries rearrangement of aryl formates

Alessandro Bagno[a], Willi Kantlehner[b] and Giacomo Saielli[c]*

We present an NMR and DFT investigation of the reaction of phenyl formate with 3-methoxyphenol and 3,5-dimethoxyphenol with excess BCl_3. The products obtained (3-methoxy- and 3,5-dimethoxy-salicylaldehyde, respectively) are the same as those resulting from the Fries rearrangement of 3-methoxy- and 3,5-dimethoxy-phenyl formate. These results represent a novel regioselective synthetic route to aromatic aldehydes, using phenyl formate as a source of formylating agent. They also unambiguously prove that the Fries rearrangement of aryl formates (that we recently investigated in *J. Org. Chem*. 71, 9331–9340, 2006) is intermolecular: the intermediate formyl chloride is released *in situ* and, in turn, it formylates the intermediate dichloroborate ester of 3-methoxy- and 3,5-dimethoxy-phenol in a second independent step. The —BCl_2 moiety bound to the aryl oxygen of the substituted phenol interacts with the formyl chloride strongly favouring the *ortho* substitution. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: Fries rearrangement; ^{11}B NMR; reaction mechanisms; DFT calculations; formylation

INTRODUCTION

The Fries rearrangement transforms an aryl ester into a hydroxycarbonyl compound, typically a ketone.[1,2] Excess of a Lewis acid is needed; whether the *para* or *ortho* isomer is obtained it depends strongly on the experimental conditions like temperature, substrate and, most important, the Lewis acid. In the last decade new catalysts, such as heteropoly acids[3,4] and metal triflates,[5] as well as new reaction methodologies, such as microwave irradiation[6] and ionic liquids as solvents,[7] have been successfully applied to the Fries rearrangement.

Despite the importance of the reaction in organic synthesis, the details of the mechanism are still unclear. Intramolecular mechanisms have been proposed, particularly in those cases where the *ortho* isomer is the main or the only product,[8] as well as intermolecular ones, particularly where the *para* isomer is the dominant product.[9–13]

Recently, the Fries rearrangement has been extended to aryl formates, thus providing a convenient route to the synthesis of hydroxybenzaldehydes, as shown in Scheme 1.[14]

BCl_3 and BBr_3, under appropriate experimental conditions, were found to be good catalysts for this reaction.[14] The choice of the Lewis acid appears particularly important since earlier attempts to perform the Fries rearrangement of aryl formates using BF_3, $AlCl_3$, HF, or polyphosphoric acid failed.[15–17]

We have been involved in a detailed mechanistic study of the Fries rearrangement of aryl formates promoted by BCl_3, using NMR spectroscopy (^1H, ^2H, ^{13}C, and ^{11}B) and DFT calculations.[18,19] The general picture that emerged was the following: the reaction, after the rapid complexation of the substrate at the carbonyl oxygen (shown in Scheme 2), proceeds with two main steps: in the first step, the aryl oxygen–carbon bond is cleaved and formyl chloride is released *in situ*, together with the formation of a dichloroborate ester of the corresponding phenol. Therefore the reaction is intermolecular. In the second step, a Friedel-Crafts acylation takes place; nevertheless, only the *ortho* product is obtained since the Ar—$OBCl_2$ moiety of the intermediate interacts with the formylating agent (formyl chloride) driving the reaction through the *ortho* path. MP2 calculations (on DFT-optimized geometries) agreed with this view: in fact, at the level of theory used in our previous work, the *para* Wheland intermediate was not found on the potential energy surface.[19]

Despite the clear-cut evidence collected in our previous work, regarding the formation of formyl chloride as formylating agent, the intermolecular nature of the reaction remained open to doubt, for example, concerning the extent of separation of the two intermediates in the solvent cage.

The proposed mechanism amounts to a formylation of activated arenes (the intermediate obtained from the substrate in the first step) using an aryl formate (the substrate itself) as a source of formyl chloride. It is then conceivable a "cross" Fries rearrangement where the aryl formate providing the formylating agent is different from the substituted phenol to be formylated.

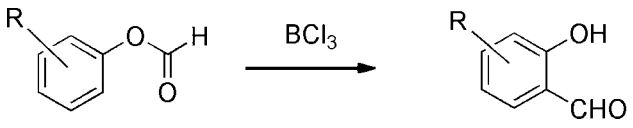
* *Correspondence to: G. Saielli, Istituto per la Tecnologia delle Membrane del CNR, Sezione di Padova, Via Marzolo, 1-35131 Padova, Italy.*
E-mail: giacomo.saielli@unipd.it

a *A. Bagno*
Dipartimento di Scienze Chimiche, Università degli Studi di Padova, Via Marzolo, 1-35131 Padova, Italy

b *W. Kantlehner*
Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany

c *G. Saielli*
Istituto per la Tecnologia delle Membrane del CNR, Sezione di Padova, Via Marzolo, 1-35131 Padova, Italy

Journal of Physical Organic Chemistry



Scheme 1. Fries rearrangement of aryl formates

The outcome of such an experiment would be twofold: first, it would provide further evidence of the proposed reaction mechanism of the Fries rearrangement of aryl formates, definitely supporting the intermolecular, regioselective, path; second, it would represent a novel synthetic route to aromatic aldehydes using a proper aryl formate as a source of the formyl group.

EXPERIMENTAL

Preparation of samples

The reaction mixtures were prepared by mixing the substituted phenol and phenyl formate directly in the NMR tube with a concentration of *ca.* 0.06 M each (*ca.* 0.6 ml), and then adding *ca.* 0.1 ml of a 1 M solution of BCl_3 in heptane, that is, with a nominal 0.15 M concentration of BCl_3. This 2.5-fold excess is necessary in order to allow for the consumption of one equivalent of BCl_3 by reaction with the phenol, thus leaving another equivalent to form the complex with phenyl formate and still leaving some excess free BCl_3.

The reaction mixture was kept in ice during the first few minutes before inserting the tube into the probehead, except for the time needed to mix the reactants using a vortex and to insert the tube into the spinner and wiping it. Usually the tube was allowed to equilibrate for a few minutes before starting the acquisition. The solution turns to a pale orange/yellow colour as soon as BCl_3 is added and eventually it becomes dark red as the substrate has completely reacted.

NMR spectroscopy

^1H measurements have been run at 400 MHz with a 5-mm multinuclear BBI probehead and at 300 MHz with a 5-mm multinuclear BBO probehead. ^{11}B NMR measurements have been run with a 5-mm multinuclear BBO probehead at 96 MHz.

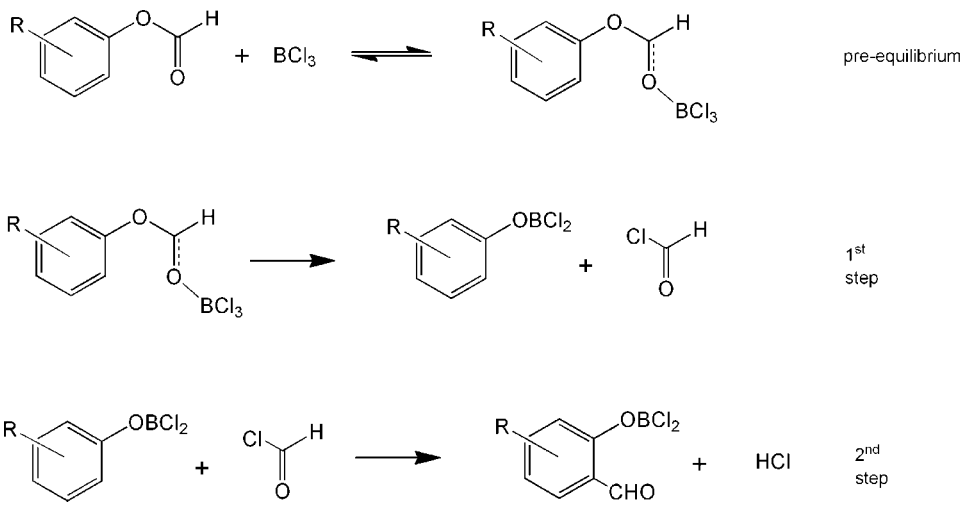
DFT calculations

Dealing with boron compounds requires an appropriate description of dative bonds. The MPW1K functional[20] has proved to be effective, in conjunction with 6-311+G** basis set, for boron compounds. This level of theory has been used in this work for geometry optimization, frequency analysis, and for the calculation of the Gibbs free energy corrections and ZPE corrections at 298 K. The electronic energy has been calculated at the MP2/6-311+G** level of theory, using the structures optimized at the DFT level, and the final Gibbs free energy has been calculated adding the thermal corrections calculated at the DFT level, following the protocol of Reference [19]. Calculations were run using the Gaussian 03 software package.[21]

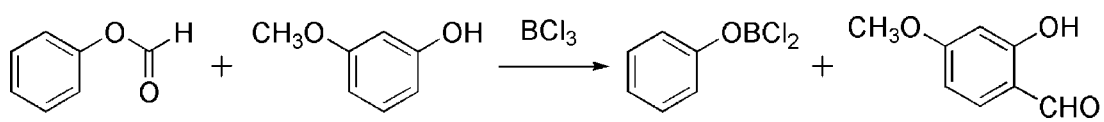
RESULTS AND DISCUSSION

In order to get more insight on the reaction mechanism of the Fries rearrangement of 3-methoxyphenyl formate we have investigated the behaviour of a mixture of phenyl formate and 3-methoxyphenol with excess BCl_3, shown in Scheme 3.

Phenyl formate, with excess BCl_3, does not rearrange to the Fries product: neither the *para*- nor the *ortho*-hydroxy-aldehyde are observed.[14] Nonetheless, according to our proposed



Scheme 2. The main steps of the Fries rearrangement of aryl formates as proposed in Reference [19]. The occurrence of the 2nd step depends on the substituent R



Scheme 3. Reaction of phenyl formate and 3-methoxyphenol with excess BCl_3

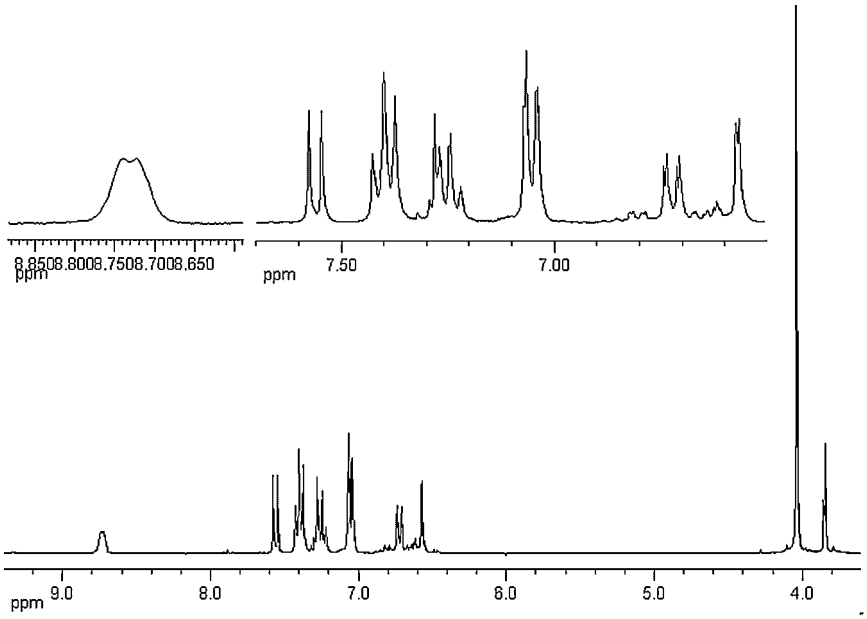


Figure 1. Final ^{1}H NMR spectrum (300 MHz, 283 K, $CDCl_3$) of the 1:1 mixture (0.06 M) of phenyl formate and 3-methoxyphenol with excess (0.15 M) of BCl_3

mechanism, the first step of Scheme 2 takes place after the pre-equilibrium, producing the intermediate phenol dichloroborate ester with the release of formyl chloride.[19] The latter, in absence of a sufficiently reactive substrate to formylate, slowly decomposes into CO and HCl. However, in the presence of 3-methoxyphenyl dichloroborate, which is the intermediate in the 1st step of Scheme 2 for the rearrangement of 3-methoxyphenyl formate, we should obtain 3-methoxysalicylaldehyde exactly as from the Fries rearrangement of 3-methoxyphenyl formate itself.

The initial spectrum of the equimolar mixture of phenyl formate and 3-methoxyphenol with excess BCl_3 is just the superposition of the ^{1}H NMR spectrum of the complex of phenyl formate with BCl_3 at the carbonyl oxygen (e.g., we observe the formyl resonance at 9.23 ppm[19]) and the dichloroborate ester of 3-methoxyphenol.

In Fig. 1, we show the final ^{1}H NMR spectrum of the same reaction mixture. The formation of the Fries product (3-methoxysalicylaldehyde) is clearly demonstrated by the aldehyde resonance at 8.73 ppm with its typical broad, doublet-like signal, due to long-range coupling with ^{10}B and ^{11}B, as obtained from the direct Fries rearrangement of 3-methoxyphenyl formate.[19]

Also, the time evolution of the ^{11}B NMR spectrum of the above reaction mixture closely resembles the one observed for 3-methoxyphenyl formate with excess BCl_3.[19] The ^{11}B signal of the final product is observed at 8.3 ppm.

Therefore, the mixture of phenyl formate and 3-methoxyphenol with an excess of BCl_3 yields the same product as the Fries rearrangement of 3-methoxyphenyl formate under the same experimental conditions.

One might reasonably wonder whether or not a transesterification occurs, in such acidic conditions, first producing 3-methoxyphenyl formate which then would undergo a Fries rearrangement as observed in Reference [19]. In such a case, the fact that the mixture of phenyl formate and 3-methoxyphenol yields the same product as 3-methoxyphenyl formate would not add any new information. However, we can safely discard this occurrence. In fact, during the course of the reaction, only three aldehyde signals (phenyl formate at 8.98 ppm, formyl chloride at 9.70 ppm and final product at 8.70 ppm) and two methoxy signals (3-methoxyphenol at 3.83 ppm and final product at 4.02 ppm) are observed. More important, the aromatic region between 6.80 and 7.00 ppm, where most aromatic signals of the complex of 3-methoxyphenyl formate with BCl_3 lie,[19] shows no new resonances. It is likely that the quantitative reaction of 3-methoxyphenol with BCl_3 (note that the phenol OH resonance at 4.83 ppm disappears after the addition of BCl_3) prevents any nucleophilic attack of 3-methoxyphenol to phenyl formate.

In the proposed mechanism, an essential role is played by the Ar—$OBCl_2$ intermediate, where the tri-coordinated boron can still act as Lewis acid, in coordinating formyl chloride and driving the reaction through the *ortho* pathway.[15] The transition state for the formylation that we identified in Reference[19], regarding 3-methoxyphenyl formate, is shown in Fig. 2.

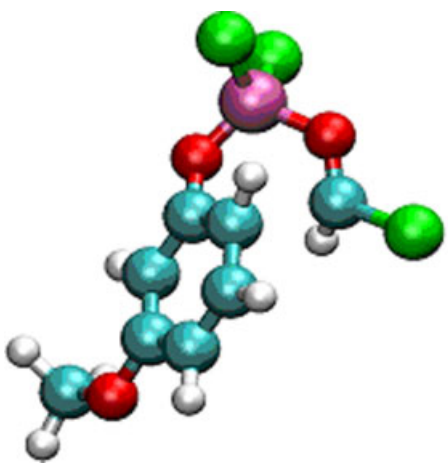


Figure 2. Structure of the transition state for the formylation of 3-methoxyphenyl dichloroborate (MPW1K/6-311+G**). The B–O distance (oxygen of formyl chloride) is 1.553 Å, while the C–C distance of the C–C bond being formed is 2.192 Å. C blue; H grey; O red; Cl green; B purple

Journal of Physical Organic Chemistry

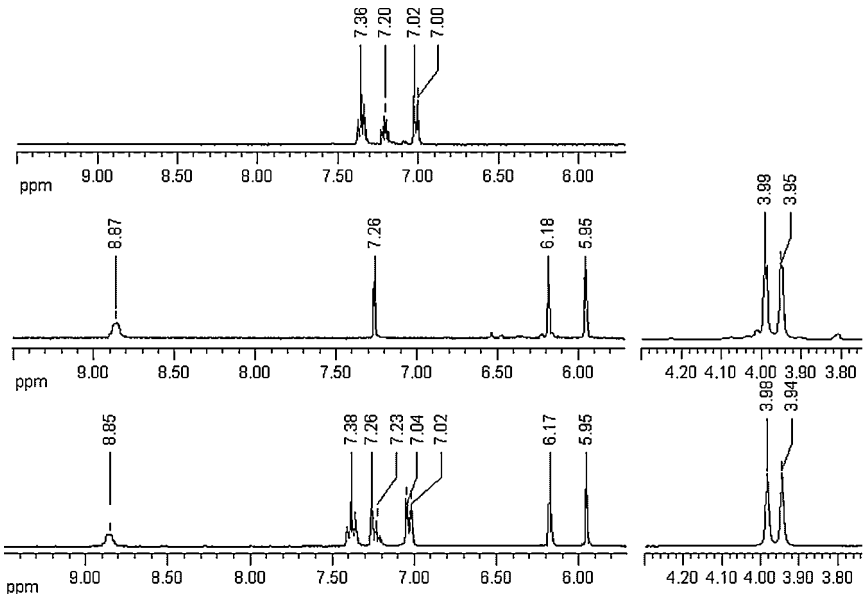


Figure 3. Final ^{1}H NMR spectra of the reaction mixtures (0.06 M in substrates) obtained from treatment with excess BCl_3 (0.08 M in the first two cases and 0.15 M in the last case) of: (top) phenyl formate, 400 MHz, 298 K, $CDCl_3$; (middle) 3,5-dimethoxyphenyl formate, 300 MHz, 301 K, $CDCl_3$; 1:1 mixture of phenyl formate and 3,5-dimethoxyphenol, 300 MHz, 301 K, $CDCl_3$

We note that the B—O bond is formed ahead of the C—C bond. Therefore, the interaction of the oxygen of HCOCl with the Lewis acid moiety is essential to lower the reaction barrier for the formylation. Accordingly, we have investigated the reaction of a 1:1 mixture of phenyl formate and anisole with excess BCl_3: in agreement with the proposed mechanism, no anisaldehyde was observed in the ^{1}H NMR spectrum (as inferred from the lack of resonances above 8 ppm), while the final ^{11}B NMR spectrum showed only the signal of free BCl_3 (46.5 ppm) and phenyl dichloroborate (31.8 ppm).

These results represent an unambiguous proof that the Fries rearrangement of aryl formates proceeds via an intermolecular, albeit highly regioselective, pathway. Phenyl formate, in the presence of an excess of boron trichloride, behaves as a source of formyl chloride which, in turn, formylates 3-methoxyphenyl dichloroborate present in the mixture. This observation may be exploited to devise a synthetic route to aromatic aldehydes using phenyl formate as a source of formylating agent.

However, the substrate to be formylated needs to be activated for electrophilic substitution: phenyl dichloroborate does not react, in contrast to the analogous 3-methoxyphenyl dichloroborate. Similarly, toluene was not formylated to tolualdehyde under the same experimental conditions.[19] It is then interesting to study the reaction of a substrate more reactive towards formylation than 3-methoxyphenyl formate, like 3,5-dimethoxyphenyl formate.

In Fig. 3 we show the final ^{1}H NMR spectra of solutions of (top) phenyl formate, (middle) 3,5-dimethoxyphenyl formate and (bottom) a 1:1 mixture of phenyl formate and 3,5-dimethoxyphenol, all with an excess of BCl_3. The last spectrum is clearly the superposition of the first two, indicating that, also in this case, the reaction of a mixture of phenyl formate and 3,5-dimethoxyphenol with excess of BCl_3 leads to 3,5-dimethoxysalicylaldehyde exactly as obtained from the Fries rearrangement of 3,5-dimethoxyphenyl formate under the same experimental conditions.

^{11}B data can be fitted by first-order kinetics in the product (Fig. 4). However, only the reaction of 3-methoxyphenol with phenyl formate is sufficiently slow to allow for a reliable collection of data points, leading to an effective rate constant $k = 9.4 \times 10^{-5}\,s^{-1}$. The reaction of 3,5-dimethoxyphenol is significantly faster even at a lower temperature: by the time the NMR tube has been inserted into the probe and equilibrated about 2/3 of the product have already been formed, so that the derived rate constant is only crudely estimated. These circumstances somewhat limit the mechanistic proposals that can be drawn. At this stage, we can only make the following observations. (a) A low concentration of HCOCl is maintained

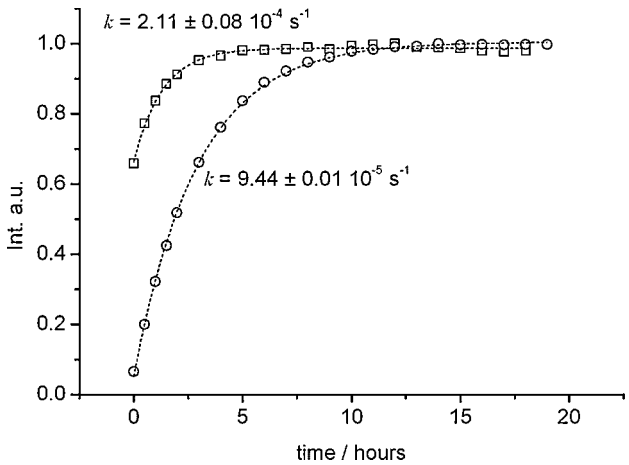


Figure 4. Time evolution of the normalized integrated intensity, *I*, of the 8.3 ppm signal of the salicylaldehyde in the ^{11}B spectrum for the solution of 1:1 mixture of phenyl formate (0.06 M) with: (open circles) 3-methoxyphenol at 283 K, (open squares) 3,5-dimethoxyphenol at 268 K, and excess of BCl_3 (0.15 M). Dashed lines represent the best fit to the function $I(t) = 1 - \exp[-k\,(t - t_0)]$ (however, this may not imply first-order kinetics; see text)

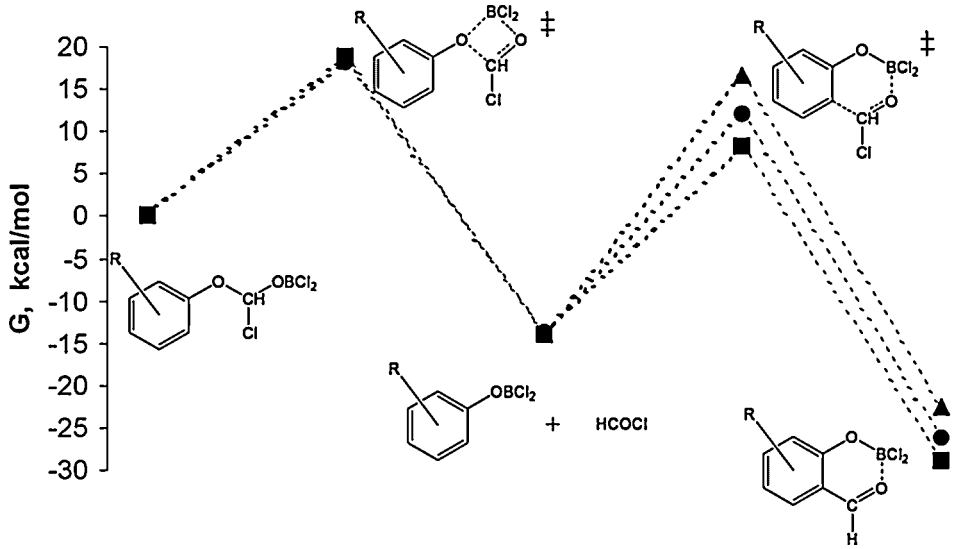


Figure 5. Gibbs free energy profile (with thermal corrections at 298 K) for the Fries rearrangement of (▲) phenyl formate; (●) 3-methoxyphenyl formate; (■) 3,5-dimethoxyphenyl formate (MP2/6-311+G**//MPW1K/6-311+G**)

during the reaction;[19] (b) the reactivity of 3,5-dimethoxyphenol is higher than that of 3-methoxyphenol. These two results provide conflicting evidence, suggesting electrophile formation or electrophilic attack to be the rate-determining step, respectively. This contradiction can be reconciled assuming that both steps have comparable rates, which may lead to a reaction profile hardly distinguishable from first-order kinetics.

A systematic investigation of the kinetics, by varying the relative concentrations of substrates and Lewis acid, and the temperature, is needed to elucidate the details of the mechanism.

QM calculations of the reaction profile are in agreement with the experimental findings. Starting from the various structures (reactants, intermediates, transition states and products) investigated in Reference [19] concerning 3-methoxyphenyl formate, we have recalculated the reaction profile for the reaction of phenyl formate and 3,5-dimethoxyphenyl formate focussing on the two transition states identified therein. The first one concerns the migration of the Lewis acid moiety from the carbonyl oxygen to the aryl oxygen (after nucleophilic attack of a chloride anion to the carbonyl[19]); the second is a standard intermolecular Friedel-Crafts acylation. A summary of the reaction profile is shown in Fig. 5.

The activation barrier for the first step ($\Delta G^{\ddagger}$ of about 18 kcal/mol) of the reaction is essentially unaffected by the substitution of the aromatic ring. In fact, we recall that all the formates investigated, in the presence of an excess of BCl_3, undergo ArO—CHO bond cleavage with the release of formyl chloride. In contrast, the activation barrier for the second step, the Friedel-Crafts acylation is, as one might expect, indeed influenced by substitution. In particular, QM calculations predict that the activation barrier for the formylation of phenyl dichloroborate is rather high, $\Delta G^{\ddagger}$ being more than 30 kcal/mol, while it is reduced to about 26 kcal/mol for 3-methoxyphenol and further reduced to 22 kcal/mol for 3,5-dimethoxyphenol. Therefore, in this qualitative scale, at least one methoxy group is necessary to activate the aromatic ring together with the presence of an —$OBCl_2$ moiety to drive the reaction through the *ortho* pathway.

CONCLUSIONS

We have presented experimental and computational results concerning the reaction of phenyl formate with activated arenes with excess BCl_3. The present study fully confirms the intermolecular mechanism of the Fries rearrangement of aryl formates proposed in our previous work.[19] Summarizing, the Fries rearrangement promoted by BCl_3 is understood to be a typical Friedel-Crafts acylation where the acylating agent is HCOCl generated *in situ* by cleavage of a formate ester. HCOCl is a weak acylating agent, also because it decomposes rapidly. However, despite the intermolecular pathway, high *ortho* regioselectivity is achieved because HCOCl remains coordinated to the —$OBCl_2$ moiety present in the intermediate phenol ester, thus driving the formylation towards the closest nucleophilic *ortho* carbon.

On the other hand, the reaction investigated here may represent a synthetically useful procedure for formylation of activated arenes, using phenyl formate as a source of formyl chloride, thereby avoiding the use of CO and HCl under high pressure as in the well-known Gattermann-Koch method.[22]

Acknowledgements

We thank Dr Ralf Kress (University of Stuttgart) for the synthesis of phenyl formate and Prof. G. Scorrano (Università di Padova) for useful comments. We also acknowledge insightful suggestions by a reviewer.

REFERENCES

[1] J. March, *Advanced Organic Chemistry*, 3rd ed. Wiley, New York, **1985**.
[2] R. Martin, *Org. Prep. Proced. Int.* **1992**, *24*, 369.
[3] E. F. Kozhevnikova, E. G. Derouane, I. V. Kozhevnikov, *Chem. Commun.* **2002**, 1178.

[4] E. F. Kozhevnikova, J. Quartararo, I. V. Kozhevnikov, *App. Catal. A* **2003**, *245*, 69.
[5] O. Mouhtady, H. Gaspard-Iloughmane, N. Roques, C. Le Roux, *Tetrahedron Lett.* **2003**, *44*, 6379.
[6] F. M. Moghaddam, M. Ghaffarzadeh, S. H. Abdi-Oskoui, *J. Chem. Res. Syn.* **1999**, 574.
[7] J. R. Harjani, S. J. Narja, M. Salunkhe, *Tetrahedron Lett.* **2001**, *42*, 1779.
[8] Y. Ogata, H. Tabuchi, *Tetrahedron* **1964**, *20*, 1661.
[9] F. Krausz, R. Martin, *Bull. Soc. Chim. Fr.* **1965**, 2192.
[10] R. Martin, *Bull. Soc. Chim. Fr.* **1974**, 983.
[11] R. Martin, *Bull. Soc. Chim. Fr.* **1979**, II-373.
[12] J. L. Dawson, J. L. Gibson, L. S. Hart, C. R. Waddington, *J. Chem. Soc. Perkin Trans.* **1989**, *2*, 2133.
[13] J. L. Gibson, L. S. Hart, *J. Chem. Soc. Perkin Trans.* **1991**, *2*, 1343.
[14] G. Ziegler, E. Haug, W. Frey, W. Kantlehner, *Z. Naturforsch. B* **2001**, *56*, 656.
[15] D. Kästner, *Angew. Chem.* **1941**, *54*, 296.
[16] G. A. Olah, in *Friedel-Crafts and Related Reactions*, Vol. I (Ed.: G. A. Olah), Wiley Interscience, New York, **1963**.
[17] G. A. Olah, in *Friedel-Crafts and Related Reactions*, Vol. III/2 (Ed.: G. A. Olah), Wiley Interscience, New York, **1964**.
[18] A. Bagno, W. Kantlehner, R. Kress, G. Saielli, *Z. Naturforsch. B* **2004**, *59*, 386.
[19] A. Bagno, W. Kantlehner, R. Kress, G. Saielli, I. Stoyanov, *J. Org. Chem.* **2006**, *71*, 9331.
[20] B. J. Lynch, P. L. Fast, M. Harris, D. G. Truhlar, *J. Phys. Chem. A* **2000**, *104*, 4811.
[21] *Gaussian 03, Revision C.02*, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr. T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, (**2004**).
[22] J. J. Li, in *Name Reactions: A Collection of Detailed Reaction Mechanism*, 2nd ed. Springer, New York, **2003**.