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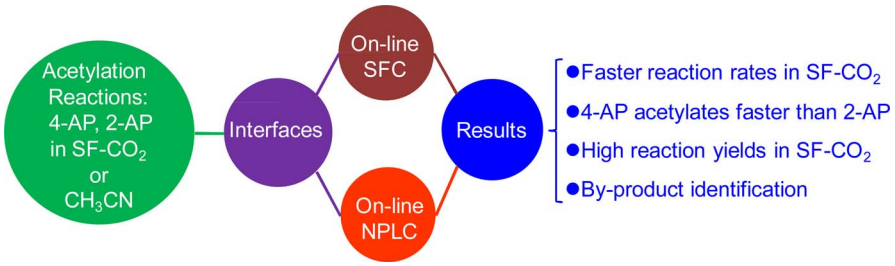
Monitoring the progress of the acetylation reactions of 4-aminophenol and 2-aminophenol in acetonitrile modified supercritical fluid carbon dioxide and pure acetonitrile using on-line supercritical fluid chromatography and on-line liquid chromatography

Ben Li, Wei Guo, Edward D. Ramsey*

Sustainable Technology Research Unit, University of Science and Technology Liaoning, Anshan 114051, China

GRAPHICAL ABSTRACT



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ABSTRACT

The progress of acetylation reactions of 4-aminophenol and 2-aminophenol in acetonitrile modified SF-CO_2 or pure acetonitrile were monitored using on-line SFC or a non-conventional type of on-line normal phase liquid chromatography. For each reaction solvent, acetylations using acetic anhydride were performed at 323 K, 333 K and 343 K. Reactions in SF-CO_2 were monitored using a single valve recirculation interface that coupled a high pressure reaction vessel operated at 17.5 MPa. Reactions in acetonitrile were monitored using a two valve interface to couple a reaction vessel operated under 0.1 MPa nitrogen atmosphere. For both aminophenol isomers, acetylation proceeded more rapidly in acetonitrile modified SF-CO_2 compared with acetonitrile. Also for each reaction solvent, the rate of acetylation of 4-aminophenol exceeded that of 2-aminophenol. On-line chromatographic analysis rapidly established that: (*i*) 4-aminophenol produced a diacetylated product only in acetonitrile modified SF-CO_2, whereas (*ii*) 2-aminophenol produced a diacetylated product only in acetonitrile.

1. Introduction

Organic solvents such as: hexane, toluene, dichloromethane, carbon tetrachloride and chloroform have been extensively used as reaction solvents for organic synthesis. The use and availability of such conventional solvents is now becoming severely restricted and in some cases banned due to environmental and human health issues [1]. This has resulted in sustained efforts to develop and introduce various types of alternative "green" solvents for a diverse range of process development and manufacturing applications [1–3].

A wide variety of small-scale synthetic organic reactions have been performed using supercritical fluid carbon dioxide (SF-CO_2) as an alternative reaction solvent [4–9]. Apart from potential to replace and/or reduce dependency on the use and manufacture of several non-polar

* Corresponding author.
E-mail address: syphir1000@126.com (E.D. Ramsey).

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organic reaction solvents [10], SF-CO_2 can be advantageously utilized to achieve more rapid rates of reaction and improved selectivity *via* control of reaction temperature and pressure [5,6]. The use of carbon dioxide is unrestricted by the US Environmental Protection Agency [11] and this is likely to remain the case for the foreseeable future [12].

On-line process analytical technology (PAT) is now being successfully introduced for an expanding range of applications in the chemical manufacturing industries ranging from small-scale early stage R&D through to production scale process monitoring and control [13]. Currently, the majority of PAT techniques involve the use of spectroscopic procedures to help design, optimize and monitor processes that frequently involve the use of organic solvents [14]. A major advantage of PAT spectroscopic procedures is their ability to potentially obtain information concerning reaction intermediates that cannot be detected or monitored using off-line analytical procedures [15]. Provision of such information can lead to a better fundamental understanding of reaction mechanisms and factors that affect reaction kinetics [16]. Although chromatographic PAT techniques are less frequently used, they may become particularly relevant in situations where the early stage detection of impurities and by-products at low to trace levels becomes important for process understanding and control [17]. The use of sophisticated instrumentation involving the use of linked and complimentary spectroscopic and chromatographic PAT stages has also been utilized to simultaneously aid process understanding and optimization [18]. Apart from PAT applications, the general development of on-line analytical techniques serve to eliminate sample collection and preparation stages that are recognized as being the major contributors to errors in analytical chemistry [19].

Whilst demonstrating considerable potential, the use of SF-CO_2 as an alternative reaction solvent for general use in synthetic organic chemistry remains at a very early stage of evaluation and development. A major issue yet to be overcome concerns the poor solubility of many compounds in pure SF-CO_2 [20,21]. Consequently, the use of organic co-solvents is widely used to improve the solvating capacity of SF-CO_2. Progress is also being made in the use of other solubility enhancing additives such as fluorinated surfactants to make SF-CO_2 a more versatile solvent [11,21]. Despite the solvation issue, several reports have already described the use of PAT procedures involving the use of FTIR and UV/Vis spectroscopy to monitor reaction progress in SF-CO_2 [22,23]. We have reported the development of a two valve interface to monitor the progress of an esterification reaction performed in SF-CO_2 using on-line HPLC [24]. However, the successful use of on-line HPLC interfaced to SF-CO_2 apparatus largely depends on mobile phase composition. With reverse phase HPLC mobile phases using low organic modifier content, sample injections of SF-CO_2 solutions decompress to form gas bubbles entrained in the mobile phase that cause UV/Vis detector instability [25]. Consequently, to avoid such problems it is more logical and easier to interface SF-CO_2 apparatus with on-line SFC [26,27]. Accordingly, we have now introduced a simplified single valve recirculation interface to couple SF-CO_2 apparatus with on-line SFC. Such integrated systems have been used to obtain solubility data for two basic drugs in SF-CO_2 [28] and to monitor the progress of a photochemical reaction performed in SF-CO_2 [29]. As part of the latter study, the use of on-line SFC and on-line HPLC were compared and the chromatographic performance of the single valve recirculation interface operated in SFC mode was measured. It was demonstrated that on-line SFC can provide significant potential advantages compared to the use of on-line HPLC for monitoring synthetic reactions in SF-CO_2 apart from eliminating phase incompatibility issues. These advantages include: (*i*) enhanced SFC chromatographic performance due to "like being injected into like" in terms of solvent composition and pressure (*ii*) faster analysis times, and (*iii*) enhanced sensitivity relative to on-line HPLC. The use of SFC is now gaining more widespread acceptance following its success particularly in the field of chiral separations [30].

To date there are apparently no reports describing the feasibility of performing synthetic reactions in SF-CO_2 involving the use of amines as the principal reactants. This may be due to the complication that primary and secondary amines can very rapidly react with carbon dioxide in organic solvents to form carbamic acids [31]. Such types of reactions also take place in SF-CO_2 [32]. However, as demonstrated by Fischer et al. [33] some *N*-alkyl-substituted secondary benzylamines do not react with SF-CO_2 to form carbamic acids. This was attributed to steric effects of some of the *N*-alkyl substituents. The situation regarding the stability and potential use of aniline based compounds in SF-CO_2 requires better understanding since such aromatic amines are important in synthetic organic chemistry. For example, acetylation of 4-aminophenol is used for the manufacture of the pharmaceutical compound 4-acetamidophenol more commonly known as acetaminophen or paracetamol.

The principal objective of this study was to initially evaluate whether on-line SFC can be used to monitor the progress of acetylation reactions of 4-aminophenol and 2-aminophenol in SF-CO_2 and a conventional organic solvent. Further objectives included whether the use of on-line SFC could provide information concerning relative rates of reaction of the two aminophenol isomers and also the early stage detection and characterization of any acetylation reaction by-products. It was anticipated that the degree of correlation of reaction yields with reactant consumption measured in almost near time using on-line chromatography would provide an insight as to whether the extent and rate of progress of acetylation reactions of 4-aminophenol and 2-aminophenol in SF-CO_2 are influenced by carbamic acid formation. In this study we also describe the use of a non-conventional form of on-line normal phase liquid chromatography (NPLC) that involved the use of a mobile phase with high liquid carbon dioxide content. This closely related alternative to SFC was introduced to monitor the acetylation reactions of 2-AP in acetonitrile modified SF-CO_2 and acetonitrile.

2. Experimental

2.1. Materials and reagents

Information concerning the reagents and solvents used in this study are provided in Table 1.

For acetylation reactions performed in acetonitrile modified SF-CO_2 the following standard solutions were prepared: (1) 152 mg of either 4-AP or 2-AP dissolved in 50 mL acetonitrile, and (2) 780 μL acetic anhydride diluted with 25 mL acetonitrile. For acetylation reactions performed in pure acetonitrile the following solutions were prepared: (3) 137 mg of either 4-AP or 2-AP dissolved in 1 L acetonitrile, and (4) 1.12 mL acetic anhydride diluted with 25 mL actonitrile.

Table 1
Information concerning compounds and reagents.

Chemical name	Abbreviation	Source	Purity (%)	CAS no.
4-aminophenol	4-AP	J & K	97	123-30-8
2-aminophenol	2-AP	J & K	99	95-55-6
4-acetamidophenol[a]	AC	Aladdine	99	103-90-2
2-acetamidophenol	*iso*-AC	Aladdine	99	614-80-2
4-acetamidophenyl acetate	4-ACA	Aladdine	98	2623-33-8
2-acetamidophenyl acetate	2-ACA	Fluorochem	99	5467-64-1
aniline	–	Aladdine	99	62-53-3
4-methylaniline	–	Aladdine	99	106-49-0
2-methylaniline	–	Aladdine	98	95-53-4
acetonitrile	–	Sigma-Aldrich	99.9	75-05-8
methanol	–	Sigma-Aldrich	99.9	67-56-1
acetic anhydride	–	Sinopharm	99.9	64-19-7
CO_2	–	Airichem	99.9	124-38-9

[a] More commonly known as acetaminophen or paracetamol.