S. Afr. J. Chem., 2009, **62**, 33–38,
<http://journals.sabinet.co.za/sajchem/>.

One-pot Synthesis of Substituted Pyrroles with *N,N,N′,N′*-Tetrachlorobenzene-1,3-disulphonamide and *N,N′*-Diiodo-*N,N′*-1,2-ethanediyl*bis*(*p*-toluenesulphonamide) as Novel Catalytic Reagents

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Received 6 October 2008, revised 26 January 2009, accepted 2 February 2009.

ABSTRACT

In this research, *N,N,N′N′*-tetrachlorobenzene-1,3-disulphonamide as novel catalytic reagent and *N,N′*-diiodo-*N,N′*-1,2-ethanediyl*bis*(*p*-toluenesulphonamide) as new catalyst were used for the synthesis of *N*-substituted pyrroles in good to excellent yields under mild conditions. These reusable reagents were compared with existing reagents and it is clear that this study is a welcome addition in the field of pyrrole synthesis.

KEYWORDS

Pyrroles, Paal-Knorr reaction, TCBDA, NIBTS, catalytic reagent.

1. Introduction

The pyrrole heterocycle is a very attractive target in heterocyclic and combinatorial chemistry because it forms the basic motif in many bioactive compounds.[1] One of the most common approaches to pyrrole synthesis is the Paal-Knorr reaction in which 1,4-dicarbonyl compounds are converted to pyrroles in the presence of primary amines. In this reaction, the 1,4-dicarbonyl compounds provide the four carbons of the pyrroles with the possible substituents, whereas the amine provides the nitrogen with its substituent. Many catalysts have been used for this conversion such as Montmorillonite KSF,[2] microwave irradiation,[3,4] $Bi(NO_3)_3.5H_2O$,[5] $Sc(OTf)_3$,[6] $TolSO_3H$,[7] layered zirconium phosphate and zirconium sulphophenyl phosphonate,[8] titanium[9] or $TiCl_4/Et_3N$.[10] Some other methods for the synthesis of pyrroles include conjugate addition reactions,[11] annulation reactions,[12,13] multi-component reactions[14,15] and aza-Wittig reactions.[16] However, several of these methods require prolonged reaction times using various metals.[2–6] Thus, a milder, selective, non-hazardous, inexpensive, recyclable and eco-friendly organic catalyst is still in demand. The use of organic catalysts instead of inorganic Lewis acids has some advantages, including (i) the possibility of using acid-sensitive substrates and (ii) substrates with basic functional groups or electron-donating substituents that are prone to capture the acidic catalysts and that do not affect the reaction results.

2. Results and Discussion

Herein, we report a convenient method for the one-step synthesis of pyrroles under mild conditions using the novel catalytic reagent *N,N,N′,N′*-tetrachlorobenzene-1,3-disulphonamide (TCBDA) and a new catalytic reagent *N,N′*-diiodo-*N,N′*-1,2-ethanediyl*bis*(*p*-toluenesulphonamide) (NIBTS).[17–23] Since NIBTS and TCBDA contain halogen atoms which are attached to nitrogen atoms, it is likely that they release X^+ *in situ* which can act as a catalyst in the reaction medium. This is expected to be sufficient to catalyze the synthesis of pyrroles *via* the Paal-Knorr mechanism. The route for the synthesis of pyrrole derivatives is shown in Scheme 1.

Accordingly, treatment of hexan-2,5-dione with aniline in the presence of a catalytic amount of NIBTS afforded 2,5-dimethyl--*N*-phenylpyrrole in 90 % yield under solvent-free conditions. Then, the effect of solvents on this reaction was investigated. Several solvents, including acetonitrile, dichloromethane, chloroform, water and ethanol were examined during the course of this study. These experiments show that CH_3CN is a better solvent than the other solvents tested (96 % yield). Synthesis of 2,5-dimethyl-*N*-phenylpyrrole in acetonitrile using *N,N,N′,N′*-tetrachlorobenzene-1,3-disulphonamide (TCBDA) as a novel catalytic reagent at room temperature was also studied.

These results prompted us to investigate the scope and generality of these new protocols to various amines (aliphatic and aromatic) under optimized conditions. In the same manner, a variety of amines were coupled with hexan-2,5-dione in the presence of a catalytic amount of NIBTS and TCBDA at room temperature in order to give the corresponding pyrroles in good to excellent yields (Table 1). The less basic aromatic amines require only slightly more time than the more basic amino compounds, and both lead to high yields of the pyrrole products.

As shown in Table 1, aromatic amines with electron-donating groups (Table 1, entries 6, 7 and 11) or an electron-withdrawing group (Table 1, entries 9 and 10) are both effective in the Paal-Knorr reaction. The heterocyclic amines (Table 1, entries 16 and 17) exhibited analogous behaviour to that of aromatic amines and aliphatic amines.

The reaction conditions were also applicable to the di- or triamino substrates, in giving bipyrrole (Table 1, entries 4, 11–13, 15, 19 and 20) or tripyrrole compounds (Table 1, entry 21) in excellent yields.

In order to compare the current protocol with previously published methods for the synthesis of *N*-substituted pyrroles with benzyl-, naphthyl- and 2-pyridinylamine, the experiments listed in Table 2 were carried out. These results clearly demon-

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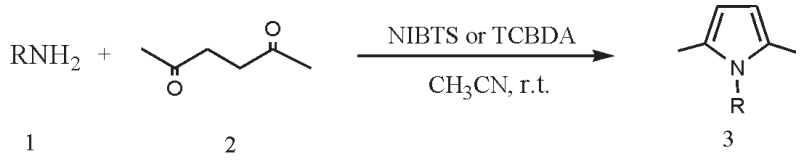
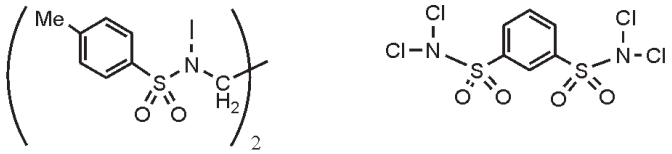


R: alkyl and aryl



NIBTS TCBDA

Scheme 1

strate that NIBTS and TCBDA are good catalytic reagents for the preparation of *N*-alkyl and *N*-aryl-2,5-dimethylpyrroles. Much shorter reaction times with similar to better yields were typically obtained.

Our experiments also indicated that NIBTS and TCBDA are reusable catalysts and after five runs, the catalytic activities of the reagents were almost the same as those of fresh catalysts. Thus, after the successful synthesis of 2,5-dimethyl-*N*-phenylpyrrole in the first run, which gave the corresponding product in 98 % isolated yield (Table 1, entry 1), the *N,N,N′,N′*-tetrachlorobenzene-1,3-disulphonamide (TCBDA) catalyst was subjected to a second run reaction from which it gave the product in 98 % yield; the average chemical yield for five consecutive runs was 78 %. The reusability of catalysts is shown in Fig. 1. In Scheme 2, the suggested mechanism for synthesis of pyrroles with our catalytic reagents is shown.[24]

In conclusion, we have introduced the novel catalytic reagent *N,N,N′,N′*-tetrachlorobenzene-1,3-disulphonamide (TCBDA) and new catalytic reagents *N,N′*-diiodo-*N,N′*-1,2-ethanediyl*bis* (*p*-toluenesulphonamide) (NIBTS) for the synthesis of various substituted pyrroles. The availability, ease of synthesis and reusability of the catalytic reagents, clean work-up, and high yields of this method make this method attractive for large-scale operations.

3. Experimental

3.1. Procedure for the Preparation of *N,N,N′,N′*-Tetrachlorobenzene-1,3-disulphonamide (TCBDA)

A sample of white finely-powdered benzene-1,3-disulphonamide (1 g) was dissolved in a solution of NaOCl (50 mL, 14 %), at 25 °C for 30 min. The colour of the solution did not change. After this time, acetic acid (20 mL, 50 %) was added to the solution. The insoluble chlorinated reagent was removed by filtration and washed with water (5 mL).

Analytical data for *N,N,N′,N′*-tetrachlorobenzene-1,3-disulphonamide: white solid, m.p. 145–147 °C. IR (KBr): ν_{max} 3050, 2950, 2900, 1570, 1462, 1417, 1377, 1304, 1167, 1082, 807, 776, 675 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 7.95–8.09 (m, CH aromatic, 1H), 8.11–8.58 (m, CH aromatic, 2H), 8.79 ppm (s, CH aromatic, 1H). m/z ($[M+H]^+$): 374, 339, 337, 321, 319, 305, 303, 272, 269, 267, 156, 154, 139, 125, 120, 104, 91, 77, 63. Anal. Calcd. for $C_6H_4N_2S_2O_4Cl_4$: C, 19.25; H, 1.06; N, 7.48; S, 17.11, Cl, 37.96. Found: C, 19.32; H, 0.95; N, 6.95; S, 17.00, Cl, 37.16.

3.2. General Procedure for the Synthesis of Pyrroles with NIBTS and TCBDA

To a solution of amine **1** (1 mmol) and 2,5-hexanedione **2** (1 mmol) in CH_3CN (2 mL) at room temperature, catalyst NIBTS (0.15 mmol, 0.05 g) or TCBDA (0.042 mmol, 0.016 g) were added. The mixture was allowed to stir at this temperature for a period of time as specified in Table 1. The reaction was monitored by TLC (3:1 n-hexane/acetone). After completion of the reaction, the solvent was evaporated. Then CH_2Cl_2 (10 mL) was added, and the catalyst was removed by filtration. Evaporation of the solvent under reduced pressure gave the products. Further purification was achieved by thin-layer chromatography using n-hexane:acetone (70:30) as the solvent system to afford the purified pyrroles.

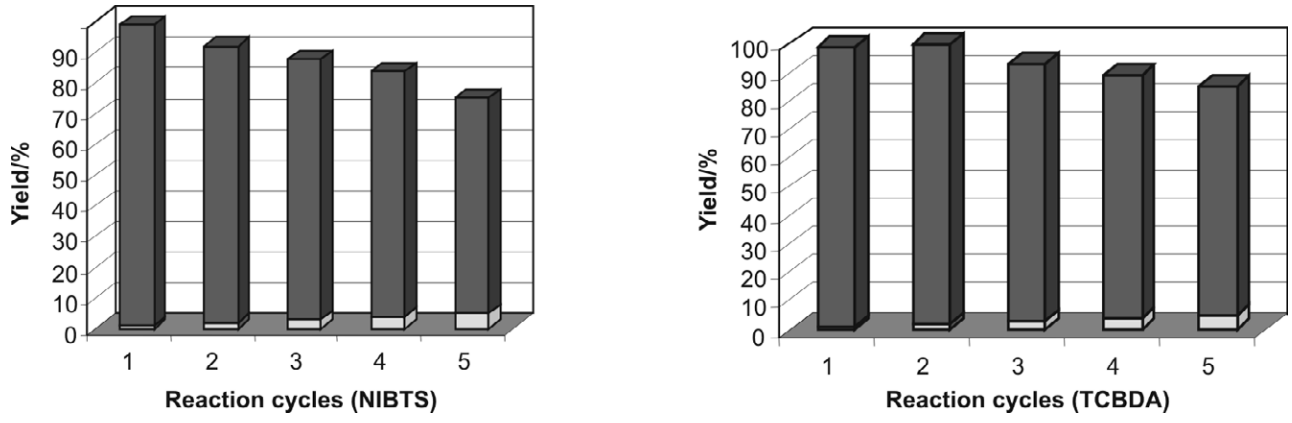
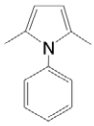
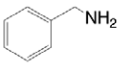
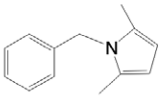
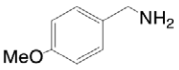
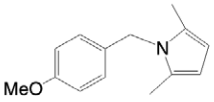
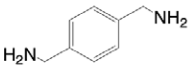
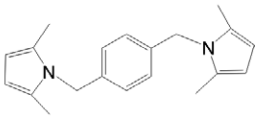
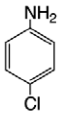
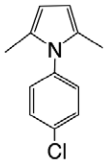
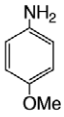
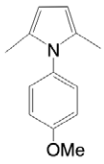
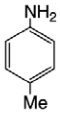
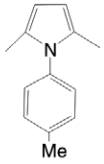
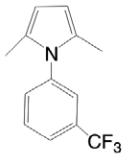
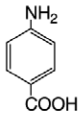
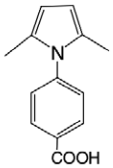
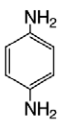
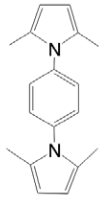
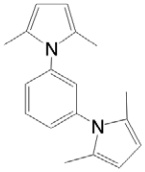


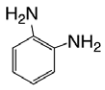
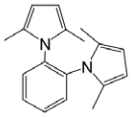
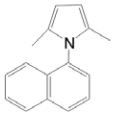
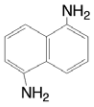
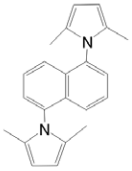
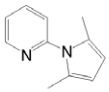
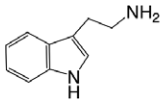
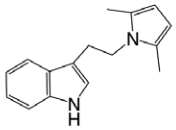
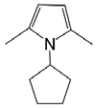
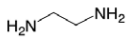
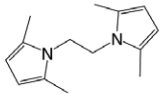
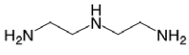
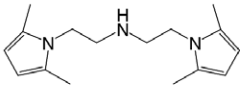
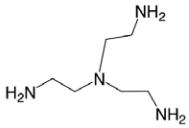
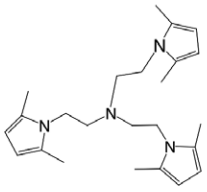
Figure 1 Reusability of catalysts used in this study.

Table 1 Synthesis of pyrroles catalyzed by NIBTS and TCBDA at room temperature.

Entry	Amine (1)	Product	NIBTS		TCBDA	
			Reaction time/min	Yield [a]/%	Reaction time/min	Yield [a]/%
1			20	96	5	98[5]
2			10	98	2	99[5]
3			12	95	3	99[5]
4			15	92	6	95
5			25	80	10	90[6]
6			20	85	10	92[25]
7			30	90	10	95[6]
9			90	75	25	90[25]
10			130	60	50	60
11			45	90	20	95
12			60	85	25	92

Continued on p. 36

Table 1 (*continued*)

Entry	Amine (1)	Product	NIBTS		TCBDA	
			Reaction time/min	Yield [a]/%	Reaction time/min	Yield [a]/%
13			200	60	100	70
14			65	85	30	90[5]
15			150	75	60	85[5]
16			200	70	80	60
17			50	90	30	92
18			10	96	2	98[25]
19			8	96	1	99[5]
20			12	95	5	98
21			15	90	5	95

[a] Products were characterized from their physical properties, comparison with authentic samples and by spectroscopic methods.

3.3. Analytical Data for Selected Compounds

Compound 4: (cream solid, m.p. 197–198 °C). IR (KBr): ν_{max} 1515, 1462, 1410, 1377, 1303, 1019 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.13 (s, CH_3, 12H), 4.97 (s, CH_2, 4H), 5.84 (s, pyrrolics, 4H), 6.82 ppm (s, PhH, 4H). Found: M$^+$ 292.1939. $C_{20}H_{24}N_2$ requires M, 292.1946. Anal. Calcd. for $C_{20}H_{24}N_2.0.5\,H_2O$: C, 78.29; H, 8.54; N, 9.96. Found: C, 79.88; H, 8.16; N, 8.97.

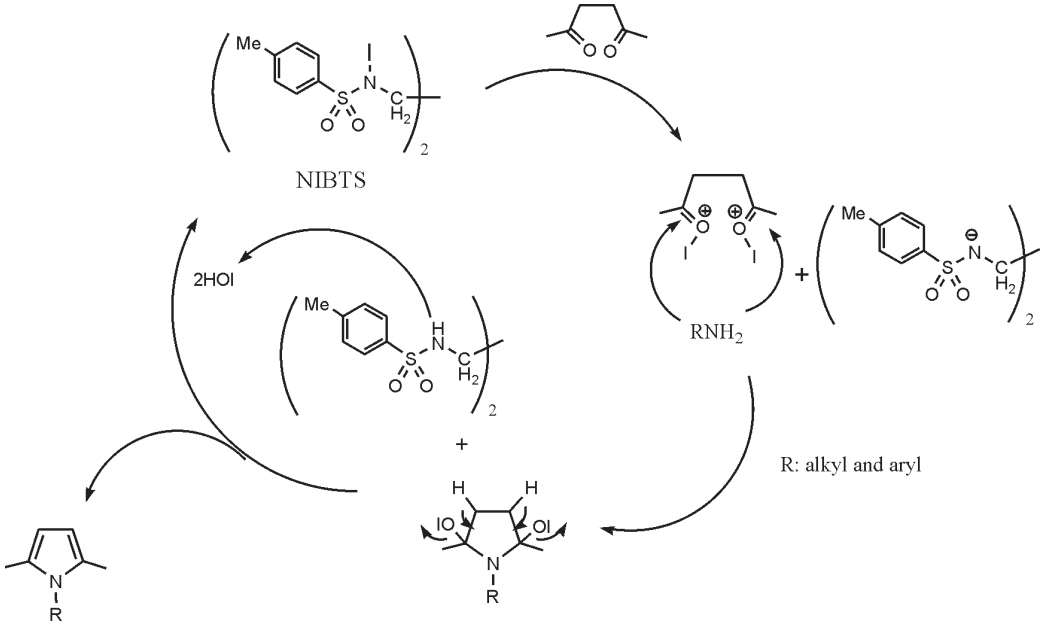
Compound 10: (pale yellow solid, m.p. 174–175 °C). IR (nujol): ν_{max} 2400–2200, 1678, 1607, 1463, 1377, 1324, 1129, 1106 cm^{-1}. ^{1}H NMR ($CDCl_3$ 250 MHz): δ 2.00 (s, CH_3, 6H), 5.90 (s, pyrrolics, 2H), 7.30 (d, J = 10.1 Hz, PhH, 2H), 8.20 (d, J = 10.1 Hz, PhH, 2H), 11.39 ppm (b, COOH, 1H). Found: M$^+$ 215.0946. $C_{13}H_{13}NO_2$ requires M, 215.1125. Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.55; H, 6.04; N, 6.51. Found: C, 71.84; H, 6.00; N, 6.22.

Compound 11: (pale yellow solid, m.p. 256–257 °C). IR (KBr): ν_{max} 1514, 1463, 1378, 1310, 1211, 1001 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.10 (s, CH_3, 12H), 5.90 (s, pyrrolics, 4H), 7.25 ppm (s, PhH, 4H). Found: M$^+$ 264.1626. $C_{18}H_{20}N_2$ requires M, 264.1632. Anal. Calcd. for $C_{18}H_{20}N_2.H_2O$: C, 76.59; H, 7.09; N, 9.92. Found: C, 77.37; H, 6.99; N, 9.61.

Compound 12: (brown solid, m.p. 99–100 °C). IR (nujol): ν_{max} 1600, 1521, 1499, 1459, 1377, 1321, 1006 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.10 (s, CH_3, 12H), 5.94 (s, pyrrolics, 4H), 7.12–7.68 ppm (m, PhH, 4H). Found: M$^+$ 264.1626. $C_{18}H_{20}N_2$ requires

Table 2 Reaction times and yields for previously published methods.

Substrate	Conditions	Reaction time	Yield/%	Ref.
Benzylamine	NIBTS	10 min	98	–
Benzylamine	TCBDA	2 min	99	–
Benzylamine	Montmorillonite, KSF	10 h	95	2
Benzylamine	I_2	30 min	92	2
Benzylamine	$Bi(NO_3)_3.5H_2O$	10 h	95	5
Benzylamine	Microwave	30 s	90	3
Benzylamine	$Sc(OTf)_3$	30 min	94	6
Benzylamine	α-$Zr(KPO_4)_2$	2 h	78	8
1-Naphthylamine	NIBTS	65 min	85	
1-Naphthylamine	TCBDA	30 min	90	-
1-Naphthylamine	$Sc(OTf)_3$	40 min	90	6
1-Naphthylamine	Montmorillonite, KSF	11 h	83	2
1-Naphthylamine	I_2	1 h	85	2
1-Naphthylamine	$Bi(NO_3)_3.5H_2O$	11 h	83	5
2-aminopyridine	NIBTS	200 min	70	–
2-aminopyridine	TCBDA	80 min	60	–
2-aminopyridine	$Bi(NO_3)_3.5H_2O$	25 h	70	5
2-aminopyridine	Montmorillonite, KSF	25 h	70	2



Scheme 2

M, 264.1637. Anal. Calcd. for $C_{18}H_{20}N_2.0.5H_2O$: C, 79.12; H, 7.32; N, 10.25. Found: C, 79.46; H, 7.62; N, 10.75.

Compound 13: (brown solid, m.p. 110–112 °C). IR (nujol): ν_{max} 1605, 1520, 1499, 1455, 1370, 1016 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 2.20 (s, CH_3, 12H), 5.96 (s, pyrrolics, 4H), 7.14–7.76 ppm (m, PhH, 4H). Found: M^+ 264.1626. $C_{18}H_{20}N_2$ requires M, 264.1635. Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.81; H, 7.57; N, 10.60. Found: C, 80.95; H, 7.42; N, 10.95.

Compound 17: (brown solid, m.p. 175–176 °C). IR (nujol): ν_{max} 3250, 3020, 1605, 1520, 1499, 1455, 1370, 1016 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 2.24 (s, CH_3, 6H), 3.06 (t, J = 15.5 Hz, CH_2, 2H), 4.04 (t, J = 15.5 Hz, CH_2, 2H), 5.83 (s, pyrrolics, 2H), 6.87 (s, CH, 1H), 7.12–7.73 (m, PhH, 4H), 7.94 ppm (s, NH, 1H). Found: M^+ 238.1524. $C_{16}H_{18}N_2$ requires M, 238.1536. Anal. Calcd. for $C_{16}H_{18}N_2.H_2O$: C, 75.00; H, 7.03; N, 10.93. Found: C, 74.49; H, 6.98; N, 10.39.

Compound 20: (yellow solid, m.p. 74–75 °C). IR (nujol): ν_{max} 3312, 2915, 2854, 1663, 1571, 1517, 1463, 1404, 1377, 1298, 1121, 1108 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz), δ 2.30 (s, CH_3, 12H), 2.70 (t, J = 17.91 Hz, CH_2, 4H), 3.75 (t, J = 18.5 Hz, CH_2, 4H), 5.70 ppm (s, pyrrolics, 4H). Found: M^+ 259.2048. $C_{16}H_{25}N_3$ requires M, 259.2055. Anal. Calcd. for $C_{16}H_{25}N_3$: C, 74.13; H, 9.65; N, 16.21. Found: C, 73.48; H, 9.88; N, 16.07.

Compound 21: (pale yellow solid, m.p. 110–111 °C). IR (nujol): ν_{max} 3100, 2854, 2739, 1571, 1518, 1464, 1407, 1378, 1298, 1166, 1061, 1016, 745 cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz) 2.25 (s, CH_3, 18H), 2.74 (t, J = 19.7 Hz, CH_2, 6H), 3.75 (t, J = 19.7 Hz, CH_2, 6H), 5.78 ppm (s, pyrrolics, 6H). Found: M^+ 380.3021. $C_{24}H_{36}N_4$ requires M, 380.3044. Anal. Calcd. for $C_{24}H_{36}N_4.0.5H_2O$: C, 74.04; H, 9.51; N, 14.39. Found: C, 74.11; H, 9.67; N, 14.79.

Acknowledgements

We are thankful to the Bu-Ali Sina University, Center of Excellence and Development of Chemical Methods (CEDCM)

for financial support and to the University of Sheffield for the NMR and mass spectra and CHN analyses. One of the authors (RG-V) acknowledges Prof. I. Coldham from the University of Sheffield for his kindness in hosting him as a research visitor. We heartily thank Dr Saeed Khodabakhsh for editing the manuscript.

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