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RESEARCH ARTICLE

Microwave-induced Synthesis of *N*-Substituted 1-Alkyl and 1-Aryl 3-Aminoisoquinolines

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Abstract: ***Background***: Aminoisoquinolines are an important class of heterocyclic compounds. These compounds present a wide range of pharmacological properties including antimalaric, anticonvulsant and anti-inflammatory. Although several preparation routes may be found in the literature for the preparation of these compounds, many of these methods present difficulties, including laborious isolation methods, drastic conditions and extended reaction times.

Methods: The synthesis of *N*-substituted 1-alkyl and 1-aryl- 3-aminoisoquinolines is developed through the reaction of 2-acylphenylacetonitriles with amines under microwave irradiation conditions. The reactions were performed in ethanol as a solvent without the use of catalyst. In parallel, these reactions were performed under identical conditions of temperature using P_2O_5/SiO_2 as a catalyst in different amounts.

Results: A series of *N*-substituted 1-alkyl and 1-aryl- 3-aminoisoquinolines were synthesized using microwave irradiation with as high selectivity, short reaction times and without the use of catalyst. The use of P_2O_5/SiO_2 as catalyst under microwave irradiation conditions was not effective for these reactions.

Conclusion: The results show an efficient method for the synthesis of *N*-substituted 1-alkyl and 1-aryl-3-aminoisoquinolines by the reaction of 2-acylphenylacetonitriles with amines using microwave irradiation. Some important advantages for this method include a strong decrease in reaction time, a good selectivity, and the absence of catalyst, with simplicity in operation and a benefit to the environment.

Keywords: 3-Aminoisoquinolines, Microwave irradiation, Cyclocondensation, 2-Acylphenylacetonitriles.

INTRODUCTION

Aminoisoquinolines are an important class of heterocyclic compounds that occur in natural and synthetic products. These compounds exhibit remarkable antimalaric [1, 2], anticonvulsant and anti-inflammatory activities [3, 4].

In addition, aminoisoquinolines were evaluated as Rho-associated protein kinase (ROCK) inhibitors, involved in a variety of important physiological functions including the regulation of smooth muscle contraction, migration and cell proliferation, cytoskeletal rearrangement, and inflammatory responses [5, 6].

Several synthesis pathways are described in the literature to obtain these compounds [7]. Within the scope of investigation of this broad family of substances, the synthesis of 3-aminoisoquinolines has been studied in the literature through different methods. Furthermore, only a few of these methods allow obtaining 1-substituted 3-aminoisoquinolines [8].

Noteworthy, among others, is the preparation of 1-substituted 3-aminoisoquinolines and 1,4-disubstituted derivatives reported by Tandel and Biel from 2-cyanobenzylcyanide using lithium amides, alkyl and aryllithium reagents in good yields [9].

In spite of their potential utility, some of these methods include long reaction times, large amounts of catalysts and expensive reagents.

In our research group, we have previously studied the synthesis of *N*-substituted 1-alkyl and 1-aryl 3-aminoisoquinolines. This involves the cyclocondensation of 2-acylphenylacetonitriles **1** with amines **2** using trifluoroacetic acid as catalyst to obtain a series of 3-aminoisoquinolines **3** in good yields [10] (Scheme **1**).

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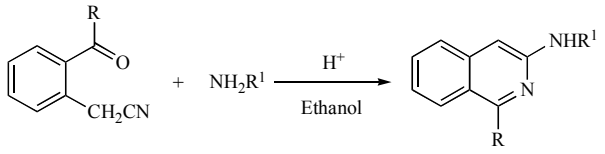


1 **2** **3**

R= CH_3; C_6H_5

R^1= CH_2CH_3; *i*-$CH(CH_3)_2$; $CH_2C_6H_5$; C_6H_5; *4*-ClC_6H_5; *4*-$CH_3C_6H_5$

Scheme (1). Cyclocondensation of 2-acylphenylacetonitriles **1** with amines **2**.

Although the reaction has good yields, this process presents problems related with the use of polluting acids and extensive reaction time required to complete the reactions (2-5 days).

More recently, we studied the reaction using P_2O_5/SiO_2 and $HClO_4/SiO_2$ as heterogeneous catalysts as eco-friendly alternatives. The results indicate that both catalysts are efficient for the reaction with similar yields [11]. However, P_2O_5/SiO_2 demonstrated to have a much better performance: a minor amount of catalyst was needed; it showed greater selectivity as well as a lower formation of byproducts than $HClO_4/SiO_2$. Additionally, $HClO_4$ is known to be potentially explosive; hence safety problems represent a serious limit for the use of this reagent for large scale preparations.

Nevertheless, although the yields of the final products were good with the use of both types of catalysts a similar problem was observed in relation to extensive reaction time required to afford the final products. In addition, reactions performed using P_2O_5/SiO_2 required high proportions of catalyst (10% w/w), with environment consequences. In this sense, an eco-safe and efficient alternative method for the preparation of 3-aminoisoquinolines is highly desirable.

The drive to environmentally sustainable or also called "green chemistry" has provided one of the greatest challenges for chemistry in this era. [12]. In this context, the use of microwave (MW) irradiation in reactions is well documented in the literature for their reduced reaction times, increased product yields and enhanced product purities by reducing undesired side reactions compared to conventional heating methods [13]. For this reason, microwave irradiation has been widely applied in organic synthesis in the last decades and achieved great success for many reactions, including Friedel Crafts acylation [14], Biginelli reaction in aqueous medium [15], carbon-carbon cross-coupling reactions [16], transesterification reactions [17], Diels-Alder cycloaddition [18], *N*-alkylation of amines [19], Hantzsch condensation [20] among many others.

As a part of our search for new methods of synthesis of biologically active heterocyclic compounds, we focused on the possibility of optimizing this procedure to obtain the products in shorter reaction times with a lower amount of catalyst. According to this goal, we report an optimization of the synthesis of 3-aminoisoquinolines **3** *via* cyclocondensation of 2-acylphenylacetonitriles **1** with amines **2** using microwave irradiation.

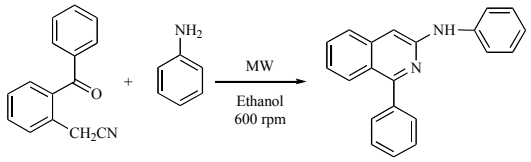
RESULTS AND DISCUSSION

The substrates **1** were prepared following a procedure previously reported by our group *via* reaction of 2-cyanomethylbenzoylchloride with Grignard reagents in the presence of cuprous iodide at –5°C [21]. P_2O_5/SiO_2 was prepared according to the literature procedures [22].

Initially, to optimize the reaction conditions, we studied the reaction between 2-benzoylphenylacetonitrile (**1a**) (1 mmol) and aniline **2a** (2.5 mmol) to obtain 1-phenyl-*N*-phenylisoquinolin-3-amine (**3a**). The reactions were performed using P_2O_5/SiO_2 in ethanol as solvent using various reaction conditions (catalyst amount, temperature and reaction time). Regarding the temperature, tests determined as optimum 180°C (850 W) for carrying out these process. In parallel these reactions were performed under identical conditions of temperature without the use of catalyst (Table **1**).

We believe the most significant advance was the speed with which the reaction proceeded under microwave conditions.

Table 1. Reaction of 2-benzoylphenylacetonitrile 1a with aniline 2a in the absence or presence of P_2O_5/SiO_2, under microwave conditions.



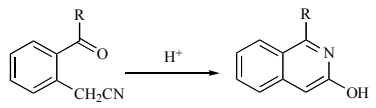
1a **2a** **3a**

Entry	Time (min)	Isolated yield (%)[a)]	Isolated Yield (%) with catalyst (10 % w/w) [b)]
1	20	-	-
2	30	27	5
3	40	40	10
4	50	36	10
5	60	37	5

[a)] Without use of catalyst [b)] The maximum proportion of P_2O_5/SiO_2 used.

The optimal reaction yield of 40% (Table **1**, entry **3**) obtained after 40 minutes, was significantly lower than that obtained via conventional method (120 hours), although the latter performance yield was slightly higher, i.e, 48% [11]. No increase in performance yield was observed at longer reaction times under microwave conditions (entries **4** and **5**).

Another important fact was that the microwave reaction occurred in significantly better yields in the absence of catalyst. In this regard, we observed a lower yields of product **3a** using the catalyst P_2O_5/SiO_2 in varying proportions from 1 to 10 % (w/w), showing the formation of byproducts, among them 1-phenyl-(*2H*)isoquinolin-3-one, generated by intramolecular cyclization in acid medium of substrate **2a** [23] (Scheme **2**).



Scheme (2). Intramolecular cyclization in acid medium of 2-acylphenylacetonitriles **1**.

After completion of the reaction, the resulting yellow solid was washed three times with hexane/ethyl acetate (7:3) to remove unreacted reagent accompanied by a small percentage of impurities. The aminoisoquinoline **3a** was obtained in good purity in a moderate yield (40%).

The reagent **1a** was recovered in 36 % yield, after purification of the combined organic extracts by flash column chromatography.

With the optimized microwave conditions, we expanded the scope of the reaction to various 2-acylphenylacetonitriles **1** and amines **2** in ethanol as solvent. The reaction is applicable to both aromatic and aliphatic amines.

The yields of the reactions are summarized in Table **2**. All products are known compounds and were identified by comparison of their physical and spectroscopic data with those of reported ones [10, 11]. Assignments of carbon resonance were performed using both 1D and 2D NMR (COSY) and heteronuclear $^1H/^{13}C$ (HSQC and HMBC) experiments.

As observed in Table **2**, the reactions proceeded with various amines in moderate to good yields. Examination of the results revealed that the steric effects play an important role in the yield of the reactions, resulting in minor yields when either substrates or amines with bulky substituents were employed.

Unreacted reagents, 2-acylphenylacetonitriles **1** were recovered in all reactions. This may be considered an important advantage of this method.

Comparisons of synthetic method using the conventional thermal with the microwave assisted reaction revealed a drastic reduction in the reaction time (Table **3**).

EXPERIMENTAL

Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} sheets (Merck). Column chromatography was carried out using silica gel (Merck 60, 70-230 mesh). All reagents were of commercial quality or were purified before use. Melting points were determined with a Büchi apparatus. NMR spectra were recorded on a Varian Mercury Plus spectrometer at 200 MHz using TMS as the internal standard. Initially, 2-acylphenylacetonitriles **1** was obtained via reaction of 2-cyanomethylbenzoylchloride with Grignard reagents in the presence of cuprous iodide at –5 ºC [21]. P_2O_5/SiO_2 was prepared according to the literature procedures [22].

Microwave reactions were carried out using a commercially available Anton-Paar-monowave-300 reactor at 180°C (monowave, maximum power 850 W, temperature control via IR-sensor) employing a 10 mL Pyrex vial in a closed vessel mode. Reactions were carried out with simultaneous cooling with stirring at a fixed rate of 600 rpm.

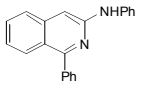
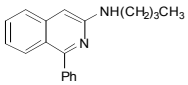
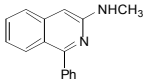
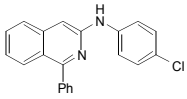
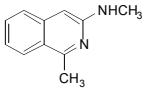
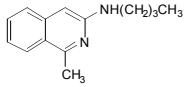
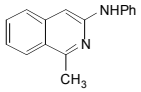
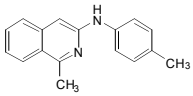
General Procedure for the Preparation of *N*,1-substituted Isoquinolin-3-amines Using Microwave Irradiation

A mixture of 2-acylphenylacetonitriles **1** (1 mmol) and amine **2** (2 mmol) in ethanol was taken in a sealed teflon vessel and irradiated at the temperature indicated for a set time. The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting yellow solid was washed three times with hexane/ethyl acetate (7:3) to

Table 2. Synthesis of isoquinolin-3-amines 3 under microwave irradiation conditions.

Product 3	R	R^1	Isolated Yield (%)	Mp (°C) Found/Lit.
3a	Ph	Ph	40	89-90/89-90 [10]
3b	Ph	*n*-Bu	44	164-165/164-166[11]
3c	Ph	Me	52	142-143/142-144[10]
3d	Ph	*p*-Cl-Ph	34	192-194/192-193[11]
3e	Me	Me	77	80-81/81-82[11]
3f	Me	*n*-Bu	59	123-124/123-124.5[11]
3g	Me	Ph	51	63-64/63-64[11]
3h	Me	*p*-Tolyl	48	87-88/88-89[11]

Table 3. Comparison between reactions performed with conventional heating and microwave irradiation for the conversion of 2-acylphenylacetonitriles 1 **and amines** 2 **to *N*,1-substituted isoquinolin-3-amines 3.**

Entry	Products	Conventional heating[a]		Microwave irradiation	
		Yield 3 (%)	Time (h)	Yield 3 (%)	Time (min)
1		48 (**3a**)	120	40 (**3a**)	40
2		60 (**3b**)	120	44 (**3b**)	40
3		67 (**3c**)	120	52 (**3c**)	40
4		38 (**3d**)	120	34 (**3d**)	40
5		83 (**3e**)	36	77 (**3e**)	40
6		80 (**3f**)	48	59 (**3f**)	40
7		59 (**3g**)	96	51 (**3g**)	40
8		58 (**3h**)	120	48 (**3g**)	40

[a] Using P_2O_5 /SiO_2 (10%) as catalyst in ethanol[10]

remove unreacted reagent accompanied by a small percentage of impurities. The reactions carried out with catalyst are performed in the same way.

Characterization Data of the Compounds

N-Phenyl-1-phenylisoquinolin-3-amine (3a)

Yield % 40, yellow solid, mp: 89-90ºC; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.09-7.44 (m, 12 H, NH, H-7, Ph), 6.70 (s, 1H, H-4), 7.49 (d, 1H, *J* = 8.1 Hz, H-6), 7.49 (d, 1H, *J* = 8.1 Hz, H-5), 7.78 (dd, 1H, *J* = 8.5, 0.7 Hz, H-8). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 98.31 (C-4), 119.69 (C-2'', C-6'', NHPh), 122.30 (C-8a), 123.27 (C-7), 125.53 (C-5), 127.63 (C-4'', NHPh), 128.22 (C-2', C-6', Ph), 128.53 (C-8), 129.30 (C-3'', C-5'', NHPh), 129.74 (C-4', Ph), 130.12 (C-3', C-5', Ph), 130.14 (C-6), 139.24 (C-1'', NHPh), 139.59 (C-1', Ph), 140.93 (C-4a), 150.80 (C-1), 160.34 (C-3). The RMN data obtained for **3a** are in agreement with previously reported literature values [10].

N-(n-Butyl)-1-phenylisoquinolin-3-amine (3b)

Yield % 44, orange solid, mp: 80-81ºC; ^{1}H NMR (200 MHz , $CDCl_3$):δ 0.98 (t, 3H, *J* = 7.3 Hz, $CH_2CH_2CH_2C\underline{H}_3$), 1.36-146 (m, 2H, $CH_2CH_2C\underline{H}_2CH_3$), 1.58-65 (m, 2H, $CH_2C\underline{H}_2CH_2CH_3$), 3.27 (t, 2H, *J* = 7.1 Hz, $C\underline{H}_2CH_2$ CH_2CH_3), 6.15 (s, 1H, H-4), 6.50 (1H, NH), 7.24 (td, 1H, *J* = 7.3 Hz, 7.2, 0.9, H-7), 7.39-7.48 (m, 3H, H-6, Ph), 7.51-7.72 (m, 4H), 7.78 (d, 1H, *J* = 7.1 Hz, H-8). .^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.17 ($CH_2CH_2CH_2\underline{C}H_3$), 20.50 ($CH_2CH_2$ $\underline{C}H_2CH_3$), 31.59 ($CH_2\underline{C}H_2CH_2CH_3$), 43.08 ($\underline{C}H_2CH_2CH_2$ CH_3), 95.06 (C-4), 121.66 (C-2', C-6', Ph), 122.40 (C-8a), 123.89 (C-7), 126.01 (C-5), 126.78 (C-8), 129.13 (C-3', C-5', Ph), 130.27 (C-4', Ph, C-6), 132.88 (C-1', Ph), 140.48 (C-4a), 154.92 (C-1), 160.46 (C-3). The RMN data obtained for 3a are in agreement with previously reported literature values [11].

N-Methyl-1-phenylisoquinolin-3-amine (3c)

Yield % 52, yellow solid, mp: 142-143ºC; ^{1}H NMR (200 MHz , $CDCl_3$) δ 2.88 (d, 3H, *J* = 5.1 Hz, $NHCH_3$), 5.01 (brs, 1H, NH), 6.48 (s, 1H, H-4), 7.10 (ddd, 1H, *J* = 8.30, 7.08, 0.98 Hz, H-7), 7.41-7.53 (m, 4H, H-6, H-2', H-4', H-6'), 7.59-7.66 (m, 3H, H-5, H-3', H-5'), 7.81 (dd, 1H, *J* = 8.3, 0.97 Hz, H-8). ^{13}C NMR (62.9 MHz): δ 29.80 (CH_3), 94.51 (C-4), 121.51 (C-8a), 122.23 (C-7), 125.31 (C-5), 127.88 (C-8), 128.24 (C-2', C-6', Ph), 128.43 (C-4', Ph), 129.70 (C-3',

C- 5', Ph), 129.94 (C-6), 139.60 (C-1', Ph), 140.25 (C-4a), 155.71 (C-1), 160.16 (C-3). The RMN data obtained for **3c** are in agreement with previously reported literature values [10].

N-(4-Chlorophenyl)-1-phenylisoquinolin-3-amine (3d)

Yield % 34, brownish yellow solid, mp: 192-193ºC; ^{1}H NMR (200 MHz, $CDCl_3$):δ 5.29(s, NHPh) 6.88 (s, 1H, H-4), 7.11 (ddd, 1H, *J* = 7.1, 8.2, 0.9 Hz, H-7), 7.12-7.25 (m, 4H), 7.53-7.57 (m, 8 H), 7.77 (dd, 1H, *J* = 8.2, 0.9 Hz, H-8) .^{13}C NMR (62.9 MHz, $CDCl_3$): δ 97.6 (C-4), 119.8 (C-2'', C-6'', NHPh), 122.54 (C-8a) 123.0 (C-7), 124.22 (C-5), 127.15 (C-4'', NHPh), 128.32 (C-6), 129.36 (C-8), 129.87 (C-2', C-6', Ph), 130.77 (C-3'', C-5'', NHPh), 130.80 (C-3', C-5', Ph), 131.99 (C-4', C-1', Ph), 138.16 (C-1'', NHPh), 140.11 (C-4a), 151.22 (C-1), 160.99 (C-3). The RMN data obtained for **3d** are in agreement with previously reported literature values. [11]

N,1-Dimethylisoquinolin-3-amine (3e)

Yield % 77, green solid, mp: 80-81ºC; ^{1}H NMR (200 MHz , $CDCl_3$): δ 2.81 (s, 3H, $NHCH_3$), 2.91 (s, 3H, CH_3), 6.27 (s, 1H, H-4), 7.11 (ddd, 1H, *J*= 8.2, 6.9, 1.5 Hz, H-7), 7.32-7.42 (m, 1H, H-6), 7.47 (d, 1H, *J*= 8.1 Hz, H-5), 7.82 (d, 1H, *J*= 8.2 Hz, H-8); ^{13}C NMR (62.9 MHz): δ 21.79(1-CH_3), 29.68 ($NHCH_3$), 93.48 (C-4), 122.25 (C-7), 122.45 (C-8a), 125.80 (C-5), 123.08 (C-8), 130.19 (C-6), 139.60 (C-4a), 155.61(C-3), 158.38 (C-1). The RMN data obtained for 3e are in agreement with previously reported literature values [11].

N-(n-Butyl)-1-methylisoquinolin-3-amine (3f)

Yield % 59, greenish yellow solid, mp: 123-124.5 ºC; ^{1}H NMR (200 MHz, $CDCl_3$):δ 0.91 (t, 3H, *J* = 7.2 Hz ,$CH_2CH_2CH_2C\underline{H}_3$), 1.18 (s, 3H, CH_3),1.32-1.49 (m, 2H, $CH_2CH_2C\underline{H}_2CH_3$), 1.54-1.70 (m, 2H, *J* = 13.0, 7.8, Hz , $CH_2C\underline{H}_2CH_2CH_3$), 2.77 (t, 2H, *J* = 8.4 Hz, $C\underline{H}_2CH_2CH_2CH_3$), 3.92 ($N\underline{H}CH_2$), 6.29 (s, 1H, H-4), 6.94-7.17 (m, 1H, H-7), 7.41 (d, 1H, H-6), 7.53 (d, 1H, *J*= 8.1 Hz, H-5) 7.81 (dd, *J* = 8.4, 0.8 Hz, 1H, H-8),^{13}C NMR (62.9 MHz): δ 12.85 ($CH_2CH_2CH_2\underline{C}H_3$), 19.30 ($CH_2CH_2\underline{C}H_2CH_3$), 20.84 ($CH_2\underline{C}H_2CH_2CH_3$), 31.06 ($\underline{C}H_2CH_2CH_2CH_3$), 41.71 ($NH\underline{C}H_2$), 92.91 (C-4), 121.16 (C-5), 123.70 (C-9), 124.44 (C-7), 124.98 (C-8a), 125.46 (C-8), 127.33 (C-6), 129.11 (C-4a),129.30 (C-10) 129.46 (C-3), 129.73 (C-1). The RMN data obtained for 3f are in agreement with previously reported literature values [11].

1-Methyl-N-phenylisoquinolin-3-amine (3g)

Yield % 59, **y**ellow solid, mp: 63-64ºC; ^{1}H NMR (200 MHz, $CDCl_3$):δ 2.86 (s, 3H, 1-CH_3), 6.63 (brs, 1H, NH), 7.07 (s, 1H, H-4), 7.22-7.40 (m, 5H), 7.44-7.57 (m, 2H), 7.94 (dd, 1H, *J*=8.4, 0.9 Hz, H-8). ^{13}C NMR (62.9 MHz): δ 22.29 (1-CH_3), 97.75(C-4), 119.98(C-2', C-6´, NPh), 122.78 (C-8a), 123.51(C-7), 123.62 (C-4', NPh), 125.97 (C-5), 126.17(C-8), 129.63 (C-3', C-5', N-Ph), 130.40(C-6), 139.03 (C-1'), 141.36 (C-4a), 150.71 (C-3), 158.89 (C-1). The RMN data obtained for **3g** are in agreement with previously reported literature values [11].

1-Methyl-N-(4-methylphenyl)isoquinolin-3-amine (3h)

Yield % 48, yellow solid, mp: 88-89ºC; ^{1}H NMR (200 MHz, $CDCl_3$):δ 2.34 (s, 3H, $C_6H_4CH_3$) 2.85, (s, 3H, NH-$C\underline{H}_3$), 6.56 (s, 1H, NH), 6.97 (s, 1H, H-4), 7.11-7.29 (m, 5H), 7.41-7.53 (m, 2H), 7.92 (dd, 1H, *J*=8.4, 0.8 Hz, H-8). ^{13}C NMR (62.9 MHz): δ 21.09 $N\underline{C}H_3Ph$), 22.28 (1-CH_3), 97.00 (C-4), 120.90 (C-2',C-6´, Ph), 123.31 (C-8a), 123.35 (C-7), 126.00 (C-8), 126.09 (C-5), 130.17(C-3', C-5', Ph), 130.39 (C-6), 132.41(C4', Ph), 138.56 (C-1', Ph), 139.12 (C-4a), 151.42(C-3), 158.83 (C-1). The RMN data obtained for **3h** are in agreement with previously reported literature values [11].

CONCLUSION

We have developed a rapid and efficient method for the synthesis of *N*-substituted 1-alkyl and 1-aryl- 3-aminoisoquinolines by reaction of 2-acylphenylacetonitriles with amines using microwave irradiation. The most significant progress includes a significant decrease in reaction times and carrying out the reaction in the absence of catalyst, with greater simplicity in operation and a benefit to the environment.

Finally, it should be noted that although the reaction has moderate yields, this has a high selectivity with recovered reagent **1** in good purity, which could be used in a second process.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

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