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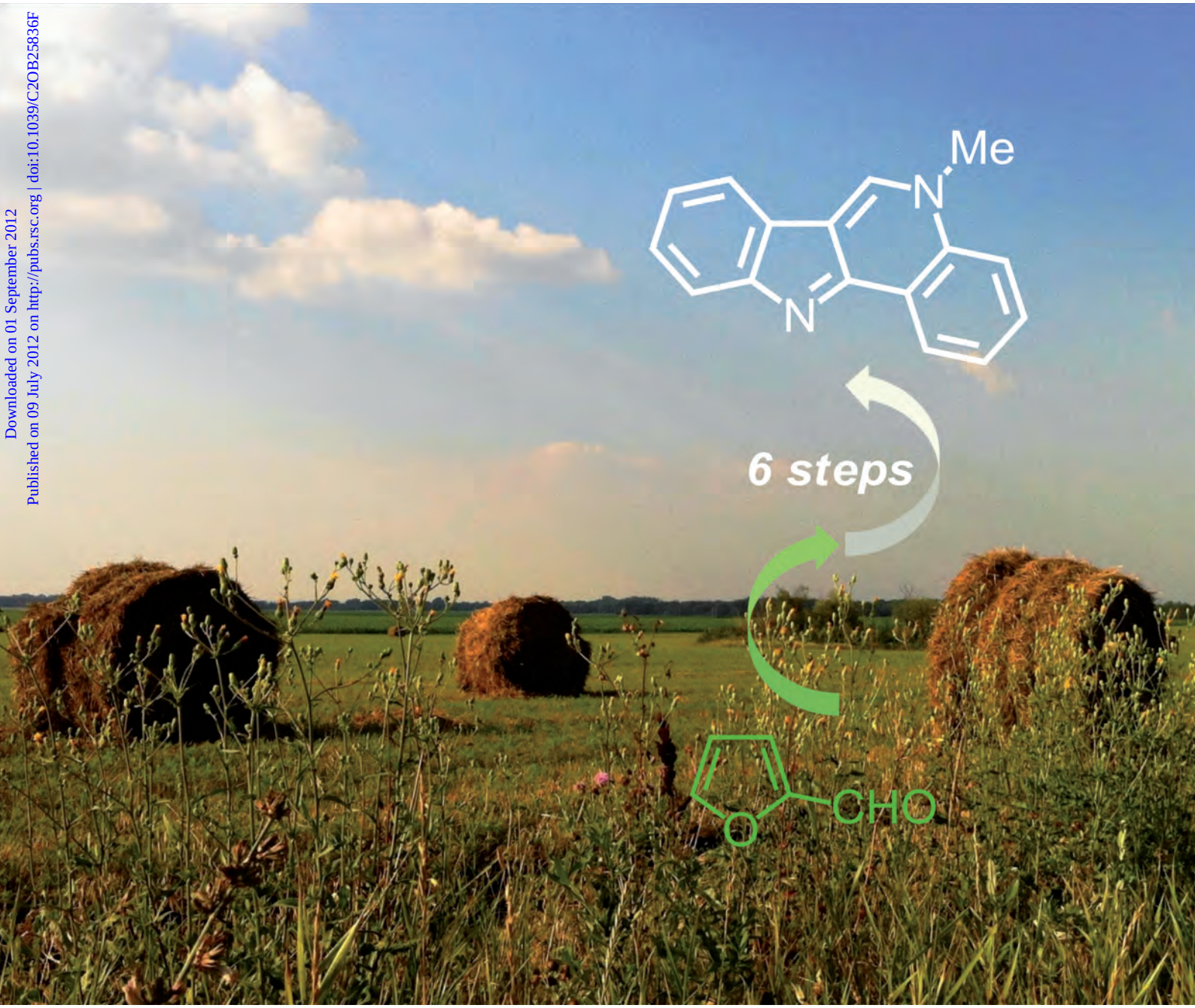

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From biomass to medicines. A simple synthesis of indolo[3,2-*c*]quinolines, antimalarial alkaloid isocryptolepine, and its derivatives†

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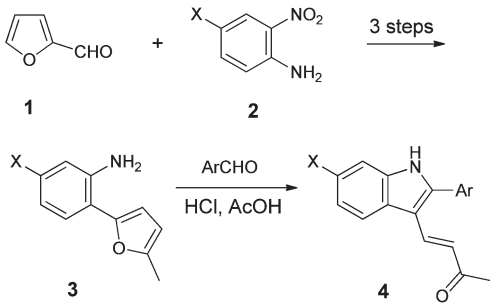
Indolo[3,2-*c*]quinolines are pharmacologically attractive class of heterocyclic compounds. The method of their synthesis, based on transformation of furfural, which is a large-scale product of treatment of biomass including agricultural and forestry wastes, has been developed. This method was utilized for the total synthesis of antimalarial alkaloid isocryptolepine and its derivatives.

A sustainable conversion of biomass into drugs, chemicals, biofuels, and various materials is one of the most challenging tasks for the modern chemistry and industry.[1,2] Promising ways to solve this problem are depolymerization and fermentation of biopolymers affording molecules which can be either directly used or easily transformed into other valuable products. Thus, the current world production of furfural from agricultural and forestry wastes is 280 000 tonnes per year.[3] It is mainly employed as an intermediate for furan, tetrahydrofuran, and furfuryl alcohol production,[2a] as well as in fine organic synthesis.

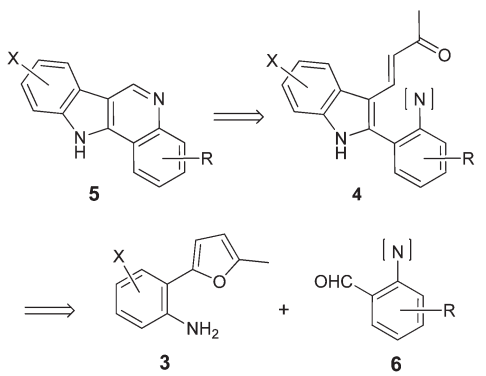
For a long time, we are dealing with the development of procedures for transformations of furfural into diverse furan derivatives and a broad variety of other heterocycles.[4] Recently, we have discovered a simple route from furfural (**1**) to 3-(2-acylvinyl)-2-(hetero)arylindoles **4**, the key step of which is unusual furan-to-indole recyclization (Scheme 1).[5] This transformation is based on the acid-induced reaction of 2-furylanilines **3**[6] with (hetero)aromatic aldehydes followed by attack of the formed iminium ion onto the C(2) atom of the furan ring.

Herein, we describe the utilization of this new method of indoles synthesis for preparation of indolo[3,2-*c*]quinolines **5**[7] (Scheme 2) which attract attention due to their ability to form strong complexes with DNA,[8] antimalarial activity,[9] antiproliferative properties,[10] *etc.*[8b,11] We supposed that indoles **4** can be suitable precursors of **5** if they have a latent amino group in the *ortho*-position of 2-aryl substituent. The liberation of amine functionality should allow for easy pyridine ring formation through Michael addition to α,β-enone moiety affording the corresponding tetracyclic compounds.[12] In turn, such indoles can be synthesized from 2-furylanilines **3** and the corresponding aldehydes **6**.

We selected 2-nitrobenzaldehydes as starting aldehydes since: (1) a broad range of substituted 2-nitrobenzaldehydes is commercially available or can be easily synthesized that allows for



Scheme 1 Synthesis of 3-(2-acylvinyl)-2-arylindoles **4**.



Scheme 2 Retrosynthetic scheme for indolo[3,2-*c*]quinolines **5**.

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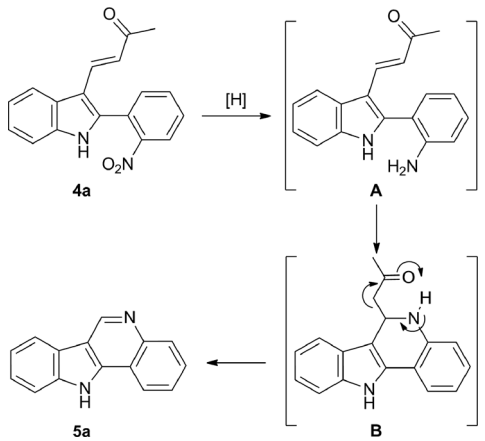
†Electronic supplementary information (ESI) available: Experimental procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. See DOI: 10.1039/c2ob25836f

preparation of a library of indolo[3,2-*c*]quinolines; (2) the reduction of nitroarenes to anilines is the simple and environment-friendly process.

To our delight, 2-nitrobenzaldehydes **6a–g** afford the corresponding 2-(2-nitrophenyl)indoles **4a–k** in reaction with 2-furylanilines **3a–c** (Table 1). However, the nitro group in the *ortho*-position of aromatic aldehydes was found to decrease the product yields in this furan-to-indole transformation. We believe it is a result of a combination of unfavourable steric and electronic effects of *ortho*-nitro-group rendering the iminium ion attack onto the furan ring. Substituents in *ortho*-nitrobenzaldehydes and 2-furylanilines have no significant influence on yields of indoles **4**. Despite the moderate yields of the isolated products (54–67%), this reaction is very convenient from a preparative point of view. The formed 2-(2-nitrophenyl)indoles are precipitated from reaction mixture and can be used in further transformations without additional purification.

Then, we studied the reductive cyclization of 3-(2-acetylvinyl)-2-(2-nitrophenyl)indole **4a**. We have found that the utilization of Zn/NaOH or RANEY® nickel leads to a complex mixture of products. Heating of **4a** with Zn/AcOH or $SnCl_2$ was also shown to be ineffective. However, the treatment of **4a** with Fe in AcOH under reflux for 5 min afforded directly 11*H*-indolo[3,2-*c*]quinoline (**5a**). The formation of **5** can be explained by mechanism including the reduction of nitro group with formation of the corresponding aniline **A**, the intramolecular Michael addition leading to 6-acetonyl-5,6-dihydro-11*H*-indolo[3,2-*c*]quinoline **B** and the aromatization of **B** by acetone elimination (Scheme 3). The last step seems to be quite unusual, however, ketone elimination from dihydroarenes leading to substrate aromatization is



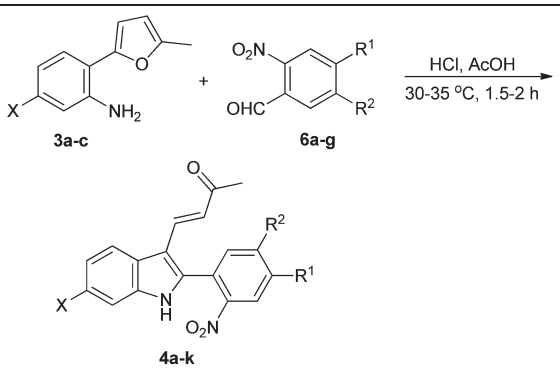
Scheme 3 The proposed mechanism of indolo[3,2-*c*]quinoline **5** formation.

not an unprecedented process.[13] The similar nitromethane, malonitrile, and dimethyl malonate eliminations during Fe/AcOH-mediated reductive cyclizations of nitro derivatives to quinolines were also recently reported.[14]

With the optimized conditions in hand, we performed this reductive cyclization for a series of 2-(2-nitrophenyl)indoles **4a–k** synthesized above. The results demonstrated that the reaction has a general character; electron-donating alkyl and alkoxy groups as well as electron-withdrawing halide substituents have no significant effect on the yields of indolo[3,2-*c*]quinolines (Table 2).

Methylation of **5a** is known[15] to afford alkaloid isocryptolepine (**7a**)[16] which was isolated in 1995 from the West African plant *Cryptolepis sanguinolenta*[17] and demonstrated to have a significant antiprotozoal activity.[18]

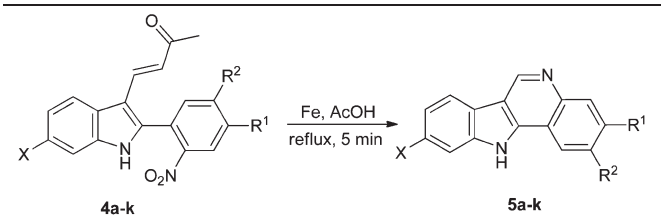
Table 1 Synthesis of 3-(2-acetylvinyl)-2-(2-nitrophenyl)indoles **4**



Entry	Substrate	X	R^2	R^3	Product	Yield of **4**[a] (%)
1	**3a/6a**	H	H	H	**4a**	58
2	**3a/6b**	H	OMe	H	**4b**	56
3	**3a/6c**	H	OMe	OMe	**4c**	59
4	**3b/6a**	Cl	H	H	**4d**	67
5	**3b/6c**	Cl	OMe	OMe	**4e**	58
6	**3b/6d**	Cl	OCH_2O		**4f**	59
7	**3c/6a**	Me	H	H	**4g**	65
8	**3c/6e**	Me	OCH_2CH_2O		**4h**	56
9	**3c/6c**	Me	OMe	OMe	**4i**	57
10	**3c/6f**	Me	H	Cl	**4j**	54
11	**3c/6g**	Me	H	Br	**4k**	55

[a] Isolated yield.

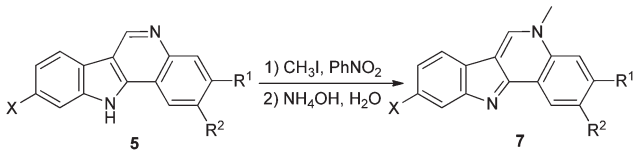
Table 2 Reductive cyclization of 2-(2-nitrophenyl)indoles **4** to indolo[3,2-*c*]quinolines **5**



Entry	Substrate	X	R^1	R^2	Product	Yield of **5**[a] (%)
1	**4a**	H	H	H	**5a**	86
2	**4b**	H	OMe	H	**5b**	74
3	**4c**	H	OMe	OMe	**5c**	79
4	**4d**	Cl	H	H	**5d**	75
5	**4e**	Cl	OMe	OMe	**5e**	77
6	**4f**	Cl	OCH_2O		**5f**	72
7	**4g**	Me	H	H	**5g**	73
8	**4h**	Me	OCH_2CH_2O		**5h**	70
9	**4i**	Me	OMe	OMe	**5i**	78
10	**4j**	Me	H	Cl	**5j**	79
11	**4k**	Me	H	Br	**5k**	76

[a] Isolated yield.

Table 3 Synthesis of isocryptolepine **7a** and its derivatives **7b–f**



Entry	Substrate	X	R^2	R^3	Product	Yield of **7**[a] (%)
1	**5a**	H	H	H	**7a**	86
2	**5c**	H	OMe	OMe	**7b**	75
3	**5e**	Cl	OMe	OMe	**7c**	74
4	**5g**	Me	H	H	**7d**	85
5	**5i**	Me	OMe	OMe	**7e**	82
6	**5k**	Me	H	Br	**7f**	77

[a] Isolated yield.

As a structural analogue of chloroquine and related drugs used for treatment of malaria, which is one of the most serious parasitic diseases in the world as it was fatal for 655 000 people in 2010,[19] isocryptolepine can be considered as a good lead compound for the development of new medication with antiplasmodial activity.

Therefore, we studied the methylation of the synthesized indolo[3,2-*c*]quinolines **5** to demonstrate that the developed approach can be utilized for preparation of series of substituted isocryptolepines allowing for structure–activity relationship study and determination of derivatives with good therapeutic properties.

We examined a number of reported procedures for the methylation of 11*H*-indolo[3,2-*c*]quinolines **5**[16a,c,e,20] using unsubstituted **5a** as a model substrate. The best result was obtained when **5a** was heated with methyl iodide in nitrobenzene according to the Kermack–Storey procedure.[21] This reaction finished the total synthesis of isocryptolepine **7a** from furfural in six steps. Under the same conditions isocryptolepine derivatives **7b–f** were obtained in 74–86% yields (Table 3).

The selection of substituted indolo[3,2-*c*]quinolines for this transformation was performed according to the known data that halide introduction increases antiplasmodial activity of the related 4-aminoquinolines and methoxy groups are often important for good bioavailability of the potent drug. Moreover, these substituents allow for easy modification of synthesized compounds. A broad variety of isocryptolepines containing many other substituents can also be obtained directly by this reaction sequence.

In conclusion, we developed a simple method for transformation of furfural, the large-scale product of processing of agricultural and forestry wastes, into indolo[3,2-*c*]quinolines and isocryptolepines, which are potent pharmacologically active compounds. This method is based on the utilization of cheap reagents as well as environmentally- and industry-friendly reaction conditions. On the contrary to the previously reported approaches, our method allows for preparation of various 9-substituted indolo[3,2-*c*]quinoline and isocryptolepine derivatives. It expands significantly opportunities for synthesis of libraries of these two classes of heterocyclic compounds as a part of a program for development of new drugs for treatment of malaria. The study of antiplasmodial activity of the synthesized compounds is currently under investigation.

Acknowledgements

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