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Mendeleev Commun., 2022, **32**, 634–636

Mendeleev Communications

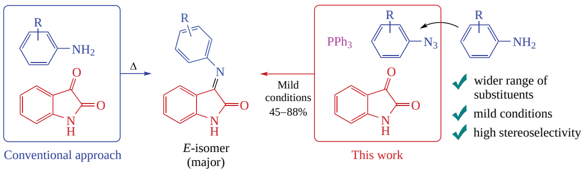
A convenient *E*-diastereoselective synthesis of *NH*-isatin *N′*-arylimines *via* the aza-Wittig reaction

Vadim E. Filatov, Dmitrii A. Iuzabchuk, Boris N. Tarasevich, Nikolai V. Zyk and Elena K. Beloglazkina*

*Department of Chemistry, M. V. Lomonosov Moscow State University,
119991 Moscow, Russian Federation. E-mail: beloglazki@mail.ru*

DOI: 10.1016/j.mencom.2022.09.022

A general synthesis of *NH*-isatin *N′*-arylimines involves the aza-Wittig reaction of isatin and aryl azides, providing higher *E*-diastereoselectivity as compared to previously described methods. The procedure is applicable even to anilines which do not directly react with isatins.

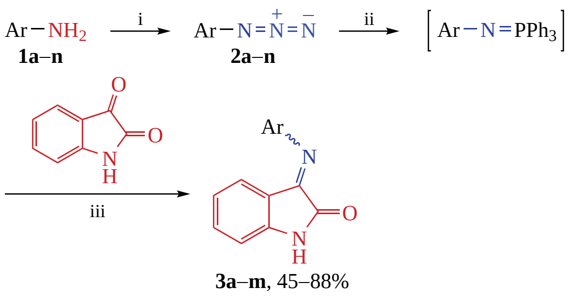


Keywords: aryl isatin imines, aryl azides, imines, isatins, aza-Wittig reaction, stereoselectivity.

Isatin imines are compounds of significant interest to organic and medicinal chemists being an attractive scaffold with great synthetic potential. 2-Oxindole fragment has a capacity of bioisosteric replacement for tryptophan depending on side substituents.[1] For example, isatin arylimines exhibit analgesic activity.[2,3] Several functional groups of isatin imines can be further modified resulting in a wide series of derivatives with diverse therapeutic effects.[4–6] *N*-Arylaminoindolin-2-ones may inhibit growth of *P. falciparum* which is the cause of malaria,[7] while spirooxindole derivatives demonstrated high potential as antitumor agents.[8–16]

It should be noted that isatin arylimines obtained by the condensation of isatins with anilines[17–19] usually represent mixtures of *E*,*Z*-isomer mixtures without a significant predominance of one of them, while their separation is difficult. At the same time, one of the formed stereoisomers, as a rule, showed a significantly higher biological activity than the other, that makes the stereoselective synthesis of isatin imines topical. Besides, some isatin imines, including hydroxy-substituted ones, cannot by accessed through the aniline-isatine condensation.[19]

The aza-Wittig reactions being in service for over a decade are known as an efficient way of synthesis of imines including heterocyclic compounds.[20–25] However, the known relevant syntheses of isatin imines were focused, as a rule, on *N*-Boc-isatin imines and other similar carbamates.[26–32] We have demonstrated in this work that the aza-Wittig reaction enables the synthesis of 3-(arylimino)indolin-2-ones **3** from *N*-unprotected isatine with good yields, wide range of substituents in the starting anilines **1** and relatively high stereoselectivity (Scheme 1).



a Ar = 4-MeC_6H_4
b Ar = 3-MeC_6H_4
c Ar = 4-ClC_6H_4
d Ar = 3-ClC_6H_4
e Ar = 4-BrC_6H_4
f Ar = 3-BrC_6H_4
g Ar = 4-$MeOC_6H_4$
h Ar = 2-$MeOC_6H_4$
i Ar = 4-HOC_6H_4
no product for Ar = 2-$O_2NC_6H_4$
j Ar = 3-HOC_6H_4
k Ar = 2-HOC_6H_4
l Ar = 4-$O_2NC_6H_4$
m Ar = 3-$O_2NC_6H_4$

Scheme 1 *Reagents and conditions*: i, $NaNO_2$, HCl; ii, PPh_3; iii, CH_2Cl_2, room temperature.

The required phosphazenes were obtained using a simple and reliable procedure from aryl azides.[33,34] Synthesis of aryl azides **2a**–**n** with varying substituents was carried out according to the modified method[35] (see Online Supplementary Materials, Scheme S1). Neither character of substituent nor its position in aromatic ring notably impacts the product yield; this enables the employment of wide range of anilines **1a**–**m** as a source of aryl azides. The synthesized aryl azides **2a**–**n** were then introduced into one-pot two step reaction with triphenylphosphine and then with isatin.[†] A series of *N*-(arylimino)indolin-2-ones **3a**–**m** with various nature of the aryl substituent was thus obtained (see Scheme 1). The ratio of *Z*- and *E*-isomers was determined based on literature data on chemical shifts of the NH proton signals in the ^{1}H NMR spectra. An exception was the reaction of 2-nitrophenyl azide when the formation of the corresponding isatin imine was not observed at all, possible due to poor nucleophilicity of nitrogen atom in its azido group. It should be noted the aza-Wittig reaction brings about hardly separable triphenylphosphine oxide as the byproduct, so the variation in yields of isatin imines relates mostly to the purification operation.

To discuss the limitations of developed procedure as well as its advantages over conventional condensation methodology, it is necessary to mention that hydroxy-substituted imine **3j** was previously obtained through the aniline-isatin condensation using microwave irradiation,[16] however, it rapidly decomposed

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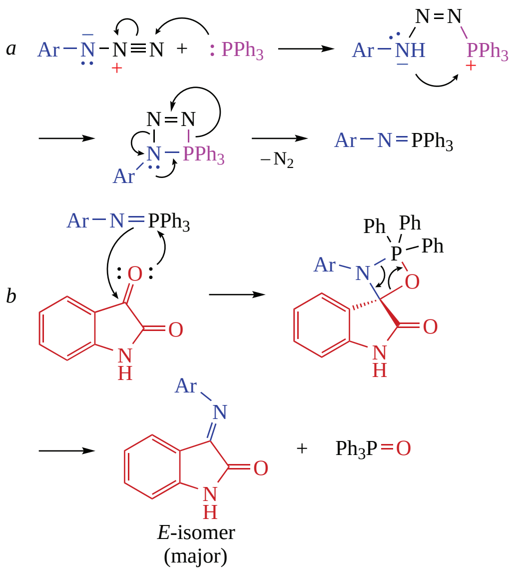
[†] *General procedure for the synthesis of isatin imines* **3a**–**m**. Aryl azide (10 mmol) in dry CH_2Cl_2 (10 ml) was slowly added to thriphenylphosphine (10 mmol) dissolved in CH_2Cl_2 (10 ml). After the end of gas evolution, isatin (10 mmol) was added in one portion. The reaction mixture was then stirred until a precipitate was formed (TLC control). The formed precipitate was separated by suction filtration and washed with methanol (2 × 5 ml) and diethyl ether (1 × 5 ml) to afford final product. An additional portion of product may be obtained by precipitating the washings. For a detailed characterization of each of compounds **3a**–**m**, see Online Supplementary Materials.



Scheme 2

during the purification. We assume that the decomposition can be due to hydrolysis by water being a byproduct of the condensation. In this aspect the aza-Wittig procedure is advantageous since this reaction is irreversible, the product remains stable under the reaction conditions and during the separation. Importantly, compounds **3h**,**k**–**m** can be obtained only by the aza-Wittig reaction because isatin-aniline condensation is sensitive to steric and electronic properties of the reactants. While steric effects obviously affect the outcome of the aza-Wittig reaction (the yields of 2-substituted arylimines are generally lower), the impact of electronic character of substituents is not so clear. To understand the reason of this effect, the reaction mechanism may be taken into consideration (Scheme 2).

The first stage of the process (see Scheme 2, stage *a*) is an addition of triphenylphosphine to azide. It can be expected that a substituent with more electron withdrawing character promotes this step. In fact, we really observed that the reactions of azides **2d**,**f**,**m** were complete in less than 1 h. The same fast reaction proceeded with azides **2c** and **2e** but not with **2n**. This indicates that substituents with too strong electron withdrawing character may slow down the rearrangement of cyclic intermediate while electron donating substituents should promote this step. On the other hand, the electronic effects of substituent may be irrelevant to the second stage (see Scheme 2, stage *b*). Electron withdrawal from nitrogen atom will lead to polarization of the P=N bond leading to higher negative charge on the nitrogen atom. At the same time, electron donating substituents should increase electron density of nitrogen even without polarization of the P=N bond, though in the case of polarization a higher positive charge on P-atom should appear. This facilitates an addition of ylide to carbonyl group. In balance, substituents with electron withdrawing character may be preferred albeit it is difficult to quantify the impact of other factors involved.

Table 1 *E*/*Z*-Selectivity of the aza-Wittig reaction *vs.* isatin-aniline condensation.

Compound	Ar	*E*/*Z* ratio^a	
		Aza-Wittig reaction (this work)	Isatin-aniline condensation[13]
3a	4-MeC_6H_4	6.7 : 1	4 : 1
3b	3-MeC_6H_4	7.3 : 1	3 : 1
3c	4-ClC_6H_4	4 : 1	2 : 1
3d	3-ClC_6H_4	3.5 : 1	2 : 1
3e	4-BrC_6H_4	3.5 : 1	3 : 1
3f	3-BrC_6H_4	3 : 1	2 : 1
3g	4-$MeOC_6H_4$	5 : 1	4 : 1
3h	2-$MeOC_6H_4$	5.4 : 1	Not isolated
3i	4-HOC_6H_4	5 : 1	5 : 1
3j	3-HOC_6H_4	11 : 1	Not isolated
3k	2-HOC_6H_4	7.8 : 1	Not isolated
3l	4-$O_2NC_6H_4$	2 : 1	Not isolated
3m	3-$O_2NC_6H_4$	2 : 1	Not isolated

^{a} Detected by ^{1}H NMR.

Imines in general are susceptible to isomerization under heating. Since the aza-Wittig reaction proceeds under relatively mild conditions, isatin imines **3** are formed with better *E*-diastereoselectively (Table 1) as compared to conventional condensation.[15]

In conclusion, we suggest a convenient synthesis of *N*-(arylimino)indolin-2-ones (*NH*-isatin imines) from commercially available anilines and isatin by the two-step sequence involving the aza-Wittig reaction. The substrate scope of the procedure is wide enough, and it is good for scaling. Mild conditions of the aza-Wittig reaction provide good *E*,*Z*-selectivity of the synthesis.

This work in part of NMR study was supported by the M. V. Lomonosov Moscow State University Program of Development.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2022.09.022.

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Received: 22nd March 2022; Com. 22/6834