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Abnormal aza-Wittig reaction on the solid-phase: chemoselectivity studies towards the parallel synthesis of 3-aryl-2,4-dioxo-1,3,5-triazino[1,2-*a*]benzimidazoles

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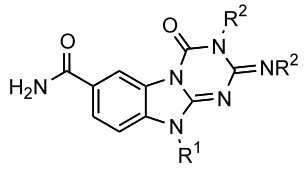
Abstract—An abnormal aza-Wittig reaction was observed when resin-bound iminophosporanes were treated with aryl isocyanates on the solid-phase. The mechanism of the reaction may involve the loss of triphenylphosphinimide instead of triphenylphosphinoxide, resulting in the formation of isocyanates instead of carbodiimides as intermediates. The selectivity of the abnormal aza-Wittig reaction versus the normal aza-Wittig reaction was shown to be strongly dependent on the reaction temperature and the nature of the aryl isocyanate employed. Optimization studies revealed that employing electron poor aryl isocyanates at high temperature leads to 95% of abnormal aza-Wittig product. The reaction was used for the parallel solid-phase synthesis of 3-aryl-2,4-dioxo-1,3,5-triazino[1,2-*a*]benzimidazoles.

The aza-Wittig reaction of iminophosphoranes with isocyanates has proven to be one of the most useful methodologies for the synthesis of nitrogen-containing heterocycles.[1] We report herein an unexpected abnormal aza-Wittig reaction observed in the course of an ongoing program directed towards the synthesis of a library consisting of 2-imino-4-oxo-1,3,5-triazino[1,2-*a*]benzimidazoles **1** via an aza-Wittig/heterocyclization on solid-phase.[2] Depending on the type of isocyanate employed, a significant amount of 2,4-dioxo-1,3,5-triazino[1,2-*a*]benzimidazoles **2** was formed along with the normal aza-Wittig products **1**. The abnormal aza-Wittig reaction involves the formation of an isocyanate instead of a carbodiimide intermediate.

Reported studies on this abnormal aza-Wittig reaction are very limited.[3] Therefore, we carried out an investigation on the chemoselectivity of the reaction.



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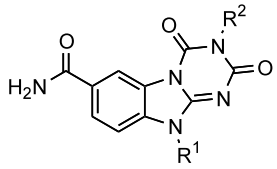

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Keywords: abnormal aza-Wittig reaction; isocyanate; 2,4-dioxo-1,3,5-triazino[1,2-*a*]benzimidazoles; 2-imino-4-oxo-1,3,5-triazino[1,2-*a*]-benzimidazoles.

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The study was directed towards the solid-phase synthesis of 2,4-dioxo-1,3,5-triazino[1,2-*a*]benzimidazole derivatives **2** as abnormal aza-Wittig products. 1,3,5-Triazinediones are reported to exhibit various pharmacological and herbicidal properties.[4] Our group successfully synthesized a library of 3-alkyl-2,4-dioxo-1,3,5-triazino[1,2-*a*]benzimidazoles **2** (R^2 = alkyl) following treatment of resin-bound 2-aminobenzimidazoles with *N*-(chlorocarbonyl)isocyanate and subsequent *N*-alkylation.[5] The presented abnormal aza-Wittig reaction provides a synthetic pathway to 3-aryl-2,4-dioxo-1,3,5-triazino[1,2-*a*]benzimidazoles **2** (R^2 = aryl).

The proposed mechanism of the abnormal aza-Wittig reaction, in contrast to the normal aza-Wittig reaction, is outlined in Scheme 1. Starting from resin-bound 2-aminobenzimidazoles **3**, the corresponding iminophosphoranes **4** were prepared under typical Mitsunobu conditions using DEAD or DIAD and triphenylphosphine.[6] Both betaines **5** and **6** can be formed upon treatment of the iminophosphoranes **4** with isocyanate. Breakdown of betaine **5** involving loss of triphenylphosphinoxide results in a carbodiimide intermediate **7** as the normal aza-Wittig product. The carbodiimide can undergo an intramolecular heterocyclization reaction with the urea moiety formed by the reaction of a second isocyanate with the benzimidazole nitrogen atom providing compounds **1**. In contrast, betaine **6** can lead to an isocyanate group as the abnormal aza-Wittig product involving the loss of

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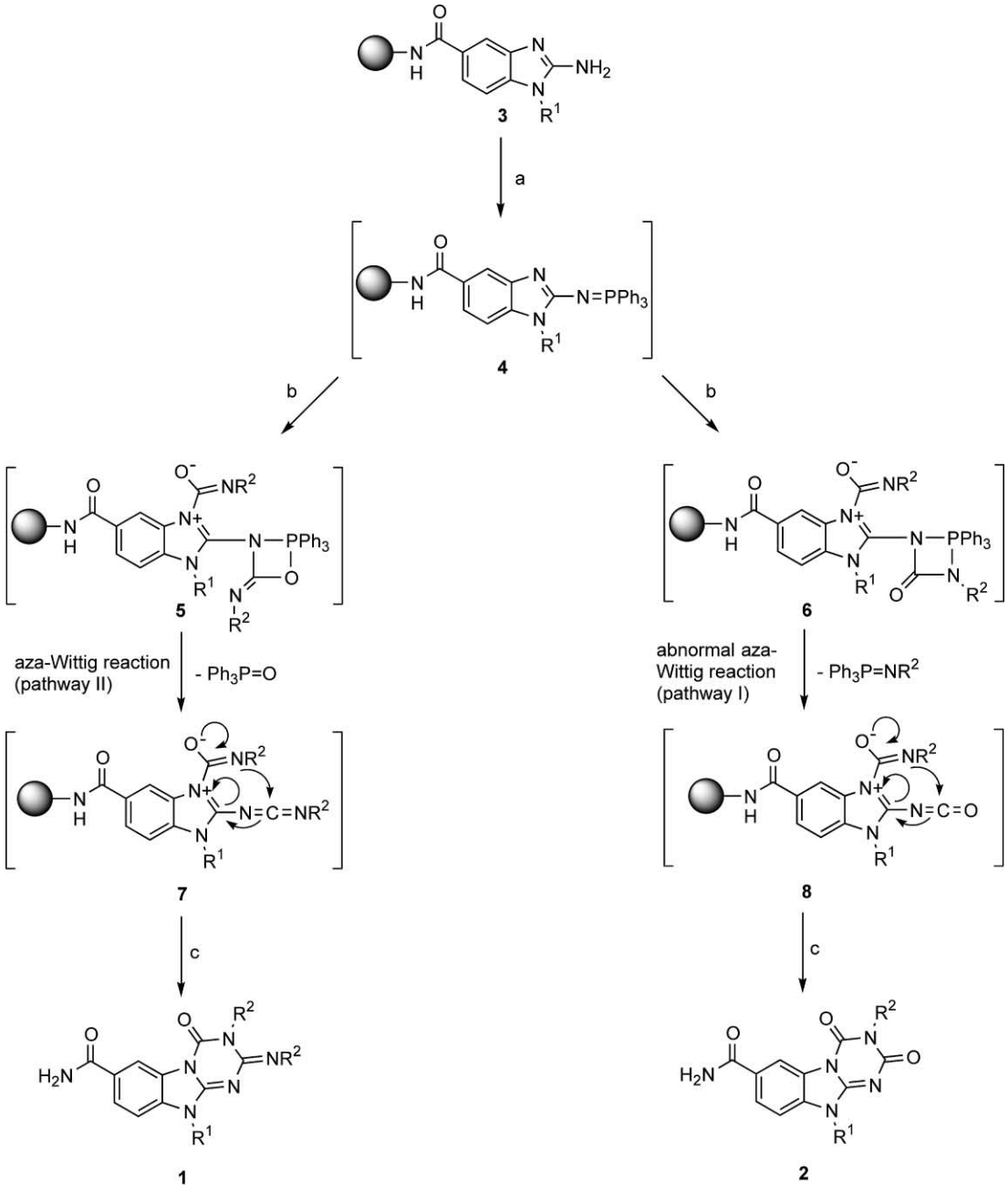

Scheme 1. Proposed mechanism of the abnormal aza-Wittig reaction leading to 2,4-dioxo-1,3,5-triazino[1,2-*a*]benzimidazoles **2** versus the normal aza-Wittig reaction. *Reagents and conditions*: (a) PPh_3, DEAD, THF, 25°C, 3 days. (b) R^2NCO, toluene, 25°C or 100°C, 2 days. (c) HF, anisole, 0°C, 1.5 h.

triphenylphosphinimide. Subsequent heterocyclization reaction yields the 1,3,5-triazinediones **2**.

Five different isocyanates were employed to investigate the influence of steric and electronic factors on the competition between pathways I and II. Alkyl isocyanates react at 100°C leading exclusively to the normal aza-Wittig product **1** (Table 1, entries 1 and 2). No 2,4-dioxo-1,3,5-triazino[1,2-*a*]benzimidazole derivates **2** resulting from abnormal aza-Wittig reaction could be detected by LC–MS. In contrast, using aryl isocyanates at 100°C significant amounts of abnormal aza-Wittig product **2** were obtained with chemoselectivity depending on the nature of the aryl isocyanate employed (Table 1, entries 4, 5 and 6). Pathway I, leading to the intermediate resin-bound isocyanates, was strongly favored when an electron-withdrawing group was present on the aromatic ring. Reaction with 4-nitrophenylisocyanate resulted almost exclusively in the formation of the abnormal aza-Wittig product with a selectivity of 95% (Table 1, entry 6, Fig. 1). These findings strongly suggest that electronic factors play a key role in the competition between the formation of betaines **5** and **6** at elevated temperature.

Table 1. Chemoselectivities for the synthesis of 2-imino-4-oxo-1,3,5-triazino[1,2-*a*]benzimidazoles **1** and 2,4-dioxo-1,3,5-triazino[1,2-*a*]benzimidazoles **2** starting from resin-bound 2-aminobenzimidazoles **3**

Entry	Comp.	R^1	R^2	Temperature (°C)	Purity[a] (**1** and **2** combined) (%)	Mass (found) ($M+H^+$)		Selectivity[a] (%)	
						1	**2**	**1**	**2**
1	**a**	3-Methoxypropyl	Ethyl	100	84	373.4	–	100	0
2	**b**	3-Methoxypropyl	Cyclohexyl	100	83	481.2	–	100	0
3	**c**	3-Methoxypropyl	Phenyl	100	94	469.2	394.2	52	48
4	**d**	Isopropyl	Phenyl	100	92	439.3	364.2	55	45
5	**e**	Isopropyl	4-Methoxyphenyl	100	89	499.3	394.1	77	33
6	**f**	Isopropyl	4-Nitrophenyl	100	90	529.3	409.1	5	95
7	**g**	Butyl	Phenyl	100	95	453.2	378.1	49	51
8	**h**	Hexyl	Phenyl	100	90	481.3	406.3	54	46
9	**i**	Cyclohexyl	Phenyl	100	89	497.1	404.0	45	55
10	**j**	2-Ethylpropyl	Phenyl	100	87	467.1	392.1	50	50
11	**k**	Butyl	Phenyl	25	88	453.4	378.2	90	10
12	**l**	Cyclohexyl	Phenyl	25	87	479.3	404.2	70	30

[a] Purities and chemoselectivities were determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 5–95% acetonitrile in water (0.05% TFA) over 10 min at 214 nm.

To investigate the influence of R^1 as well as the reaction temperature on the chemoselectivity of the reaction, different amines were incorporated as buildings blocks. At a reaction temperature of 100°C using phenylisocyanate, the chemoselectivity of the reaction is almost independent of the nature of the side chain R^1 (Table 1, entries 3, 4 and 7–10). When the reaction temperature was decreased to 25°C, the chemoselectivity was significantly shifted in favor of the normal aza-Wittig product (Tabl-e 1, entries 11 and 12). It is noteworthy that the chemoselectivity at 25°C is more greatly influenced by R^1 than at 100°C. Considering the betaine structures **5** and **6**, it is understandable that steric hindrance between bulky R^1 groups and the phenylimine group in betaine **5** can lead to the preferred formation of betaine **6** at ambient temperature.

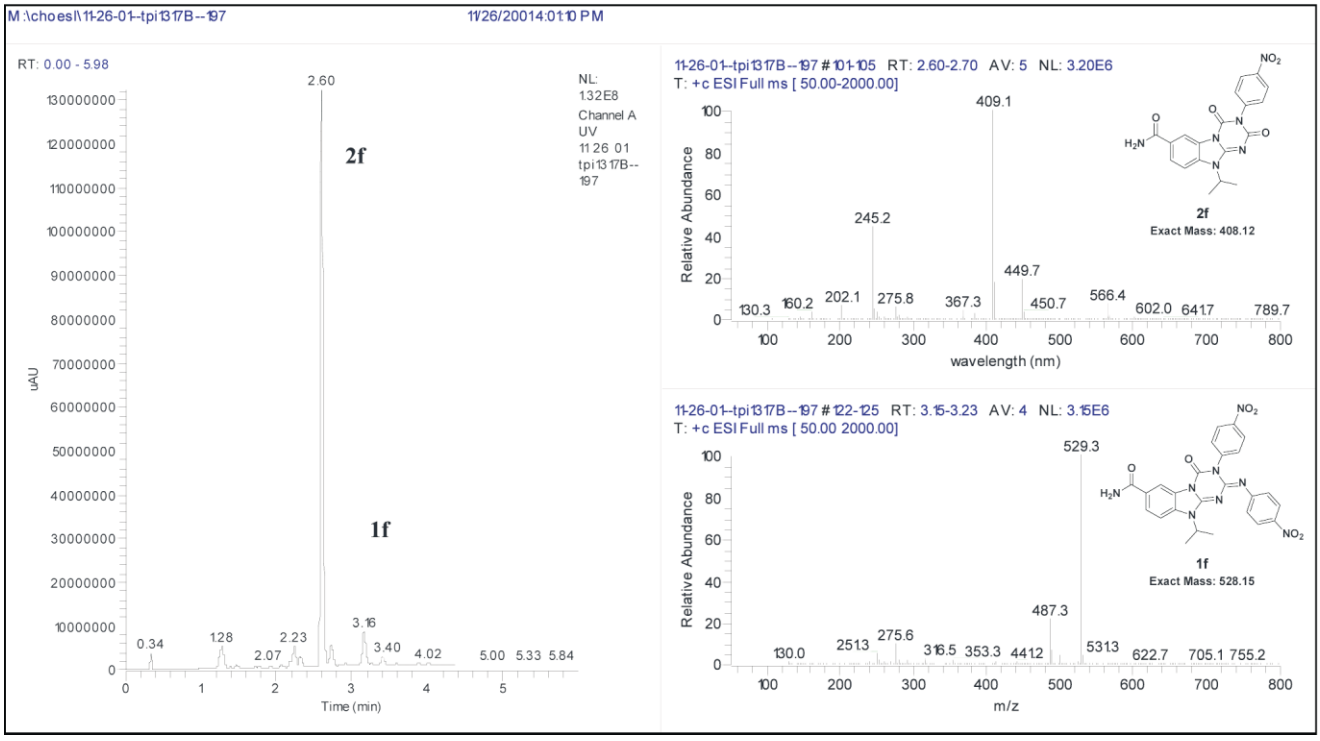

Figure 1. Representative LC–MS showing product mainly of the abnormal aza-Wittig reaction (95%) obtained using 4-nitrophenylisocyanate and isopropylamine.

Using aryl isocyanates, the average combined yields (**1** and **2**), under all reaction conditions employed, were higher than 90%, calculated based on the initial loading of the resin (1.10 meq/g) and the determined selectivities. Combined purities (**1** and **2**) ranged between 83 and 95%.[7]

In summary, we have demonstrated that resin-bound iminophosphoranes react with aryl isocyanates in an abnormal aza-Wittig reaction with a chemoselectivity that depends on the reaction temperature and the nature of the aryl isocyanate employed. The reaction was used for the parallel solid-phase synthesis of 3-aryl-2,4-dioxo-1,3,5-triazino[1,2-*a*]benzimidazoles. Due to the high chemoselectivity obtained with 4-nitrophenylisocyanate, the abnormal aza-Wittig reaction might be useful as a straightforward method for the generation of isocyanates from iminophosphoranes on the solid-phase. Further studies on the utility of the abnormal aza-Wittig reaction for the solid-phase synthesis of isocyanate intermediates and various heterocycles thereof are currently underway.

References

1. (a) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197; (b) Barluenga, J.; Palacios, F. *Org. Prep. Proced. Int.* **1991**, *23*, 1; (c) Gusar, N. I. *Russ. Chem. Rev. (Engl. Trans.)* **1991**, *60*, 146.
2. Hoesl, C. E.; Nefzi, A.; Houghten, R. A. *J. Comb. Chem.* **2002**, *5*, 155.
3. Bruché, L.; Garanti, L.; Zecchi, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2177.
4. (a) Sato, J.; Fukuda, K.; Ito, K.; Suzuki, K.; Nawamaki, T.; Watanabe, S. JP03077874, **1991**; (b) Brown, E. D. EP5911, 1979.
5. Klein, G.; Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem.* **2001**, *4*, 345.
6. Wang, F.; Hauske, J. R. *Tetrahedron Lett.* **1997**, *38*, 8651.
7. Typical procedure: Resin-bound 2-aminobenzimidazole **3g** was prepared in a polypropylene mesh packet[8] containing 50 mg of MBHA resin according to a procedure of Klein et al.[5] The reaction leading to 2,4-dioxo-1,3,5-triazino[1,2-*a*]benzimidazole and 2-imino-4-dioxo-1,3,5-triazino[1,2-*a*]benzimidazole was performed in 50 ml Kimax tubes under argon. 1.080 g of PPh_3 (4.11 mmol, 25 equiv.) and 638 μl (4.05 mmol, 25 equiv.) of DEAD were added to 150 mg of the resin-bound benzimidazole derivative **3g** in 15 ml of anhydrous THF. The reaction mixture was shaken for 48 h at room temperature. The solution was removed via cannula. The resulting resin-bound iminophosphorane intermediate **4g** was washed with anhydrous toluene (1×) under argon. The resin was treated under argon with phenyl isocyanate (15 equiv., 0.2 M) in 11 ml anhydrous toluene for 24 h at 100°C. The resin was vigorously washed with toluene (11×, 15 min each) and DCM (3×). The final compounds **2g** and **1g** were obtained after cleavage from the resin by anhydrous HF in the presence of anisole for 1.5 h at 0°C, extracted with 95% acetic acid in H_2O and lyophilized. **10-Butyl-3-phenyl-2-phenylimino-4-oxo-2,3,4,10-tetrahydro[1,3,5]triazino[1,2-*a*]benzimidazole-7-carboxamide (1g)**. ^{1}H NMR (DMSO-d_6): δ 0.85 (t, J=7.3 Hz, 3H), 1.27–1.34 (m, 2H), 1.74–1.79 (m, 2H), 4.21 (t, J=6.8 Hz, 2H), 7.33–7.37 (m, 3H), 7.44–7.47 (m, 2H), 7.58 (br, 1H), 7.64–7.66 (m, 2H), 7.68–7.75 (m, 3H), 8.01 (d, J=8.7 Hz, 1H), 8.17 (d, J=8.7 Hz, 1H), 8.28 (br, 1H), 8.62 (s, 1H), 10.17 (br, 1H). ^{13}C NMR (DMSO-d_6): δ 13.3, 19.0, 29.4, 42.6, 111.6, 113.8, 124.5, 126.0, 126.5, 127.1, 128.6, 129.0, 130.7, 131.0, 131.4, 132.0, 132.5, 144.6, 150.0, 166.5. MS (ESI) m/z 453.2 ($M+H^+$). **10-Butyl-3-phenyl-2,4-dioxo-2,3,4,10-tetrahydro[1,3,5]triazino[1,2-*a*]-benzimidazole-7-carboxamide (2g)**. ^{1}H NMR (DMSO-d_6): δ 0.94 (t, J=7.3 Hz, 3H), 1.37–1.42 (m, 2H), 1.75–1.82 (m, 2H), 4.17 (t, J=7.2 Hz, 2H), 7.34–7.36 (m, 2H), 7.42 (br, 1H), 7.44–7.46 (m, 1H), 7.49–7.53 (m, 2H), 7.74 (d, J=8.7 Hz, 1H), 8.00–8.02 (dd, J=8.7, 1.6 Hz, 1H), 8.13 (br, 1H), 8.51 (d, J=1.6 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 13.6, 19.3, 29.5, 41.8, 109.8, 113.2, 125.2, 128.2, 128.8, 128.9, 129.6, 133.3, 135.7, 147.0, 151.7, 154.2, 167.0. m/z 378.1 ($M+H^+$).
8. Houghten, R. A. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 5131.