Solid-Phase Synthesis of 1,2-Diketones via Acetylene Oxidation: A Versatile Diversity Platform for the Combinatorial Synthesis of Heterocycles

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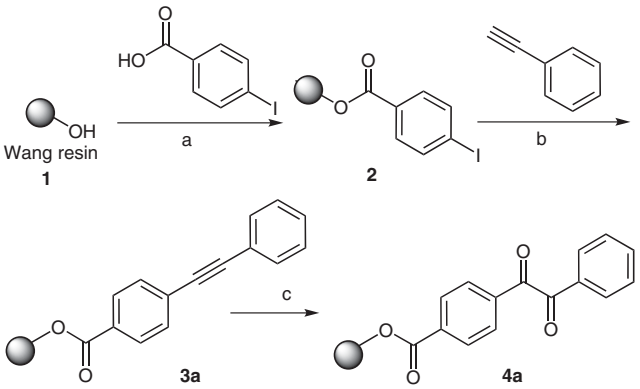
Received 18 June 2010

Abstract: Investigations towards the solid-phase synthesis of 1,2-diketones via the oxidation of acetylenes and their use in the combinatorial synthesis of heterocycles such as imidazoles and quinoxalines are described.

Key words: solid-phase synthesis, imidazole, quinoxaline, oxidation, 1,2-diketone

The solid-phase synthesis of low-molecular-weight compounds along with high-throughput screening has been and continues to be a powerful tool in the discovery of new pharmaceutical lead structures. Hence, the discovery of new synthesis methods to further expand the synthetic toolbox that allows for the rapid exploration and customization of the pharmaceutical diversity space is one major focus for synthetic organic chemists. In the course of our ongoing efforts directed toward the solid-phase synthesis of general-purpose screening libraries, we were particularly interested in the synthesis of 1,2-diketones immobilized on a solid support.

1,2-Diketones are known to be versatile and thus important intermediates for the synthesis of various types of heterocycles like imidazoles or quinoxalines. However, a literature survey revealed only few examples of the use of 1,2-diketones in combinatorial solid-phase synthesis,[1] while, to the best of our knowledge, the on-resin synthesis and use of 1,2-diketones in this context has no documented precedents.[2]



Scheme 1 *Reagents and conditions*: (a) 2,6-dichlorobenzoyl chloride, pyridine, DMF, r.t., 16 h; (b) CuI, $(Ph_3P)_2PdCl_2$, DIPEA, DMF, r.t., 16 h; (c) iodine, DMSO, 155 °C, 1 h (for other reaction conditions and reagents, see Table 1).

SYNLETT 2010, No. 17, pp 2639–2643
Advanced online publication: 23.09.2010
DOI: 10.1055/s-0030-1258570; Art ID: G18310ST

We envisaged to prepare the intermediate 1,2-diketones by the oxidation of resin-bound acetylenes, which are easily accessible through Sonogashira coupling of aryl halides with terminal alkynes. The Sonogashira reaction is a powerful and well-established tool in solid-phase synthesis[3] and proceeds, in the majority of cases, in excellent yields and purities. Although absent in solid-phase chemistry, the oxidation of alkynes to 1,2-diketones is a well-documented reaction in solution-phase chemistry.[4] Examples, among others,[5] include the use of dimethyl sulfoxide in combination with iodine,[6] palladium(II),[5,7] and *N*-bromosuccinimide[8] as the oxidation-promoting reagents.

Initially, we investigated the oxidation of the resin-bound diaryl acetylene **3a** using various reagents and reaction conditions. Resin-bound acetylene **3a** was build up in two steps as outlined in Scheme 1. 4-Iodobenzoic acid was loaded onto commercially available Wang resin **1** [4-(hydroxymethyl)phenoxymethyl polystyrene resin cross-linked with 1% divinylbenzene] using the 2,6-dichlorobenzoyl chloride technique first describe by Sieber.[9]

Subsequent Sonogashira coupling with phenylacetylene provided the resin-bound diaryl acetylene **3a**, whose purity was determined by cleaving the product from the resin with trifluoroacetic acid (TFA) in CH_2Cl_2 (v/v = 1:1, r.t., 1 h). The crude product was obtained in excellent purity[10]

Table 1 Reagents and Reaction Conditions for the Oxidation of Diaryl Acetylene **3a**

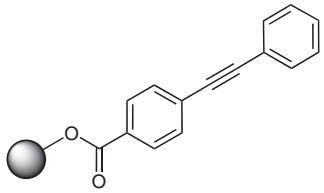
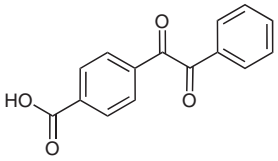
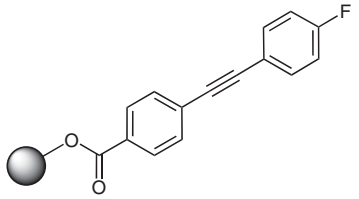
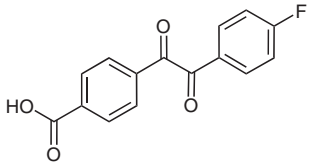
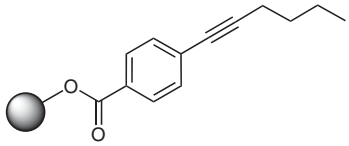
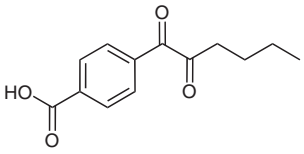
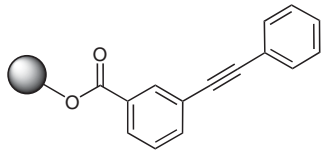
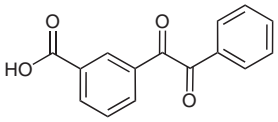
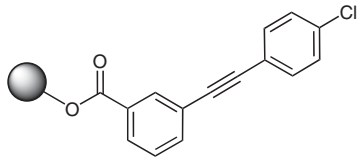
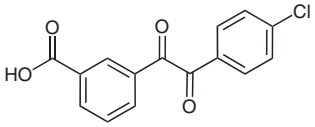
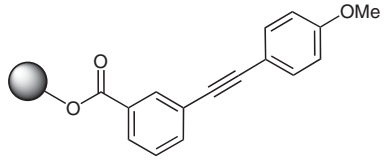
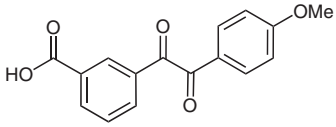
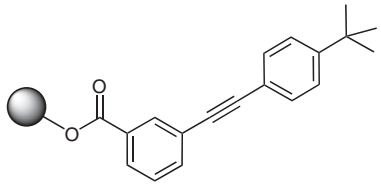
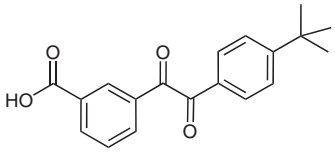
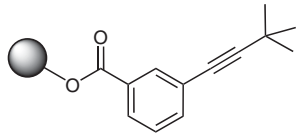
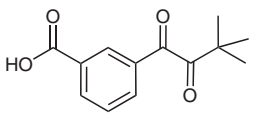
Entry	Reagents[a]	Conditions	Purity (%)
1	Na_2PdCl_4 (0.1 equiv), DMSO	4 h, 100 °C	0
2	Na_2PdCl_4 (0.1 equiv), DMSO	1.5 h, 140 °C	5
3	Na_2PdCl_4 (0.4 equiv), DMSO	5 h, 140 °C	50
4	Na_2PdCl_4 (0.4 equiv), DMSO	18 h, 140 °C	90
5	$PdCl_2$ (0.1 equiv), DMSO	18 h, 140 °C	90
6	PdI_2 (0.1 equiv), DMSO	18 h, 140 °C	95
7	I_2 (1.0 equiv), DMSO	4 h, 80 °C	0
8	I_2 (1.0 equiv), DMSO	1 h, 120 °C	10
9	I_2 (1.0 equiv), DMSO	18 h, 120 °C	90
10	I_2 (1.0 equiv), DMSO	1 h, 155 °C	95
11	NBS (5.0 equiv), DMSO	18 h, 100 °C	50

[a] In all cases DMSO was used as solvent.

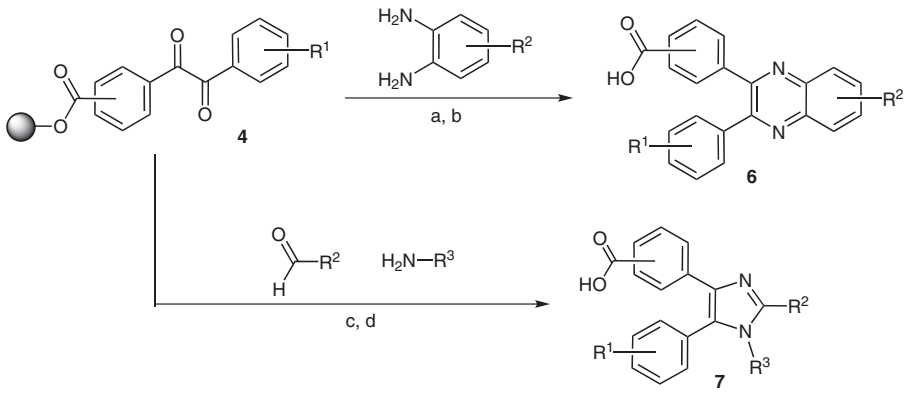
(99%) and good yield[11] (84%). Resin-bound diaryl acetylene **3a** was subjected to different oxidation protocols as outlined in Table 1.

Instead of the commonly employed catalyst palladium(II) chloride,[7] sodium tetrachloropalladate(II) was used because of its better solubility in DMSO. Purity of the formed 1,2-diketone was determined after cleaving the

Table 2 Scope and Limitations of the Acetylene Oxidation

Entry	Substrate[a]	Purity (%)[b]	Product	Purity (%)[b]	Yield (%)[c]
1	**3a** 	99	**5a** 	95	52
2	**3b** 	72	**5b** 	75	48
3	**3c** 	57	**5c** 	dec.[d]	–
4	**3d** 	97	**5d** 	86	49
5	**3e** 	100	**5e** 	86	42
6	**3f** 	18 (54)[e]	**5f** 	94	59
7	**3g** 	77	**5g** 	89	47
8	**3h** 	100	**5h** 	dec.[d]	–

[a] Substrates were analyzed after cleavage from the resin (TFA–CH_2Cl_2, v/v = 1:1, r.t., 1 h).
[b] Purities were calculated from the integrated peak areas recorded by HPLC analysis (UV detection, 210 nm) of the crude products.
[c] Yields refer to the crude products and were calculated on the basis of the initial loading of the resin.
[d] dec. = decomposition.
[e] Hydration of the triple bond was observed.



Scheme 2 *Reagents and conditions*: (a) trimethyl orthoformate (TMOF), r.t., 18 h; (b) TFA–CHCl (v/v = 1:1), r.t., 1 h; (c) NH_4OAc, AcOH, 110 °C, 16 h; (d) TFA–CH_2Cl_2 (v/v = 1:1), r.t., 1 h; **6**: R^1 = H, 4-F, 4-Cl, 4-*t*-Bu, R^2 = H, OMe; **7**: R^1 = 4-H, 4-Cl, 4-*t*-Bu, R^2 = phenyl, *t*-Bu, R^3 = H, Bn.

product from the resin under the conditions described above. Best results were obtained when iodine (entry 10) and palladium(II) iodide (entry 5) in DMSO were used at elevated temperatures of 155 °C and 140 °C, respectively.[12]

Because of its shorter reaction time the iodine protocol (entry 10) was utilized for further analogue synthesis. Having the optimized oxidation protocol in hand, we investigated the scope and limitations of the oxidation procedure. Various acetylenes **3a**–**h** were assembled on a solid support derived from 4- and 3-iodobenzoic acid as well as aliphatic and aromatic terminal alkynes (Table 2).

Oxidation of bisaromatic acetylenes proceeded smoothly, however, mono-aromatic substrates (**3c** and **3h**) underwent decomposition. To illustrate the versatility of this chemistry, the resin-bound 1,2-diketones **3a**,**b**,**e**–**g** were subjected to Debus–Radziszewski imidazole synthesis conditions[13] and underwent condensation reaction with 2-aminoanilines providing quinoxalines[14] as outlined in Scheme 2. For imidazol synthesis on a solid support we

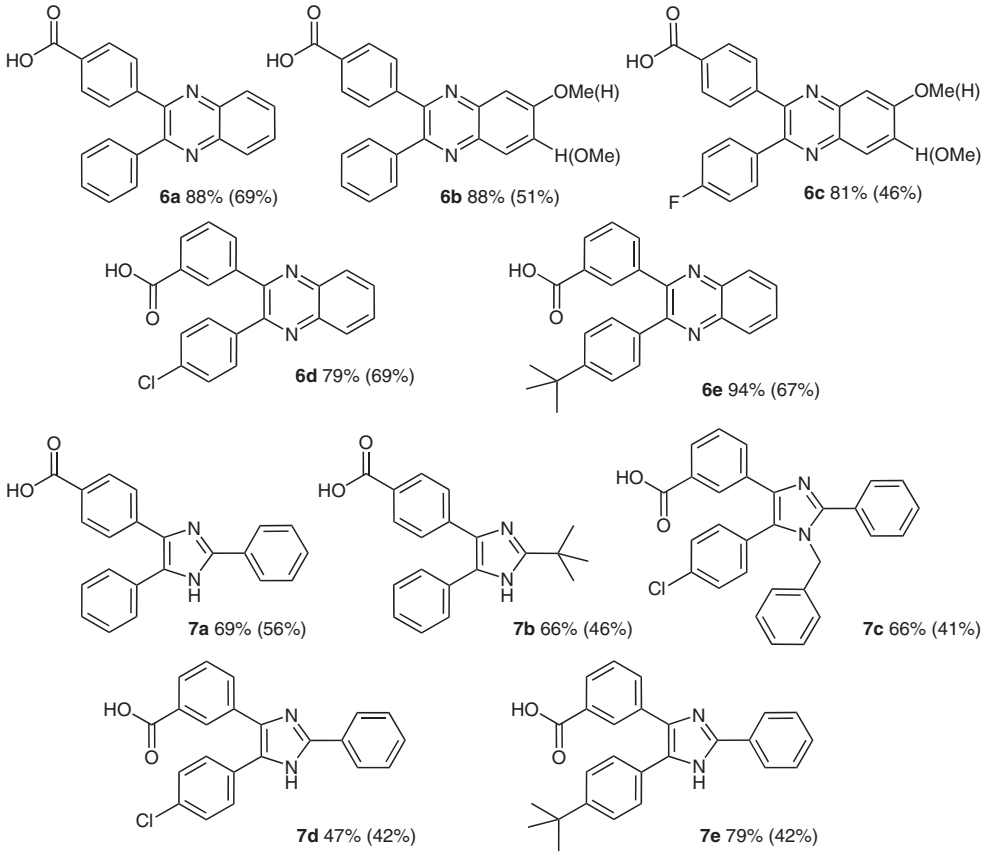


Figure 1 Purities of quinoxalines **6a**–**e** and imidazoles **7a**–**e** prepared on a solid support. Purities were calculated from the integrated peak areas recorded by HPLC analysis (UV detection, 210 nm) of the crude products. Yields in parenthesis refer to the crude products and were calculated on the basis of the initial loading of the resin. When nonsymmetric 2-aminoanilines were used in the reaction, two isomers were obtained in the ratio of 1:1 (**6b** and **6c**). In case of **7c** two isomers in the ratio of 1:1 were detected by LC-MS analysis.

employed the reaction conditions first described by Sashar et al. in 1996.[15]

A small library of quinoxalines **6**[16] and imidazoles **7**[17] were thus prepared on a solid support (Figure 1).

In the case of quinoxalines, the products were obtained in good to excellent purities (79–94%) and moderate yields (46–69%). Imidazoles were obtained in moderate to good purities (47–79%) and moderate yields (41–56%).

In conclusion, we have developed a straightforward approach to structurally diverse quinoxalines and imidazoles. Key to the synthesis is a novel procedure for the on-resin formation of 1,2-diketones via acetylene oxidation.

References and Notes

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(2) An earlier report described a mixed benzoin condensation on a solid support yielding benzils in trace amounts (4–6%) only. However, further reaction of the resin-bound benzils towards heterocycles was not reported. See: Lenzhoff, C. C.; Wong, J. Y. *Can. J. Chem.* **1973**, *51*, 3756.

(3) (a) Cironi, P.; Tulla-Puche, J.; Barany, G.; Albericio, F.; Álvarez, M. *Org. Lett.* **2004**, *6*, 1405. (b) Cironi, P.; Manzanares, I.; Albericio, F.; Álvarez, M. *Org. Lett.* **2003**, *5*, 2959. (c) Bräse, S.; Köbberling, J.; Griebenow, N. *Organopalladium Reactions in Combinatorial Chemistry,* In *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. 2; Negishi, E., Ed.; John Wiley and Sons: New York, **2002**, 3031. (d) Ljungdahl, N.; Bromfield, K.; Kann, N. *Top. Curr. Chem.* **2007**, *278*, 89. (e) Nelson, J. C.; Young, J. K.; Moore, J. S. *J. Org. Chem.* **1996**, *61*, 8160. (f) Erdélyi, M.; Gogoll, A. *J. Org. Chem.* **2003**, *68*, 6431.

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(10) Purities and product identities were determined by LC-MS analysis using a Hewlett-Packard HP 1100 liquid chromatography system coupled to a Micromass ZMD-400 spectrometer equipped with an Intersil column (ODS-3, 50 × 2.1 mm). The mobile phase was H_2O (A) and MeCN (B), both containing 0.1% TFA. A gradient was used increasing from 10–95% B in 9 min followed by a hold at 95% B for 1 min and then re-equilibration for 3 min at a flow rate of 0.5 mL/min. The column was maintained at 35 °C. Mass spectra were acquired in either the positive or negative ion mode under electrospray ionization (ESI). The compound purity was monitored based on the UV absorbency at 210 nm. The presence of all desired compounds was confirmed by their molecular mass.

(11) Yields refer to the crude products and were calculated on the basis of the initial loading of the resin.

(12) **Representative Experimental Procedure for the Preparation of 1,2-Diketones**
Wang resin (6.00 g, 7.14 mmol, loading of 1.19 mmol/g, 1% cross-linking, 100–200 mesh) was suspended in DMF (40 mL). The suspension was charged with 4-idodobenzoic acid (3.19 g, 1.8 equiv, 12.85 mmol), 2,6-dichlorobenzoyl chloride (2.99 g, 2.0 equiv, 14.27 mmol), and pyridine (1.91 mL, 1.86 g, 3.3 equiv, 23.55 mmol), and the reaction mixture was shaken at r.t. for 18 h. The resin was filtered off and washed successively with DMF, MeOH, THF, as well as CH_2Cl_2. Residual traces of solvent were removed in vacuo overnight to provide the derivatized resin **2** with a theoretical loading capacity of 0.93 mmol/g based on 100% conversion. Under an atmosphere of argon 4-iodobenzoic acid functionalized Wang resin **2** (3.00 g, 2.80 mmol, loading: 0.93 mmol/g) was suspended in a solution of phenylacetylene (3.0 equiv, 858 mg, 8.41 mmol) in DMF–DIPEA (15 mL, v/v = 3:1). Bis(triphenylphosphine)palladium(II) dichloride (197 mg, 0.1 equiv, 0.28 mmol) and copper(I) iodide (213 mg, 0.4 equiv, 1.12 mmol) were added, and the reaction mixture was shaken at r.t. for 18 h. After filtration, the resin was washed with DMF, 50% aq AcOH, MeOH, THF, and CH_2Cl_2. Residual traces of solvent were removed in vacuo overnight to provide the derivatized resin **3a** with a theoretical loading capacity of 0.96 mmol/g based on 100% conversion. An analytical sample of the resin was treated with TFA in CH_2Cl_2 (v/v = 1:1) for 1 h at r.t. Filtration and evaporation yielded 4-(phenylethynyl)benzoic acid.
LC-MS: 2.52 min, 99% (210 nm), *m/z* = 221 [M – H^-]. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.44–7.49 (m, 3 H), 7.57–7.62 (m, 2 H), 7.66–7.70 (m, 2 H), 7.96–8.00 (m, 2 H) ppm; one proton not observed in this spectrum. HRMS: *m/z* calcd for $C_{15}H_{11}O_2$ [M + H^+]: 223.0754; found: 223.0754.
4-(Phenylethynyl)benzoic acid Wang resin (**3a**, 209 mg, 0.20 mmol, loading: 0.957 mmol/g) was suspended in anhyd DMSO (2 mL) and charged with iodine (51 mg, 1 equiv, 0.20 mmol). The reaction mixture was heated to 155 °C for 1 h. The resin was then filtered off and successively washed with DMF, 50% aq AcOH, MeOH, THF, as well as CH_2Cl_2. Residual traces of solvent were removed in vacuo overnight to provide the derivatized resin **4a** with a theoretical loading capacity of 0.93 mmol/g based on 100% conversion. The resin was cleaved with TFA–CH_2Cl_2 (2 mL, v/v = 1:1) at r.t. for 1 h, filtered, and washed with CH_2Cl_2 (1 mL). The filtrate was evaporated to dryness providing 26 mg of 4-[oxo-(phenyl)acetyl]benzoic acid (**5a**) in 52% yield.
LC-MS: 2.20 min, 95% (210 nm), *m/z* = 253 [M – H^-]. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.63–7.67 (m, 2 H), 7.83 (t, *J* = 7.60 Hz, 1 H), 7.97 (d, *J* = 7.72 Hz, 2 H), 8.06 (d, *J* = 8.16 Hz, 2 H), 8.15 (d, *J* = 8.16 Hz, 2 H) ppm; one proton not observed in this spectrum. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 129.60, 129.86, 129.97, 130.04, 132.21, 135.17, 135.81, 136.41, 166.39, 194.21, 194.25 ppm. HRMS: *m/z* calcd for $C_{15}H_{11}O_4$ [M + H^+]: 255.0652; found: 255.0653.

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(14) Trimethyl orthoformate was used instead of molecular sieve as the dehydrating reagent. See: (a) Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937. (b) Quinoxaline synthesis using molecular sieve: Ott, S.; Faust, R. *Synthesis* **2005**, 3135.

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(16) **Representative Experimental Procedure for the Synthesis of Quinoxalines**
4-[Oxo(phenyl)acetyl]benzoic acid functionalized Wang

resin (**4a**, 108 mg, 0.10 mmol, loading of 0.93 mmol/g) was suspended in TMOF (3 mL) and charged with 2-aminoaniline (270 mg, 25 equiv, 2.50 mmol). The reaction mixture was shaken at r.t. for 18 h. The resin was filtered off and washed successively with DMF, THF, as well as CH_2Cl_2. The resin was cleaved with TFA–CH_2Cl_2 (2 mL, v/v = 1:1) at r.t. for 1 h, filtered, and washed with CH_2Cl_2 (1 mL). The filtrate was evaporated to dryness providing 22 mg of 4-(3-phenylquinoxalin-2-yl)benzoic acid (**6a**) in 69% yield. LC-MS: 5.70 min, 88% (210 nm), *m/z* = 327 [M + H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.36–7.43 (m, 3 H), 7.48–7.50 (m, 2 H), 7.59 (d, *J* = 8.1, 2 H), 7.90–7.94 (m, 4 H), 8.18–8.20 (m, 2 H), 13.21 (br s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 128.16, 128.86, 128.90, 128.94, 129.54, 129.78, 129.89, 130.61, 130.80, 131.31, 138.44, 140.39, 140.62, 142.76, 152.35, 153.06, 167.05. HRMS: *m/z* calcd for $C_{21}H_{15}O_2N_2$ [M + H$^+$]: 327.1128; found 327.1125. For further analytical data see: van Es, T.; Backeberg, O. G. *J. Chem. Soc.* **1963**, 1371.

(17) **Representative Experimental Procedure for the Synthesis of Imidazoles**

4-[Oxo(phenyl)acetyl]benzoic acid functionalized Wang resin (**4a**, 215 mg, 0.20 mmol, loading of 0.93 mmol/g) was suspended in AcOH (3 mL) and charged with benzaldehyde (420 mg, 20 equiv, 4.00 mmol), and NH_4OAc (310 mg, 20 equiv, 4.00 mmol). In case of **7c** 40 equiv benzaldehyde, 40 equiv benzylamine, and 1.5 equiv NH_4OAc was used. The reaction mixture was heated to 110 °C for 16 h. The resin was filtered and washed successively with 50% aq AcOH, DMF, MeOH, THF, as well as CH_2Cl_2. The resin was cleaved with TFA–CH_2Cl_2 (2 mL, v/v = 1:1) at r.t. for 1 h, filtered, and washed with CH_2Cl_2 (1 mL). The filtrate was evaporated to dryness providing 38 mg of 4-(2,5-diphenyl-1*H*-imidazol-4-yl)benzoic acid (**7a**) in 56% yield. LC-MS: 3.83 min, 69% (210 nm), *m/z* = 341 [M + H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.43–7.51 (m, 3 H), 7.52–7.59 (m 5 H), 7.67 (d, *J* = 8.60 Hz, 2 H), 7.96 (d, *J* = 8.60 Hz, 2 H), 8.13 (d, *J* = 7.45 Hz, 2 H) ppm; two protons not observed in this spectrum. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 126.08, 127.64, 128.27, 128.43, 128.54, 128.74, 128.78, 128.89, 129.18, 129.50, 129.63, 129.89, 130.12, 130.99, 145.24, 166.83. HRMS: *m/z* calcd for $C_{22}H_{17}O_2N_2$ [M + H$^+$]: 341.1285; found: 341.1280.