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Reaction between heterocyclic NH-acids and dibenzoylacetylene in the presence of triphenylphosphine. Simple synthesis of 1-(3-furyl)-1*H*-imidazole derivatives

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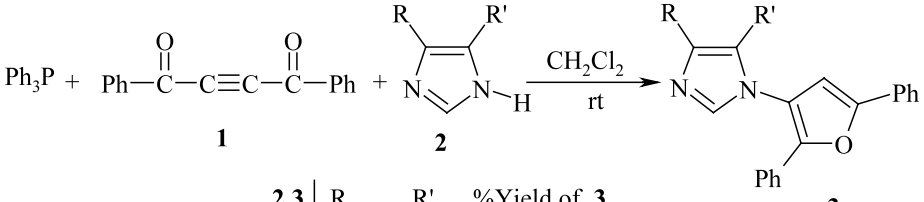
Abstract—The reactive 1:1 intermediate obtained from the addition of triphenylphosphine to dibenzoylacetylene was trapped by heterocyclic NH-acids such as imidazole, 4-nitroimidazole, or 5-methyl-4-nitroimidazole to produce 2,3,5-trisubstituted furan derivatives. Using 2-benzoylimidazole or saccharin as NH-acids leads to enamino ketones. When benzotriazole was employed as NH-acid, both types of products, namely furan derivatives and enamino ketones, were obtained.

Furan, as one of the representative five-membered heterocycles, is found in many naturally occurring compounds.[1] Polysubstituted furans play an important role in organic chemistry not only due to their presence as key structural units in many natural products and in important pharmaceuticals,[2] but they can also be employed in synthetic organic chemistry as building blocks. The formation of a carbon–carbon bond α to a nitrogen atom is of great importance for the synthesis of nitrogen-containing natural products and biologically active systems.[3] Several methods have been developed for the preparation of furans.[4] We wish to report an efficient synthetic route to polysubstituted furans using dibenzoylacetylene[5] **1** and heterocyclic N–H acids such as imidazole, 4-nitroimidazole, 5-methyl-4-nitroimidazole,[6] 2-benzoylimidazole,[7] saccharin or benzotriazole, in the presence of triphenylphosphine. Thus, the reaction between imidazole or its nitro compounds, and **1** in the presence of triphenylphosphine at ambient temperature in dichloromethane, leads to substituted furan derivatives **3** in nearly quantitative yields[8] (Scheme 1).

The reaction of imidazole **2a** with dibenzoylacetylene in the presence of triphenylphosphine proceeded spontaneously at room temperature in dichloromethane, and was complete within a few hours. ^{1}H and ^{13}C NMR spectra of the crude product clearly indicated the for-



2,3	R	R'	%Yield of 3
a	H	H	95
b	NO_2	H	98
c	NO_2	Me	98

Scheme 1.

Keywords: dibenzoylacetylene; NH-acid; furan derivatives; imidazole; triphenylphosphine.

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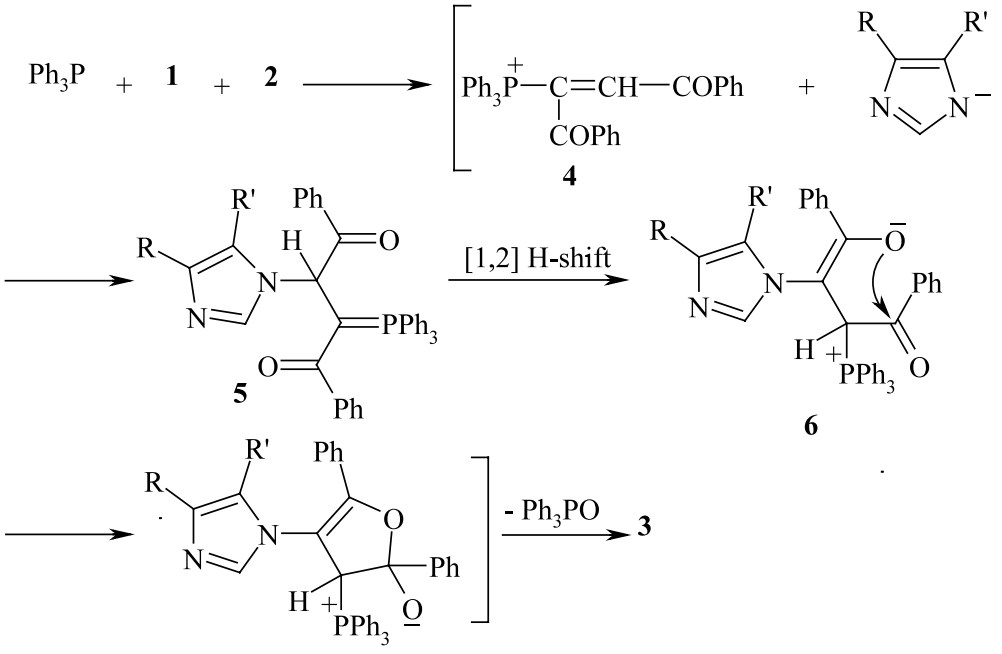


Scheme 2.

mation of 1-(2,5-diphenyl-3-furyl)-1*H*-imidazole derivative **3a**. Any product other than **3** could not be detected by NMR spectroscopy. The structures of compounds **3a**–**c** were deduced from their elemental analyses and their IR, ^{1}H NMR and ^{13}C NMR spectroscopic data. The mass spectra of these compounds displayed molecular ion peaks at $m/z = 286$, 331, and 345, respectively. The ^{1}H NMR spectrum of **3a** exhibited two single sharp lines readily recognized as arising from C-4–H of furan (δ 6.75) and C-2–H of imidazole (δ 7.63); the vicinal CH groups of the imidazole moiety appear as fairly broad signals at δ 7.07 and 7.26. The phenyl residues gave rise to characteristic signals in the aromatic region of the spectrum. The ^{13}C NMR spectrum of **3a** shows signals for the C-2 and C-5 atoms of furan at δ 145.62 and δ 152.31, which confirms the presence of the furan ring in **3**. The substitution reactions of **2b** and **2c** are regioselective, as shown by the ^{1}H NMR spectra of the reaction mixtures. Compound **2b** usually reacts at *N*-1 as indicated in Scheme 1. Compounds **2b** and **2c** are expected to have similar reactivity patterns, thus structure **3c** was assigned to the product obtained from reaction using **2c** (see Scheme 1).

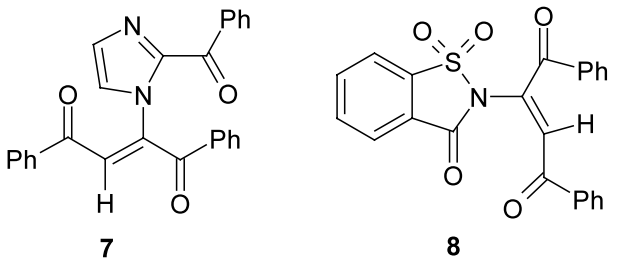
Although the mechanism of the reaction between triphenylphosphine and dibenzoylacetylene in the presence of imidazole **2** has not yet been established in an experimental manner, a possible explanation is proposed in Scheme 2. On the basis of the well established chemistry of trivalent phosphorus nucleophiles,[9–16] it is reasonable to assume that **3** results from initial addition of triphenylphosphine to dibenzoylacetylene and subsequent protonation of the 1:1 adduct by the NH-acid. Then, the positively charged ion might be attacked by the conjugate base of the NH-acid to form phosphorane **5,** which in turn is converted to betaine **6**. Cyclization of the betaine **6** and subsequent loss of triphenylphosphine oxide leads to compound **3** (see Scheme 2).

The reaction of dibenzoylacetylene with 2-benzoylimidazole or saccharin in the presence of triphenylphosphine gave only the enamino ketones **7** and **8** (Scheme 3).

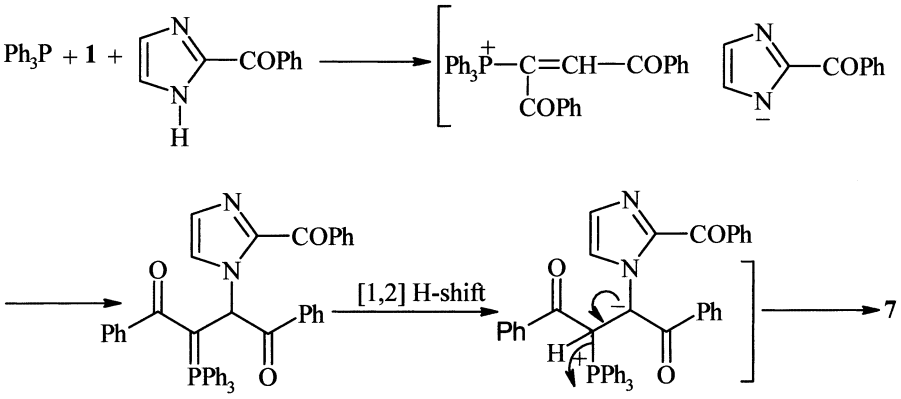
These compounds result from the triphenylphosphine catalyzed reaction of the NH-acid addition to dibenzoylacetylene. A mechanism for this transformation is proposed in Scheme 4. The ^{1}H and ^{13}C NMR spectra of **7** and **8** are consistent with the proposed structures.[8]

Benzotriazole is a useful synthetic auxiliary with important applications in organic synthesis.[17] We studied the reaction of benzotriazole and dibenzoylacetylene in the presence of triphenylphosphine.

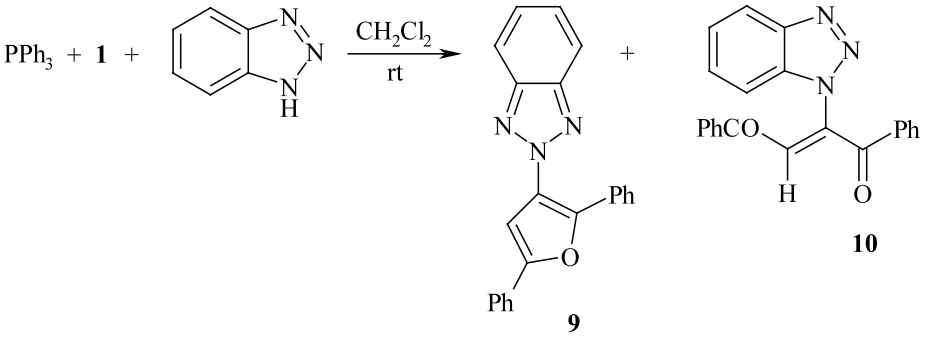
This reaction produced both types of products, namely, the 2,3,5-trisubstituted-furan derivative **9** and the enamino ketone **10** (Scheme 5). In principle, four products are possible here, but the 500 MHz ^{1}H NMR spectra of the reaction mixture is consistent with the presence of products **9** and **10**. These products were separated by



Scheme 3.



Scheme 4.



Scheme 5.

column chromatography. The ^{1}H NMR spectra of compounds **9** and **10** exhibited single sharp lines readily recognized as arising from C-3–H of furan (δ 6.85) and C-3–H of butene-1,4-dione (δ 8.11) moieties, respectively. The phenyl residues gave rise to characteristic signals in the aromatic region of the spectra of these molecules. The ^{13}C NMR spectra of compounds **9** and **10** showed 15 and 18 distinct resonances, respectively, in agreement with the proposed structures. Compounds **9** and **10** are formed by mechanisms outlined in Schemes 2 and 4, respectively.

In conclusion, the present method carries the advantage that, not only is the reaction performed under neutral conditions, but the substances can be mixed without any activation or modification. The simplicity of the present procedure makes it an interesting alternative to complex multistep approaches.

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8. The preparation of 1-(2,5-diphenyl-3-furyl)-1*H*-imidazole **3a** is described as an example. To a magnetically stirred solution of 0.52 g triphenylphosphine (2 mmol) and 0.136 g imidazole (2 mmol) in 4 mL dichloromethane was added dropwise a mixture of 0.47 g dibenzoylacetylene (2 mmol) in 2 mL dichloromethane at room temperature over 10 min. After 5 h stirring at room temperature, the solvent was removed under reduced pressure and the residual solid recrystallized from ethyl acetate. The product **3a** was obtained as light yellow needles, mp 145–150°C, 0.54 g, yield 95%. IR (KBr) (ν_{max}, cm^{-1}): 3095 (CH of furan), 1612 (C=C–O), 1587 (C=N), 1491 and 1488 (C=C, skeletal), 1306 (C–O). Anal. calcd for $C_{19}H_{14}N_2O$ (286.3): C, 79.70; H, 4.92; N, 9.78%. Found: C, 79.0; H, 4.9; N, 9.8%. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 6.75 (1H, CH of furan), 7.07 (1H, s, C-5–H of imidazole), 7.26 (1H, s, C-4–H of imidazole), 7.30–7.34, 7.42 and 7.43 (C_6H_5), 7.63 (1H, s, C-2–H of imidazole), 7.67 and 7.73 (C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 106.30 (CH of furan), 121.00 (C-3 of furan), 123.90 (C-4 of imidazole), 124.67 (C-5 of imidazole), 128.41, 128.51, 128.90, 129.61, 130.33, 131.89, 132.03 and 132.11 (C_6H_5), 137.47 (C-2 of imidazole), 145.62 (C-2 of furan), 152.31 (C-5 of furan). MS, m/z (%): 286 (M^+, 11), 201(19), 183

(15), 152 (11), 77 (34), 51 (31). **3b**: Light yellow needles, mp 185–189°C, 0.64 g, yield 98%. IR (KBr) (ν_{max}, cm^{-1}): 1589 (C=N), 1529 (NO_2), 1487 and 1436 (C=C, skeletal), 1363 (NO_2), 1258 (C–O). Anal. calcd for $C_{19}H_{13}N_3O_3$ (331.3): C, 68.87; H, 3.95; N, 12.68%. Found: C, 68.7; H, 3.9; N, 12.6%. ^1H NMR (500 MHz, $CDCl_3$): δ_H 6.85 (1H, CH of furan), 7.36–7.50 and 7.49 (C_6H_5), 7.61 (1H, s, C-5–H of imidazole), 7.77 (C_6H_5), 7.95 (1H, s, C-2–H of imidazole). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 105.33 (CH of furan), 119.60 (C-5 of imidazole), 120.14 (C-3 of furan), 124.13, 125.01, 127.57, 129.02, 129.10, 129.36 and 129.40 ($2C_6H_5$ groups), 136.65 (C-2 of imidazole), 146.36 (C-4 of imidazole), 148.90 (C-2 of furan), 153.26 (C-5 of furan). MS, m/z (%): 331 (M^+, 100), 246 (44), 217 (31), 105 (52), 77 (50), 51 (11). **3c**: Light yellow crystals, mp 170–173°C, 0.67 g, yield 98%. IR (KBr) (ν_{max}, cm^{-1}): 1610 (C=C–O), 1588 (C=N), 1559 (NO_2), 1489 (C=C, skeletal), 1433 (C=C), 1350 (NO_2), 1285 (C–O). Anal. calcd for $C_{20}H_{15}N_3O_3$ (345.3): C, 69.55; H, 4.37; N, 12.16%. Found: C, 69.2; H, 4.5; N, 12.4%. ^1H NMR (500 MHz, $CDCl_3$): δ_H 2.51 (3H, s, CH_3), 6.80 (1H, s, CH of furan), 7.27, 7.34–7.40 and 7.47 ($2C_6H_5$), 7.50 (1H, s, CH of imidazole), 7.78 ($2CH_{ortho}$ of C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$): d_C 10.63 (CH_3) 106.21 (CH of furan), 117.6 (C-3 of furan), 124.08 and 124.35 (CH_{meta} of $2C_6H_5$), 127.67 (C-4 of imidazole), 128.98, 129.07, 129.27 and 129.36 ($2C_6H_5$), 131.78 (C-2 of imidazole), 135.02 and 135.04 (CH_{para} of C_6H_5), 145.40 (C-NO_2), 147.72 (C-5 of furan), 153.32 (C-2 of furan). MS, m/z (%): 345 (M^+, 100), 260 (19), 105 (38), 77 (50), 51 (17). **7**: Pale yellow crystals, mp 132–136°C, 0.36 g, yield 90%. IR (KBr) (ν_{max}, cm^{-1}): 1657 (C=O), 1617 (C=C), 1585 (C=N), 1230 (CCOC). Anal. calcd for $C_{26}H_{18}N_2O_3$ (406.4): C, 76.83; H, 4.46; N, 6.89%. Found: C, 76.7; H, 4.4; N, 6.9%. ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.13 (1H, s, C-4–H of imidazole), 7.14 (1H, s, C-3–H of butene-1,4-dione), 7.19 (1H, s, C-5–H of imidazole), 7.32, 7.43, 7.49, 7.52–7.56, 7.65, 7.90, 8.13 and 8.23 ($2C_6H_5$). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 127.39 (C-5 of imidazole), 128.15 (2CH of C_6H_5), 128.39 (C-3 of butene), 128.72, 128.82, 128.85 and 129.97 ($2C_6H_5$), 130.22 (C-5 of imidazole), 130.71 (C-5 of imidazole), 130.92, 133.23, 133.33, 134.41, 135.50, 135.71 and 135.83 ($2C_6H_5$), 140.63 (C-2 of butene), 143.35 (C-2 of imidazole), 190.12 and 191.05 (C=O). MS, m/z (%): 406 (M^+, 11), 301 (100), 273 (2), 195 (2), 168 (4), 129 (2), 105 (100), 76 (100), 47 (16). **8**: Pale yellow crystals, mp 170–172°C, 0.37 g, yield 90%. IR (KBr) (ν_{max}, cm^{-1}): 1751 (PhCON), 1688 (C=O), 1646 (C=C), 1335 and 1195 (SO_2). Anal. calcd for $C_{23}H_{15}NO_5S$ (417.4): C, 66.18; H, 3.62; N, 3.36%. Found: C, 66.2; H, 3.7; N, 3.7%. ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.37–7.45, 7.50 and 7.56 ($2C_6H_5$), 7.78 (1H, s, C-3–H of butene), 7.85 (2H of C_6H_5), 7.86 and 7.94 (2H, of C_6H_4), 7.95 (CH_{ortho} of C_6H_5), 8.01 (2CH of C_6H_4). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 119.73 (C-3 of butene), 121.41 (C-7 of C_6H_4), 125.59 (C-3a of C_6H_4), 126.10 (C-4 of C_6H_4), 128.54, 128.65, 128.69, 128.78, 133.35 and 133.77 (C_6H_5), 135.07 and 135.95 (C_6H_4), 136.07 and 136.80 (C_{ipso} of C_6H_5), 137.92 (C-7a of C_6H_4), 139.06 (C-2 of butene), 157.00 (NCO), 188.22 (C=O), 188.96 (C=O). MS, m/z (%): 417 (M^+, 2), 353 (15), 312 (11), 105 (100), 77 (56), 51 (21). **9**: White powder, mp 137–139C, 0.13 g, yield 40%. IR (KBr) (ν_{max}, cm^{-1}): 1590 (C=C–O), 1551 (C=N), 1475 and 1430 (C=C), 1285 (C–O). Anal. calcd for $C_{22}H_{15}N_3O$ (337.4): C, 78.32; H, 4.48; N, 12.45%. Found: C, 78.3; H, 4.5; N, 12.4%. ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.29 (1H, s, CH of furan), 7.34–7.42, 7.45–7.50, 7.76, 7.81 and 7.95 (aromatic protons). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 105.00 (CH of furan), 118.28 and 124.03 (C_6H_4), 126.34 (C-3 of furan), 126.74, 127.40, 128.5, 128.71, 128.90, 128.94 and 129.65 (C_6H_5), 144.87 (C_6H_4), 145.53 (C-2 of furan), 152.50 (C-5 of furan). Ms, m/z (%): 337 (M^+, 100), 277 (31), 204 (13), 183 (5), 152 (4), 105 (32), 102 (9), 76 (29), 47 (6). **10**: Pale yellow crystals, mp 174–176°C, 0.16 g, yield 45%. IR (KBr) (ν_{max}, cm^{-1}): 1669 (C=O), 1647 (C=C). Anal. calcd for $C_{22}H_{15}N_3O_2$ (353.4): C, 74.78; H, 4.28; N, 11.89%. Found: C, 74.8; H, 4.3; N, 11.8%. ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.40–7.60, 8.00, 8.05 and 8.10 (aromatic protons), 8.11 (1H, s, C-3–H of butene-1,4-dione). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 111.62 and 113.80 (C_6H_4), 121.00 (C-3 of butene-1,4-dione), 125.48 (C_6H_4), 128.63, 128.82, 128.9 and 129.14 (C_6H_5), 129.74 (C_6H_4), 131.23 (C-2 of butene-1,4-dione), 133.85, 134.29, 135.24 and 136.85 (C_6H_5), 145.74 and 146.78 (C_6H_4), 187.97 and 189.89 (C=O). MS, m/z (%): 353 (M^+, 4), 324 (2), 296 (15), 268 (7), 220 (71), 195 (14), 165 (4), 152 (2), 115 (2), 105 (100), 76 (50), 47 (6).

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