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Resin-Bound 4*H*-1,3-Oxazine-Masked β-Diketones for Functionalizing Cleavage Strategy

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Resin-Bound 4*H*-1,3-Oxazine-Masked *β*-Diketones for Functionalizing Cleavage Strategy

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Resin-bound 4*H*-1,3-oxazines are synthesized by the stepwise condensation of an amide resin, an aldehyde, and an alkyne. Upon DDQ activation, oxazines are converted into oxazinium salts. When treated with hydrazines, these resin-bound *β*-diketone equivalents yield pyrazoles through a functionalizing release process. This multicomponent capture strategy, tedious to handle in classical synthesis in solution, is well-suited to solid-supported chemistry. It facilitates the handling of sensitive and unstable intermediates, such as *N*-α-methoxyalkylamides and 1,3-oxazinium salts.

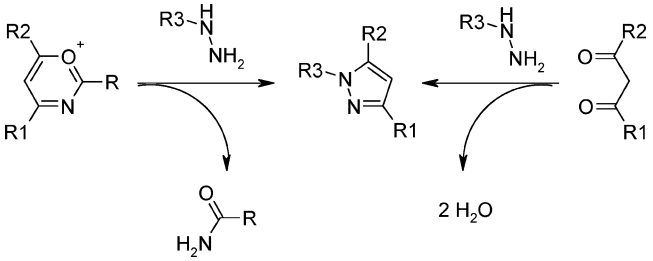
Solid-phase synthesis (SPS) is no longer just a tool to prepare large numbers of compounds through coupling chemistry. More and more, it becomes a domain on its own right, which gives rise to important research efforts and numerous publications.[1] Synthetic approaches have evolved from the direct, though not trivial, transposition of existing homogeneous phase schemes to the design of original methods that exploit the best advantages of SPS.[2] At the same time, specific linkers and anchoring strategies have been developed to better fit all synthetic approaches.[3]

As an illustration of these new strategies, we imagined a synthetic path for the preparation of novel resin-bound 1,3-diketone-like synthons. 1,3-Diketones are key intermediates in heterocyclic chemistry, being highly considered for production of libraries.[4] Early strategies derived from the well-established deprotonation/alkylation chemistry, with diversity introduced on a grafted 1,3-diketone backbone by combining various electrophiles. Further cyclodehydration reaction leads to the desired heterocycles that are released from the resin under acidic/basic cleavage conditions.[5]

Noteworthy is that the diketone's two oxygen atoms are eliminated during the cyclodehydration reaction. We therefore considered a de novo approach using these two atoms as anchors onto the resin. Such a strategy would allow multifunctional cleavage and would benefit from SPS advantages. Analysis of the literature showed that 1,3-oxazinium salts bearing two 1,3-electrophilic centers behave similarly to 1,3-diketones upon treatment with an excess of hydrazines or other bis nucleophiles (Scheme 1). Hence, if the oxazinium species was bound to a resin through the 2-position (R = resin), the trans heterocyclization reaction would result in a versatile multifunctional cleavage.

Oxazinium salts can be readily prepared by hydrogen abstraction from 1,3-oxazines.[6] The synthetic challenge is, thus, to built a resin-bound 1,3-oxazine from an amide resin.

Scheme 1. 1,3-Diketones and 1,3-Oxazinium Salts: 2 Valuable Intermediates in Heterocyclic Chemistry



Among the different synthetic paths,[7] an appealing approach for the efficient introduction of diversity would involve as a key step a hetero Diels−Alders cycloaddition of an alkyne and an acyliminium salt, the latter arising from the condensation of an amide and an aldehyde. The overall process would enable the preparation of libraries of pyrazoles by combining alkynes, aldehydes, and hydrazines. Practically, the supported 4*H*-1,3-oxazines are linked to the resin through the amide moiety, which behaves as a protecting group (Scheme 2).

The study was aimed at the preparation of a small library of heterocycles with high purities and with yields that would recover at least 5 mg of final product from 100 mg of resin. Efforts were focused on finely tuning all reaction steps to get clean final products.

We previously described a simple and straightforward preparation of resin-bound *N*-(α-methoxyalkyl)amides, versatile precursors of acyliminium salts, by condensation of aldehydes on a supported amide resin in the presence of trimethylorthoformate in acidic media.[8]

The Lewis acid-promoted hetero Diels−Alders cylclization reaction was investigated. The resulting resins were analyzed by single-bead FTIR microscopy and ^{13}C NMR spectroscopy[9] after every trial. The supported compounds present characteristic IR signals that allowed the monitoring of the transformations. In particular, the *N*-(α-methoxyalkyl)amides

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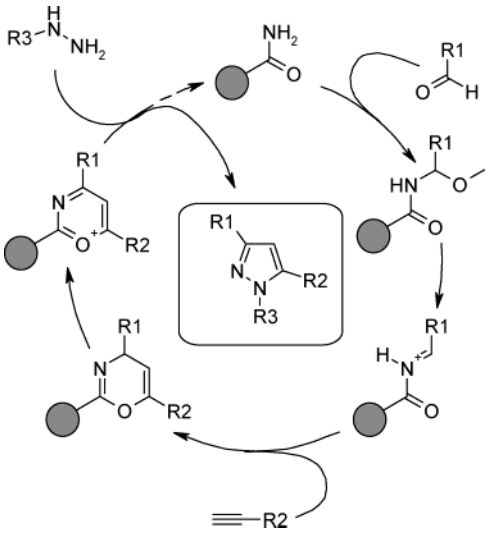
Scheme 2. Pyrazoles SPS Involving an Original Activation-Functionalizing Cleavage



showed a C═O band at around 1665 cm^{-1}, whereas the corresponding 4*H*-1,3-oxazines had a C═N band in the 1680 cm^{-1}area. Concomitantly, one expects the disappearance of N−H bands at 3330 and 3400 cm^{-1} after the cyclization reaction.

Various Lewis acids, solvents, and temperatures were evaluated. $ZnCl_2$ showed poor efficiency in converting the starting resin that was recovered unchanged; however, $AlCl_3$ and $SnCl_4$ led to chemical as well as structural degradations of the resin. The use of a more complexing solvent, such as THF, not only moderated Lewis acid activity but totally prevented the cycloaddition reaction. Finally, $BF_3 \cdot Et_2O$ in dichloromethane was identified as the most appropriate catalyst. Elemental analysis was used to assess the quantitative efficacy on a model system bearing a bromide atom on the aldehyde moiety (supported 4-(4-bromophenyl)-6-phenyl-2-resin-4*H*-[1,3]oxazine)[10] and indicated a 78% conversion for the heterocyclization reaction.

The optimized conditions consisted of swelling resin-bound *N*-(α-methoxyalkyl)amide in dichloromethane; chilling the slurry to 0 °C and adding 3 equiv of $BF_3 \cdot Et_2O$, along with 5 equiv of alkyne; followed by warming to room temperature and overnight reaction.

The protocol to form 4*H*-1,3-oxazines optimized, the last two steps were explored: activation followed by trans heterocyclization reaction as functional cleavage.

To find out the best procedure to perform the conversion of 4*H*-1,3-oxazines to oxazinium salts, diverse oxidizing reagents and reaction conditions were screened. After the activation step, the resin was washed and immediately treated with hydrazine, releasing the pyrazole. The efficacy of the overall cleavage process was measured by the yield of recovered pyrazole.

Among the reagents (CAN, DDQ, tritylium tetrafluoroborate, NBS) and reaction conditions tested (different solvents and temperatures), only DDQ enabled access to the desired pyrazole. DDQ is hardly soluble in many solvents (DCM, THF, or toluene) and appeared to be most active in acetronitile, in which the solubility was reasonable. When activation and release steps were carried out at 60 °C instead of room temperature, cumulative yields increased by more than 20%.

After filtration of the final resin, the mother liquors were concentrated in vacuo. ^1H NMR analysis of the residue gave only evidence of the presence of the pyrazole along with the excess of hydrazine, although the residue was slightly colored (presumably mainly by DDQ byproducts).

The relative purities of the crudes are an expected advantage of this approach. The release strategy can, indeed, only affect the supported 1,3-oxazinium salts. All eventual unreacted intermediates or supported side products should remain bound to the solid phase, giving noncomplex reaction mixtures. As was anticipated, the cleaved pyrazole was readily isolated by quick filtration through a silica gel cartridge, impurities being much more polar than the targeted heterocycle.

As described in the literature,[6,7] in the case of similar reactions carried out in the solution phase, a high 2-fold regioselectivity was observed. First, the resin-bound *N*-(α-methoxyalkyl)amides reacted regioselectively with disubstituted alkynes to yield one 1,3-oxazine, leading finally to one pyrazole after cleavage (compounds **7** and **8**). Second, when treated with substituted hydrazines, oxazinium salts reacted selectively to give rise to one regioisomer (compounds **12** and **13**). Regioselectivity was assessed with HMBC and HMQC NMR spectra of the pyrazoles isolated after cleavage.

To evaluate the scope and limitations of the whole synthetic scheme, some representative building blocks were tested. Illustrative structures thus obtained are presented in Scheme 3, with yields calculated from the loading of the starting Merrifield resin. An average of 5 mg of all compounds was obtained from 100 mg of Merrifield resin, with a purity of the crude mixture after evaporation exceeding 95%.

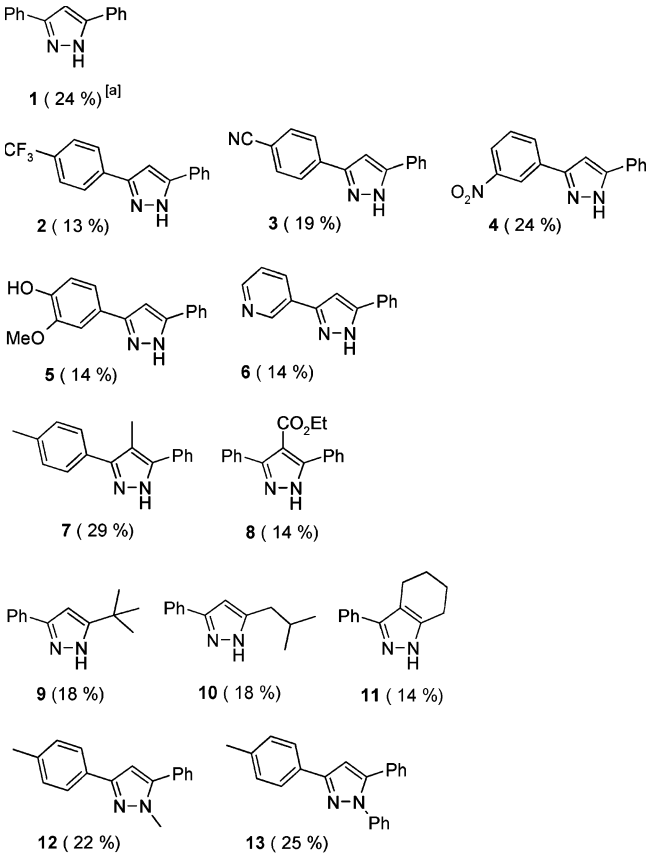
As was anticipated, the procedure is compatible with a wide variety of structures and functional groups. The first source of diversity arises from the aldehyde moiety. Many aromatic and heteroaromatic substrates bearing either electroattracting (−CF_3, −CN, −NO_2) or donating (−OMe, −OH) groups were successfully involved in the reaction. The major limitation thereby observed concerns aliphatic aldehydes, as their corresponding *N*-(α-methoxyalkyl)amides were unsuccessfully engaged into the 4*H*-1,3-oxazine cyclization.

On the contrary, both aliphatic aromatic alkynes, either mono- or disubstituted, did yield valuable pyrazoles, although aromatic ones gave better results. Interestingly, a synthetic equivalent of cyclohexyne (1-bromocyclohexene) enabled achieving a fused bicyclic structure (compound **11**).

Finally, the last point of diversity was successfully introduced with three different hydrazines.

In summary, we reported an original and efficient method involving a novel supported masked *β*-diketone moiety for the preparation of libraries of valuable small heterocycles. The developed strategy is fully adapted to SPS and takes all advantages from it. In particular, it demonstrates the potential superiority of SPS over solution chemistry by the easy handling of sensitive and unstable compounds, such as *N*-α-

Scheme 3. Representative Pyrazoles Prepared with the Reported SPS Strategy[a]



[a] Cumulated yields of isolated products based on the Merrifield resin loading (1.24 mmol g^{-1}).

methoxyalkylamides or 1,3-oxazinium salts. Furthermore, the possibility of washing off the excess of the very insoluble DDQ from the 1,3-oxazinium salts still linked to the resin saves a tremendously tedious purification of the final pyrazoles.

Finally, the whole process could be readily automated. All SPS steps can be carried out in robust reaction conditions, whereby a good control of the temperature is enough to drive the synthesis to success. The purification of the crude cleaved mixtures are straightforward, as well, since it can be achieved through evaporation of the collected mother liquors followed by filtration on a silica cartridge.

Experimental Section

Typical Procedure for the Preparation of Supported 4*H*-1,3-Oxazines. The resin-bound *N*-(α-methoxyalkyl)-amide (100 mg, 1 equiv) was allowed to swell in 1 mL of CH_2Cl_2 and cooled to 0 °C. The alkyne (5 equiv) was then added along with $BF_3.Et_2O$ (3 equiv). The slurry was shaken at 0 °C for 1 h, then allowed to warm to room temperature and to react for another 12 h. The resin was filtered and successively washed with CH_2Cl_2 (3 mL), CH_2Cl_2/Et_3N (3 mL), and then five times alternatively with CH_2Cl_2 and MeOH (3 mL).

Typical Procedure for the Functional Cleavage. To a suspension of a resin-bound 4*H*-1,3-oxazine (100 mg, 1 equiv) in acetonitrile (2 mL) was added DDQ (3 equiv). The slurry was warmed to 60 °C and allowed to react 12 h. The resin was filtered and successively washed several times with acetonitrile (3 mL); CH_2Cl_2 (3 mL); and ethyl acetate (3 mL); and finally, dried under vacuum. The activated resin was then allowed to swell in acetonitrile (1 mL). Nucleophile was added (20 equiv), and the suspension was allowed to react at 60 °C for 12 h. The resin was cooled, filtered, and washed five times alternatively with CH_2Cl_2 and MeOH (3 mL). The combined filtrates were evaporated to dryness to yield a yellow-brown solid. The resulting material was eluted through a cartridge of silica gel with ethyl acetate/hexane 1:1 to filter off the byproducts (DDQ residues).

3,5-Diphenyl-1*H*-pyrazole (1). According to the general synthesis described above, reaction of the resin bound *N*-(α-methoxyphenylmethyl)benzamide with phenylacetylene and cleavage upon nucleophilic attack of hydrazine afforded 6 mg (24% overall yield from Merrifield resin) of **1** as a white solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 6.87 (s, 1H, $H_{pyrazole}$), 7.35−7.44 (m, 6H, H_{Ar}), 7.75 (m, 4H, H_{Ar}). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 100.1 ($C_{4-pyrazole}$), 125.6, 128.2, 128.7, 131.3, 148.8 ($C_{3,5-pyrazole}$). SM (IC NH3) *m/z*: 221 $[M + H]^+$ (100%), 441 $[2M + H]^+$ (34%).

3-Phenyl-5-(4-trifluoromethylphenyl)-1*H*-pyrazole (2). According to the general synthesis described above, reaction of the resin-bound *N*-[α-methoxy-(4-trifluoromethylphenyl)-methyl]benzamide with phenylacetylene and cleavage upon nucleophilic attack of hydrazine afforded 5 mg (13% overall yield from Merrifield resin) of **2** as a white solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 6.92 (s, 1H, $H_{pyrazole}$), 7.39−7.49 (m, 3H, H_{Ar}), 7.69 (m, 4H, H_{Ar}), 7.92 (m, 2H, H_{Ar}). SM (IC NH_3) *m/z*: 289 $[M + H]^+$ (100%), 306 $[M + NH_4]^+$ (54%).

4-(5-Phenyl-2*H*-pyrazol-3-yl)benzonitrile (3). According to the general synthesis described above, reaction of the resin-bound *N*-[α-methoxy-(4-cyanophenyl)-methyl]benzamide with phenylacetylene and cleavage upon nucleophilic attack of hydrazine afforded 7 mg (19% overall yield from Merrifield resin) of **3** as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.92 (s, 1H, $H_{pyrazole}$), 7.41−7.56 (m, 4H, H_{Ar}), 7.73 (m, 3H, H_{Ar}), 8.12 (m, 3H, H_{Ar}). SM (IC NH_3) *m/z*: 246 $[M + H]^+$ (100%), 263 $[M + NH_4]^+$ (39%).

5-(3-Nitrophenyl)-3-phenyl-1*H*-pyrazole (4). According to the general synthesis described above, reaction of the resin-bound *N*-[α-methoxy-(3-nitrophenyl)-methyl]benzamide with phenylacetylene and cleavage upon nucleophilic attack of hydrazine afforded 9 mg (24% overall yield from Merrifield resin) of **4** as a beige solid. ^{1}H NMR ($CDCl_3$, MHz) δ (ppm): 6.99 (s, 1H, $H_{pyrazole}$), 7.72 (m, 2H, H_{Ar}), 7.57 (m, 3H, H_{Ar}), 7.61 (m, 2H, H_{Ar}), 8.22 (m, 1H, H_{Ar}), 8.65 (s, 1H, H_{Ar}). SM (IC NH_3) *m/z*: 266 $[M + H]^+$ (46%), 283 $[M + NH_4]^+$ (100%).

2-Methoxy-4-(5-phenyl-2*H*-pyrazol-3-yl)-phenol (5). According to the general synthesis described above, reaction of the resin-bound *N*-[α-methoxy-(4-hydroxy-3-methoxyphenyl)-methyl]benzamide with phenylacetylene and cleavage upon nucleophilic attack of hydrazine afforded 5 mg (14% overall yield from Merrifield resin) of **5** as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.96 (s, 3H, $H_{methoxy}$),

6.78 (s, 1H, $H_{pyrazole}$), 7.03 (m, 1H_{Ar}), 7.32−7.56 (m, 3H_{Ar}), 7.75 (m, 4H_{Ar}). SM (IC NH_3) *m/z*: 267 $[M + H]^+$ (100%).

3-(5-Phenyl-2*H*-pyrazol-3-yl)-pyridine (6). According to the general synthesis described above, reaction of the resin-bound *N*-[α-methoxypyridin-3-yl-methyl]benzamide with phenylacetylene and cleavage upon nucleophilic attack of hydrazine afforded 5 mg (15% overall yield from Merrifield resin) of **6** as a beige solid. ^{1}H NMR ($CDCl_3$, MHz) δ (ppm): 6.91 (s, 1H, $H_{pyrazole}$), 7.31−7.53 (m, 4H_{Ar}), 7.71 (m, 2H_{Ar}), 8.15 (m, 1H_{Ar}), 8.82 (m, 1H_{pyrim}), 9.06 (s, 1H, H_{pyrim}). SM (IC NH_3) *m/z*: 222 $[M + H]^+$ (100%).

4-Methyl-5-phenyl-3-*p*-tolyl-1*H*-pyrazole (7). According to the general synthesis described above, reaction of the resin-bound *N*-[α-methoxy-*p*-tolylmethyl]benzamide with 1-phenyl-1-propyne and cleavage upon nucleophilic attack of hydrazine afforded 8 mg (29% overall yield from Merrifield resin) of **7** as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.32 (s, 3H, $H_{Ph-methyl}$), 2.43 (s, 3H, $H_{pyrazol-methyl}$), 7.39−7.52 (m, 6H, H_{Ar}), 7,63 (m, 3H, H_{Ar}). SM (IC NH_3) *m/z*: 249 $[M + H]^+$ (100%).

3,5-Diphenyl-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester (8). According to the general synthesis described above, reaction of the resin-bound *N*-(α-methoxyphenylmethyl)-benzamide with ethylphenyl propiolate and cleavage upon nucleophilic attack of hydrazine afforded 4 mg (14% overall yield from Merrifield resin) of **8** as a beige solid. ^{1}H NMR ($CDCl_3$, MHz) δ (ppm): 1.01 (t, $^3J = 7.3$ Hz, 3H, $H_{esterCH_3}$), 3.96 (q, $^3J = 7.3$ Hz, 2H, $H_{esterCH_2}$), 7.35−7.44 (m, 6H, H_{Ar}), 7.75 (m, 4H, H_{Ar}). SM (IC NH_3) *m/z*: 310 $[M + NH_4]^+$ (100%).

5-*t*-Butyl-3-phenyl-1*H*-pyrazole (9). According to the general synthesis described above, reaction of the resin-bound *N*-(α-methoxyphenylmethyl)benzamide with *t*-butyl acethylene and cleavage upon nucleophilic attack of hydrazine afforded 4 mg (14% overall yield from Merrifield resin) of **9** as a white solid. ^{1}H NMR ($CDCl_3$, MHz) δ (ppm): 1.39 (s, 9H, 3 × 3H_{Me}), 6.40 (s, 1H, $H_{pyrazole}$), 7.32−7.45(m, 3H, $H_8 + H_9$), 7.74 (m, 2H, H_7). SM (IC NH_3) *m/z*: 201 $[M + H]^+$ (100%).

5-*i*-Butyl-3-phenyl-1*H*-pyrazole (10). According to the general synthesis described above, reaction of the resin-bound *N*-(α-methoxyphenylmethyl)benzamide with *i*-butyl acethylene and cleavage upon nucleophilic attack of hydrazine afforded 4 mg (18% overall yield from Merrifield resin) of **10** as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.99 (d, $^3J = 6.8$ Hz, 6H, 3 × 3H_{Me}), 1.97 (m, 1H, H_{ButCH}), 2.57 (d, $^3J = 6.8$ Hz, 2H, H_{ButCH_2}), 6.38 (s, 1H, $H_{pyrazol}$), 7.32−7.44 (m, 3H, H_{Ar}), 7.75 (m, 2H, H_{Ar}). SM (IC NH_3) *m/z*: 201 $[M + H]^+$ (100%).

3-Phenyl-4,5,6,7-tetrahydro-1*H*-indazole (11). According to the general synthesis described above, reaction of the resin-bound *N*-(α-methoxyphenylmethyl)benzamide with 1-bromocyclohexene and cleavage upon nucleophilic attack of hydrazine afforded 4 mg (18% overall yield from Merrifield resin) of **11** as a white solid. ^{1}H NMR ($CDCl_3$, MHz) δ (ppm): 1.75 (m, 4H, $H_{CH_2\ indazole}$), 2.75 (m, 4H, $H_{CH2\ indazole}$), 7.38−7.57 (m, 5H, H_{Ar}). SM (IC NH_3) *m/z*: 199 $[N + H]^+$ (100%).

1-Methyl-5-phenyl-3-*p*-tolyl-1*H*-pyrazole (12). According to the general synthesis described above, reaction of the resin-bound *N*-[α-methoxy-*p*-tolylmethyl]benzamide with phenylacethylene and cleavage upon nucleophilic attack of *N*-methylhydrazine afforded 6 mg (22% overall yield from Merrifield resin) of **12** as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.39 (s, 3H, H_{ArMe}), 3.94 (s, 3H, H_{N-Me}), 6.59 (s, 1H, $H_{pyrazole}$), 7.22 (d, $^3J = 7.9$ Hz, 2H, H_{P-tol}), 7.47 (m, 4H, H_{Ar}), 7.77 (m, 3H, H_{Ar}). RMN ^{13}C ($CDCl_3$, 75 MHz) δ (ppm): 21.4 (C_{ArMe}), 35.8 (C_{N-Me}), 102.1 ($C_{4\ pyrazole}$), 125.8, 128.3, 128.6, 131.3, 132.5. SM (IC NH_3) *m/z*: 249 $[M + H]^+$ (100%).

1,5-Diphenyl-3-*p*-tolyl-1*H*-pyrazole (13). According to the general synthesis described above, reaction of the resin-bound *N*-[α-methoxy-*p*-tolylmethyl]benzamide with phenylacethylene and cleavage upon nucleophilic attack of *N*-phenylhydrazine afforded 8 mg (25% overall yield from Merrifield resin) of **13** as a white solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 2.40 (s, 3H, H_{ArMe}), 6.82 (s, 1H, $H_{pyrazole}$), 7.24−7.44 (m, 12H, H_{Ar}), 7.83 (d, $^3J = 8.1$ Hz, 2H, H_9). SM (IC NH_3) *m/z*: 311 $[M + H]^+$ (100%).

Acknowledgment. We would like to thank Aventis for fiancial support.

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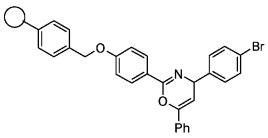
(10) This resin was prepared from the commercially available Merrifield resin (1.2 mmol g^{-1}, 200−400 mesh) in three steps: (a) 4-hydroxybenzamide (5 equiv), NaH (5 equiv), DMF, rt, 14 h; (b) 4-bromobenzaldehyde (5 equiv), trimethyl orthoformiate (10 equiv), TFA (1 equiv), rt, 12 h (see ref 8 for a detailed procedure); (c) phenylacetylene (5 equiv), $BF_3 \cdot Et_2O$ (3 equiv), 0 °C 1 h, then rt 12 h.



Maximal theoretic loading: 0,4 mmol/g

IR (ν cm^{-1}) : 3023 (Ar) ; 3060 (Ar) ; 3026 (Ar) ; 2923 (CH_2 bisbenzylic) ; 2850 (CH_2 bisbenzylic) ; 1681 (C=N) ; 1605 (Ar-C) ; 1510 ; 1493 ; 1452 ; 1373 (C-N) ; 1250; 1173 (symetrically para-disubstitued aromatic) ; 1029 (out of plane vibrations of C-C or C-H of benzenic rings) ; 842 ; 760 ; 699.

Elemental analysis :

Élement	% calculated	% found
N	1,00	0,78
O	2,26	1,81
Br	2,78	2,19
Cl	0	0,05

CC030109D