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A Versatile and Regiospecific Synthesis of Functionalized 1,3-Diarylisobenzofurans

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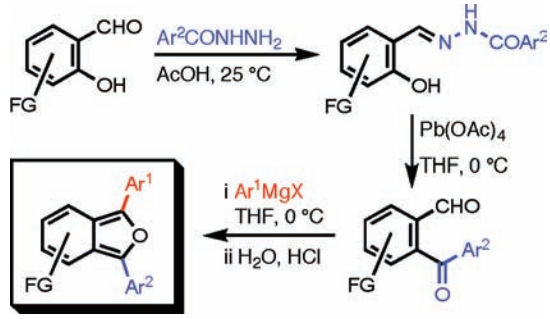
ABSTRACT



A convenient, versatile, and regiospecific synthesis of functionalized 1,3-diarylisobenzofurans has been developed. It involves chemoselective addition of arylmagnesium reagents to the aldehyde function of *o*-aroylbenzaldehydes, themselves readily obtained by lead tetraacetate oxidation of *N*-aroylhydrazones of salicylaldehydes. Various functional groups, including nitro, iodo, or ester functionalities, have thus been positioned with complete regiospecificity on the 1,3-diphenylisobenzofuran backbone.

Benzo[*c*]furans or isobenzofurans constitute a valuable class of heterocyclic compounds, possessing structural features and reactivity profiles closely related to *o*-quinodimethanes.[1] They are highly reactive dienes, and their Diels−Alder reaction with dienophiles for the synthesis of natural and non-natural products is well documented.[2] During our ongoing research on new analogues of *N*-hydroxyphthalimide (NHPI),[3] we have been searching for convenient access to functionally diverse 1,3-diarylisobenzofurans. Whereas various synthetic pathways to 1,3-diarylisobenzofurans are known,[1,4] none of them were totally satisfactory for our purpose.

One of the most convenient and general syntheses of 1,3-diarylisobenzofurans is the reaction of an arylmagnesium reagent with 3-arylphthalides.[5] Isobenzofurans are formed via 1,4 water elimination from an intermediate lactol[6] under acidic conditions (Scheme 1, path A).

Among numerous methods, 3-arylphthalides can be prepared by reacting two equivalents of an arylmagnesium

(1) For reviews on isobenzofuran chemistry, see: (a) Friedrichsen, W. *Adv. Heterocycl. Chem.* **1980**, *26*, 135. (b) Friedrichsen, W. *Adv. Heterocycl. Chem.* **1999**, *73*, 1. (c) Steel, P. G. *Sci. Synth.* **2001**, *10*, 87.

(2) (a) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093. (b) Peters, O.; Friedrichsen, W. *Trends Heterocycl. Chem.* **1995**, *4*, 217.

(3) (a) Einhorn, C.; Einhorn, J.; Marcadal-Abbadi, C.; Pierre, J.-L. *J. Org. Chem.* **1999**, *64*, 4542. (b) Nechab, M.; Einhorn, C.; Einhorn, J. *Chem. Commun.* **2004**, 1500. (c) Nechab, M.; Kumar, D. N.; Philouze, C.; Einhorn, C.; Einhorn, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3080.

(4) For recent methods, see for example: (a) Kuninobu, Y.; Nishina, Y.; Nakagawa, C.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 12376. (b) Benderradji, F.; Nechab, M.; Einhorn, C.; Einhorn, J. *Synlett* **2006**, 2035.

(5) (a) Guyot, A.; Catel, J. *Bull. Soc. Chim. Fr. (3)* **1906**, *35*, 1124. (b) Newman, M. S. *J. Org. Chem.* **1961**, *26*, 2630. (c) Cava, M. P.; Van Meter, J. P. *J. Am. Chem. Soc.* **1962**, *84*, 2008. (d) Cava, M. P.; Van Meter, J. P. *J. Org. Chem.* **1969**, *34*, 538. (e) Dodge, J. A.; Bain, J. D.; Chamberlin, A. R. *J. Org. Chem.* **1990**, *55*, 3214.

(6) (a) Baker, W.; Mc Omie, J. F. W.; Pope, G. A.; Preston, D. R. *J. Chem. Soc.* **1961**, 2965. (b) Courtot, P.; Sachs, D. H. *Bull. Soc. Chim. Fr.* **1965**, 2259.

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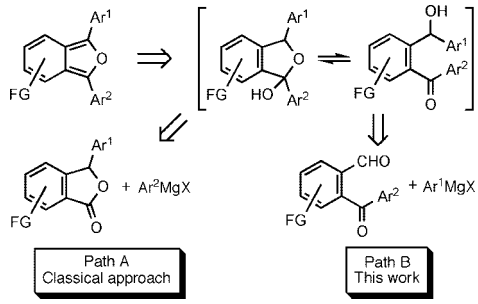
Scheme 1. Synthetic Strategies to 1,3-Diarylisobenzofurans



reagent with an *o*-carboxybenzaldehyde.[7] Thus, two different aryl groups can be placed at the 1 and 3 positions of the isobenzofuran core. While using this methodology, however, we faced several of its limitations: functionalized 3-arylphthalides are not commercially available and have to be prepared via multisteps and nongeneral syntheses. The reactivity of 3-arylphthalides toward arylmagnesium reagents strongly depends on the nucleophilicity of these. Thus, weakly nucleophilic Grignard reagents such as pentafluorophenylmagnesium bromide or Knochel's *o*-nitrophenylmagnesium iodide[8] did not react at all with 3-phenylphthalide. Finally, the weak electrophilicity of the lactone function leads to unselective reactions with Grignard reagents if the 3-phenylphthalide backbone is substituted with other electrophilic functions, such as nitro groups.

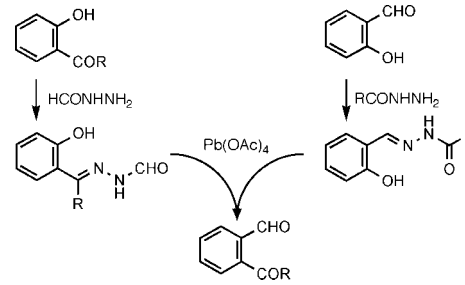
Our reasoning was that a lactol should similarly be formed by Grignard addition to the aldehyde function of an *o*-aroylbenzaldehyde (Scheme 1, path B). This alternative approach could possibly overcome some of the prior limitations, as the electrophilic character of an aldehyde is much more pronounced than that of a lactone. In this context, however, the availability of *o*-aroylbenzaldehydes becomes a deciding issue. In fact, *o*-ketobenzaldehydes remain a seldom used class of compounds, and older methods for their synthesis are rather tedious. Fortunately, Kotali discovered a very interesting synthesis of *o*-diacylbenzenes, by lead tetraacetate (LTA) oxidation of *N*-acylhydrazones of *o*-hydroxyacylbenzenes.[9] The mechanism of this original carbon−carbon bond forming reaction, where the acyl group

(7) Canonne, P.; Plamondon, J.; Akssira, M. *Tetrahedron* **1988**, *44*, 2903.

(8) (a) Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 1610. For reviews on functionalized organomagnesium reagents, see: (b) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountsis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302. (c) Knochel, P. In *Handbook of Functionalized Organometallics*; Wiley-VCH: New York, 2005. (d) Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583.

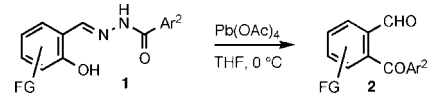
(9) (a) Kotali, A.; Tsoungas, P. G. *Tetrahedron Lett.* **1987**, *28*, 4321. (b) Kotali, A.; Glaveri, U.; Pavlidou, E.; Tsoungas, P. G. *Synthesis* **1990**, 1172. (c) Katritzky, A. R.; Kotali, A. *Tetrahedron Lett.* **1990**, *31*, 6790. (d) Katritzky, A. R.; Harris, P. A.; Kotali, A. J. *J. Org. Chem.* **1991**, *56*, 5049. (e) Kotali, A. *Tetrahedron Lett.* **1994**, *35*, 6753. (f) Kotali, A.; Papapetrou, M.; Dimos, V. *Org. Prep. Proced. Int.* **1998**, *30*, 159. (g) Kotali, A.; Lafazanis, I. S.; Harris, P. A. *Tetrahedron Lett.* **2007**, *48*, 7181. For similar reactions using phenyliodosodiacetate, see: (h) Moriarty, R. M.; Berglund, B. A.; Rao, M. S. C. *Synthesis* **1992**, 318. (i) Kotali, A.; Koulidis, A.; Wang, H.-M.; Chen, L.-C. *Org. Prep. Proced. Int.* **1996**, *28*, 622. For reviews, see:(j) Kotali, A. *Cur. Org. Chem.* **2002**, *6*, 965. (k) Kotali, A.; Harris, P. A. *Org. Prep. Proced. Int.* **2003**, *35*, 583.

Scheme 2. Kotali's Approaches to *o*-Acylbenzaldehydes



of the hydrazone formally replaces the phenolic hydroxyl group, has been elucidated by Kotali and Katritzky.[9d] The reaction has been extended to the synthesis of tris- and

Table 1. Lead(IV) Acetate Oxidation of *N*-Aroylhydrazones of Salicylaldehydes



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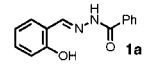
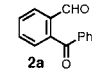
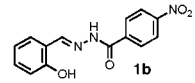
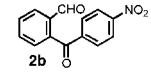
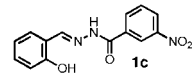
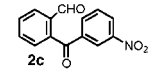
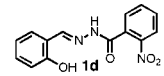
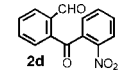
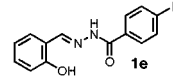
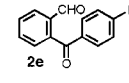
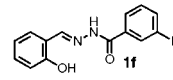
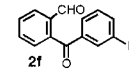
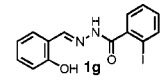
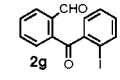
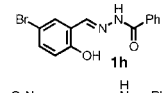
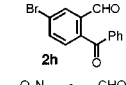
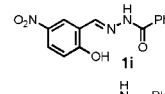
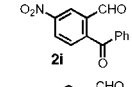
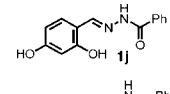
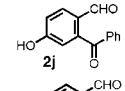
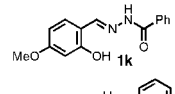
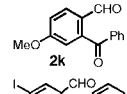
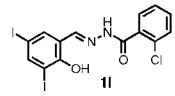
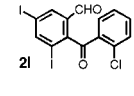
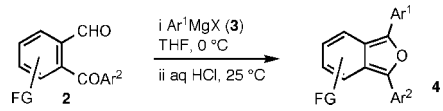
1	 1a	 2a	89
2	 1b	 2b	64
3	 1c	 2c	62
4	 1d	 2d	51
5	 1e	 2e	75
6	 1f	 2f	68
7	 1g	 2g	82
8	 1h	 2h	70
9	 1i	 2i	82
10	 1j	 2j	3
11	 1k	 2k	46
12	 1l	 2l	78

[a] Isolated yields.

Table 2. Synthesis of Functional 1,3-Diarylisobenzofurans



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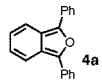
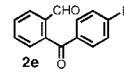
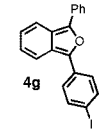
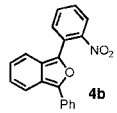
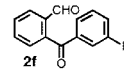
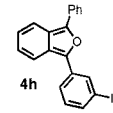
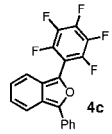
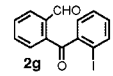
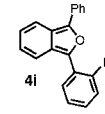
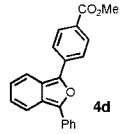
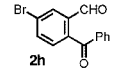
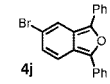
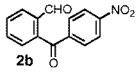
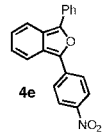
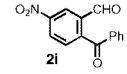
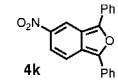
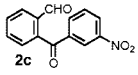
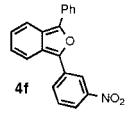
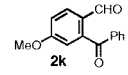
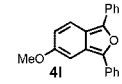
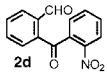
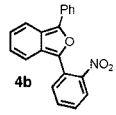
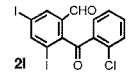
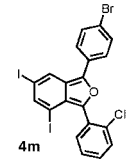
1	 2a	**3a**	 4a	88 (89)	8	 2e	**3a**[d]	 4g	80 (90)
2	 2a	**3b**[b]	 4b	75 (81)	9	 2f	**3a**[d]	 4h	74 (80)
3	 2a	**3c**	 4c	77 (81)	10	 2g	**3a**[d]	 4i	91 (92)
4	 2a	**3d**[c]	 4d	39 (87)	11	 2h	**3a**	 4j	80 (93)
5	 2b	**3a**	 4e	78 (98)	12	 2i	**3a**	 4k	56 (62)
6	 2c	**3a**	 4f	84 (87)	13	 2k	**3a**	 4l	86 (87)
7	 2d	**3a**[d]	 4b	87 (90)	14	 2l	**3e**	 4m	79 (81)

[a] Isolated yields; yields determined by ^{1}H NMR of the crude reaction product are shown in parentheses. [b] Reaction performed by adding a THF solution of **2a** to a THF solution of **3b** at −40 °C. [c] Reaction performed by adding a THF solution of **2a** to a THF solution of **3d** at −20 °C. [d] Reaction performed at −78 °C.

tetraacylbenzenes,[9b,e] of *o*-acylbenzoic acid esters,[9c,i] and of *o*-acylbenzaldehydes.[9f] Kotali prepared *o*-acylbenzaldehydes by LTA oxidation of either *N*-formylhydrazones of *o*-hydroxyacylbenzenes or *N*-acylhydrazones of salicylaldehydes (Scheme 2).

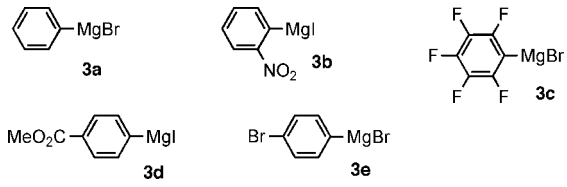
For our purpose, the second approach was by far more convenient and versatile, as numerous functional *N*-aroylhydrazides as well as functional salicylaldehydes are commercially available. We chose this approach to synthesize a series of functionally diverse *o*-aroylbenzaldehydes (Table 1). The synthesis of starting hydrazones **1a**−**1l** was straightforward.[10] LTA oxidation of *N*-acylhydrazones of salicylaldehydes has so far been limited to a few cases of unfunctionalized compounds such as **2a**. We found that the yield of **2a** can be slightly improved by performing the LTA oxidation of **1a** at 0 °C instead of 25 °C (89% versus 77% yield). The reaction could also be scaled up from 5 to 100 mmol (entry 1, Table 1).

The Kotali reaction appeared to have broad functional group tolerance. Hydrazones, functionalized at the hydrazide aromatic moiety by nitro or iodo groups at any of the para, meta, or ortho positions (**1b**−**1g**), all furnished the corresponding *o*-ketoaldehydes **2b**−**2g** in good isolated yields (entries 2−7, Table 1). The Kotali reaction was also compatible with bromo

(10) Nearly quantitative yields of hydrazones were obtained within minutes by simple mixing of a salicylaldehyde with a stoichiometric amount of *N*-aroylhydrazide, in acetic acid at room temperature. Alternatively, we found that *N*-acylhydrazones of salicylaldehyde can also be prepared conveniently in high yields by reacting 1 equiv of an acid chloride with commercially available salicylaldehyde hydrazone in the presence of Hünig's base.

or nitro groups on the salicylaldehyde moiety: thus **1h** and **1i** gave the corresponding *o*-ketoaldehydes **2h** and **2i** in 70 and 82% yields (entries 8 and 9, Table 1). A supplementary free phenol function was unfavorable, as **1j** gave *o*-ketoaldehyde **2j** in only 3% yield (entry 10, Table 1). Replacing the free phenol by a methoxy group restored more usual behavior, **1k** giving **2k** in 46% yield (entry 11, Table 1). Functional groups could also be present at both aromatic moieties: LTA oxidation of **1l** gave **2l** in 78% yield (entry 12, Table 1).

With a series of diversly functionalized *o*-ketoaldehydes in hand, we next studied their reaction with aromatic Grignard reagents (Table 2). In a first experiment, one equivalent of phenylmagnesium bromide **3a** was added to a THF solution of **2a**, at −78 °C. After acidic hydrolysis, 1,3-diphenylisobenzofuran **4a** was the unique reaction product, as indicated by TLC and NMR analysis of the crude and comparison with a commercial sample of **4a**. This result clearly indicates a chemoselective addition of Grignard reagent **3a** to the sole aldehyde function of **2a**. Grignard addition was still selective at 0 °C, as **4a** was isolated in 88% yield from the corresponding experiment (entry 1, Table 2). We next examined the reaction of **2a** with functionalized Grignard reagents[8] such as **3b**, **3c**, and **3d**. Gratifyingly the corresponding, previously unknown isobenzofurans **4b**−**4d** were all obtained in good yields (entries 2−4, Table 2).[11]



Another interesting issue was the reaction of aromatic Grignard reagents with functional *o*-ketoaldehydes. Synthetically valuable nitro-[12] and iodoisobenzofurans **4b** and **4e**−**4i** were thus readily prepared in good yields, reacting the corresponding *o*-ketoaldehydes **2b**−**2g** with Grignard reagent **3a** (entries 5−10, Table 2). Functional groups are also tolerated on the aldehyde-bearing aromatic ring. Thus, bromo-, nitro-, and methoxyisobenzofurans **4j**, **4k**, and **4l** have been prepared from **2h**, **2i**, and **2k** (entries 11−13, Table 2). These results are worthy of note, as few 1,3-diarylisobenzofurans functionalized at the central carbocycle have been synthesized so far, using lengthy and nongeneral syntheses.[13] Finally, 1,3-diphenylisobenzofurans, simultaneously and regiospecifically functionalized at all three carbocycles with various functional groups, can also be prepared without difficulty. Thus, **4m** has been obtained in 79% yield reacting *o*-ketoaldehyde **2k** with Grignard reagent **3e** (entry 14, Table 2).

In summary, we have developed convenient and general access to functional 1,3-diarylisobenzofurans, involving chemoselective addition of arylmagnesium reagents to *o*-aroylbenzaldehydes, themselves readily obtained by LTA oxidation of salicylaldehydes *N*-aroylhydrazones. This new method is highly functional group tolerant. It is also totally regiospecific, as the position of each functional group on the 1,3-diphenylisobenzofuran backbone is directly related to their original position on the *N*-aroylhydrazide-, salicylaldehyde-, or Grignard reagent aromatic rings.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Isobenzofurans have been obtained in good purities after standard workup. Isolated yields have been determined after purification by column chromatography. Yields have also been determined by ^{1}H NMR of the crude, as purification resulted, in some cases, in significant loss of product due to air oxidation.

(12) A mixture of **4e** and **4f** has been obtained by direct nitration of **4a** in sulfuric acid. See: Amat-Gerri, F.; Lempe, E.; Lissi, E. A.; Rodriguez, F. J.; Trull, F. R. *J. Photochem. Photobiol. A* **1996**, *93*, 49.

(13) See, for example: (a) Villessot, D.; Lepage, Y. *Tetrahedron Lett.* **1977**, *17*, 1495. (b) Lepage, L.; Lepage, Y. *J. Heterocycl. Chem.* **1978**, *15*, 793. (c) Schmitz, C.; Aubry, J. M.; Rigaudy, J. *Tetrahedron* **1982**, *38*, 1425. (d) Lepage, L.; Lepage, Y. *Synthesis* **1983**, 1018. (e) Christopfel, W. C.; Miller, L. L. *Tetrahedron* **1987**, *43*, 3681. (f) Passerieux, D.; Casteignau, M.; Lepage, L.; Lepage, Y. *Bull. Soc. Chim. Fr.* **1989**, 441.