Tetrahedron Letters 57 (2016) 3368–3370

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Benzene-1,3,5-triyl triformate (TFBen): a convenient, efficient, and non-reacting CO source in carbonylation reactions

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ARTICLE INFO

Article history:
Received 25 May 2016
Revised 14 June 2016
Accepted 16 June 2016
Available online 17 June 2016

Keywords:
Palladium catalyst
Carbonylation
Aryl formates
Benzene-1,3,5-triol
CO surrogate

ABSTRACT

Benzene-1,3,5-triyl triformate (TFBen) as a kind of convenient and efficient CO source has been prepared for the first time. The character of TFBen as potent and non-reacting CO source has been proven by the successful synthetic applications in carbonylation reactions. Phloroglucinol (1,3,5-trihydroxybenzene) is abundant and naturally occurring has been applied as the reusable material for TFBen synthesis.

Recently, the development of new carbon monoxide-free carbonylative procedures becomes an interesting research topic in carbonylation chemistry.[1] Strategically, the methodology establishment can be cataloged in two directions based on where the CO generated: ex situ and in situ. The ex situ CO generation procedures usually refer to the two-chamber system. That is one chamber for CO generation which is connected to the other chamber for carbonylation transformations.[2] The in situ CO generation systems are based on the producing of CO from CO surrogates in the same reaction tube. In this manner, the manipulation of CO gas with autoclave can be avoided. For the CO surrogates, many metal carbonyl complexes and organic compounds have been developed as suitable CO sources which including $Mo(CO)_6$,[3] formamides,[4] $(CH_2O)_n$,[5] formic acid,[6] aryl formates,[7] etc.[8] However, each candidates has their own advantages and disadvantages. Concerning the shortcomings, a large amount metal waste generation or specific activator requirement is the most obvious character. Taking consideration of atom efficiency and sustainable chemistry, and considered the importance of carbonylation chemistry, more efforts are required for its further development and also deserved.

On the other hand, phenyl formate has been proven to be an interesting and practical CO surrogate.[7,9] Phenyl formate is ready to decompose to CO and phenol by heating or in the presence of a small amount of base. However, due to the good nucleophilicity of phenol, depending on the other nucleophiles applied, phenol might react with acylpalladium intermediate to give phenyl benzoates or related derivatives (Scheme 1).[7] Hence carbonylative procedure with phenyl formate as CO source should be well designed.

Phloroglucinol (1,3,5-trihydroxybenzene) is a non-expensive and abundant chemical[10] which was originally found in fruit trees. Because of the unique symmetric arene substitution pattern of phloroglucinol, it is in equilibrium with its keto form (1,3,5-cyclohexanetrione; phloroglucin) in solution which has ketone-like character (Scheme 2). This distinctive property attracted our interest. The three hydroxyl groups allow the formation of the triformate compound which is more efficient as the CO source. After CO release, the ketone form of the phloroglucinol formed makes it less or not reactive with metal catalyst intermediates. Additionally, formic acid as the reaction partner here can be produced by reduction of CO_2 which is even more abundant. For these reasons, the newly produced benzene-1,3,5-triyl triformate (TFBen) can be used as a solid, stable, efficient, cheap, convenient, and efficient but non-reacting CO surrogate for CO chemistry.

In order to verify our hypotheses, we started with the synthesis of benzene-1,3,5-triyl triformate (TFBen).[11] At room temperature, 82% isolated yield of TFBen can be achieved by reacting phloroglucinol with formic acid in the presence of palladium catalyst.[6i] As a white solid, it's stable at room temperature under air (Scheme 3).

After the successful preparation of TFBen, the synthetic applications and non-reacting proven becomes the main target (Scheme 4).[12] We chose bromobenzene and phenylboronic acid

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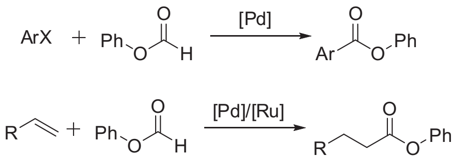
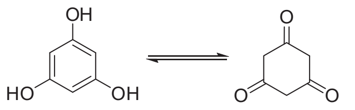
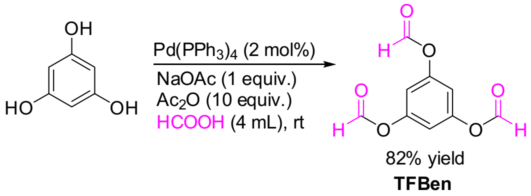
http://dx.doi.org/10.1016/j.tetlet.2016.06.071



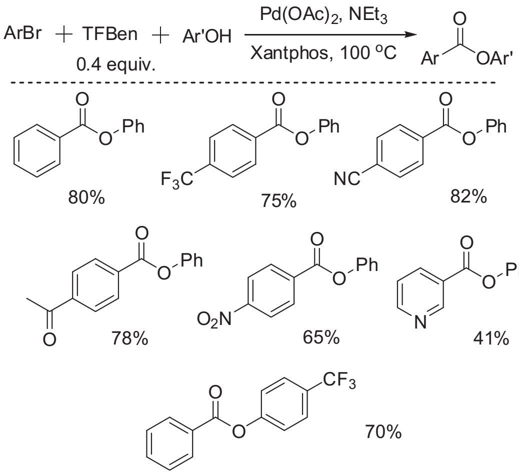
Scheme 1. Carbonylations based on phenyl formate.



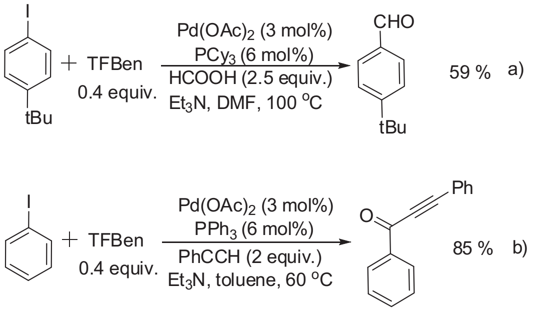
Scheme 2. Equilibrium between phloroglucinol and phloroglucin.



Scheme 3. Synthesis of TFBen.



Scheme 5. Pd-catalyzed alkoxycarbonylation with TFBen as the CO source.



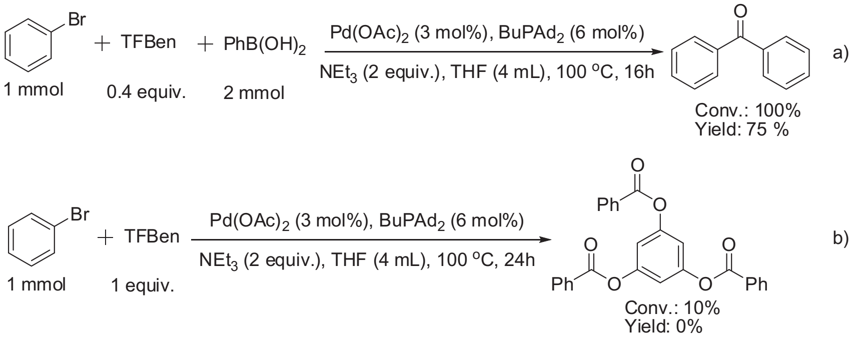
Scheme 6. Pd-catalyzed reductive carbonylation and Sonogashira carbonylation with TFBen as the CO source.

as the starting materials, with the combination of $Pd(OAc)_2$ and $BuPAd_2$ as the catalyst system and only using 0.4 equiv of TFBen as the CO source, 75% of benzophenone was isolated (Scheme 4, Eq. a). The non-reacting nature of phloroglucinol obtained from TFBen by loss of CO was demonstrated carrying out the reaction in the absence of $PhB(OH)_2$ (Scheme 4, Eq. b). Even with 1 equivalent of TFBen, none of possible benzoates derived from alkoxycarbonylation of PhBr with phloroglucinol were formed. Only traces of benzoic acid (resulting from the reaction of trace amount of water with acylpalladium intermediate) were detected. Remarkably, as the starting material 1,3,5-trihydroxybenzene can be recycled in the purification process and reused.

With this promising information in hand, and continually strength the efficient but non-reacting characters, alkoxycarbonylation transformations were performed. In the presence of palladium catalyst and 0.4 equiv of TFBen, good yields of esters can be produced from aryl bromides and phenols (Scheme 5).[13] These results strongly supported our hypotheses and confirmed the non-reacting character. Electron-withdrawing substituted aryl halides usually challenge substrates in palladium-catalyzed carbonylative coupling transformations, as they trend more towards dehalogenation. However, in our system, good yields can be achieved without further optimization. Remarkably, nitro group can be well tolerated as well which is not possible in CO gas based carbonylation chemistry. Notably, in all the experiments performed here, the 1,3,5-trihydroxybenzene can be easily recovered during the product purification process.

The applications of this new CO source in other carbonylation reactions have been explored as well. With formic acid as the reductant, 59% of 4-(*tert*-butyl)benzaldehyde can be produced from the corresponding iodide (Scheme 6, Eq. a).[14] Efficient carbonylative Sonogashira coupling for alkynone synthesis can be realized as well. Excellent yield was achieved under mild conditions (Scheme 6, Eq. b).[15]

In conclusion, benzene-1,3,5-triyl triformate (TFBen) as a kind of convenient and efficient CO source has been prepared for the



Scheme 4. Carbonylative Suzuki coupling and non-reacting proven.

first time. The character of TFBen as a potent and non-reacting CO source has been proven by the numerous synthetic applications in carbonylation reactions. Phloroglucinol (1,3,5-trihydroxybenzene), the starting material for TFBen synthesis, is an abundant and naturally occurring substance which is recovered during the product purification process.

Acknowledgments

The authors thank the financial supports from NSFC (21472174) and Zhejiang Natural Science Fund for Distinguished Young Scholars (LR16B020002). X.-F. Wu appreciates the general support from Professor Matthias Beller in LIKAT.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.06.071.

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10. 500 g, 170$, TCI America (04.21.2016).
11. TFBen synthesis: $Pd(PPh_3)_4$ (2 mol %), benzene-1,3,5-triol (1.0 mmol), and NaOAc (1.0 equiv) were transferred into an oven-dried pressure tube which was filled with nitrogen and equipped with a string bar. Then Ac_2O (10 equiv) and HCOOH (4.0 mL) were added into the reaction tube. The mixture was stirred at RT for 12 h. After the reaction was complete, the reaction mixture was filtered and concentrated, then column chromatography on silica gel (petroleum ether/ethyl acetate 3:1) to give the pure product in 82% yield as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 3H), 6.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.27, 150.22, 112.60. GC–MS (EI, 70 ev): $m/z(\%) = 210.0$ ([M]+, 13), 210.0 (23), 182.0 (15), 154.0 (12), 126.1 (100), 110.0 (10), 97.0 (11), 85.0 (19), 80.0 (12), 69.0 (27), 52.1 (11).
12. Suzuki carbonylation: $Pd(OAc)_2$ (3 mol %), $BuPAd_2$ (6 mol %), phenylboronic acid (2 mmol) and TFBen (0.4 equiv) were transferred into an oven-dried pressure tube which was filled with nitrogen and equipped with a string bar. Then bromobenzene (1 mmol), NEt_3 (2 mmol) and THF (4.0 mL) were added into the reaction tube. The mixture was stirred at 100 °C for 16 h. After the reaction was complete, the reaction mixture was filtered and concentrated, then column chromatography on silica gel (petroleum ether/ethyl acetate) to give the pure product.
13. Alkoxycarbonylation: $Pd(OAc)_2$ (3 mol %), Xantphos (4 mol %), phenol (2 mmol) and TFBen (0.4 equiv) were transferred into an oven-dried pressure tube which was filled with nitrogen and equipped with a string bar. Then bromobenzene (1 mmol), NEt_3 (2 mmol), and DMF (4.0 mL) were added into the reaction tube. The mixture was stirred at 100 °C for 12 h. After the reaction was complete, the reaction mixture was filtered and concentrated, then column chromatography on silica gel (petroleum ether/ethyl acetate) to give the pure product.
14. Reductive carbonylation: $Pd(OAc)_2$ (3 mol %), PCy_3 (6 mol %), and TFBen (0.4 equiv) were transferred into an oven-dried pressure tube which was filled with nitrogen and equipped with a string bar. Then iodo compound (1 mmol), HCO_2H (2.5 equiv), NEt_3 (2 mmol), and DMF (2.0 mL) were added into the reaction tube. The mixture was stirred at 100 °C for 16 h. After the reaction was complete, the reaction mixture was filtered and concentrated, then column chromatography on silica gel (petroleum ether/ethyl acetate) to give the pure product.
15. Sonogashira carbonylation: $Pd(OAc)_2$ (3 mol %), PPh_3 (6 mol %), and TFBen (0.4 equiv) were transferred into an oven-dried pressure tube which was filled with nitrogen and equipped with a string bar. Then iodobenzene (1 mmol), phenylacetylene (2 mmol), NEt_3 (2 mmol), and toluene (2.0 mL) were added into the reaction tube. The mixture was stirred at 60 °C for 16 h. After the reaction was complete, the reaction mixture was filtered and concentrated, then column chromatography on silica gel (petroleum ether/ethyl acetate) to give the pure product.