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4-Isocyanopermethylbutane-1,1,3-triol (IPB): a convertible isonitrile for multicomponent reactions

Ricardo A. W. Neves Filho [a], Sebastian Stark [a], Micjel C. Morejon [a], Bernhard Westermann [a,b], Ludger A. Wessjohann [a,b,*]

[a] Department of Bioorganic Chemistry, Leibniz Institute of Plant Biochemistry, Weinberg 3, 06120 Halle (Saale), Germany
[b] Martin-Luther-University Halle-Wittenberg, Institute of Chemistry, Kurt-Mothes-Str. 2, 06120 Halle (Saale), Germany

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ABSTRACT

The synthesis and applications of 4-isocyanopermethylbutane-1,1,3-triol (IPB) as a new convertible isonitrile (isocyanide) for isocyanide-based multicomponent reactions (IMCRs) like Ugi, Ugi-Smiles, and Passerini reactions are described. The primary products obtained from these IMCRs can be converted into highly activated *N*-acylpyrroles, which upon treatment with nucleophiles can be transformed into carboxylic acids, esters, amides, alcohols, and olefins. In this sense the reagent can be seen as a neutral carbanion equivalent to formate (HO_2C^-), and carboxylates or carboxamides etc. ($RNu\text{-}CO^-$).

Isonitrile-based multicomponent reactions (IMCRs) have gained much attention due to their ability to generate high structural complexity in a single step.[1] Among the IMCRs, the Ugi four-component reaction (U-4CR) is by far the most explored one.[2] The combination of this reaction with other protocols (Ugi post-modifications) has been extensively applied in the synthesis of heterocycles, macrocycles, and other compounds of medicinal interest.[3] One of the drawbacks that limit the post-modification of highly functionalized Ugi products is the poor reactivity of the terminal secondary amide, which bears the substituent of the isonitrile component. In order to overcome this problem, a family of reagents named 'convertible isonitriles' has been developed.[4] These compounds are able to generate activated amides directly or upon triggering, allowing their more or less smooth conversion with nucleophiles. The implementation of these reagents improved the scope of applications of the U-4CR, expanding considerably its usefulness, for example for the synthesis of natural products and its analogs.[5] A widely applicable convertible isonitrile must feature requirements such as: (a) easy preparation from readily available starting materials, (b) long-term handling and storage stability, (c) good reactivity in IMCRs, (d) convertibility/activation under mild conditions, ideally orthogonal to other functional groups present in the MCR product, and (e) reactivity toward functional group conversions (FGC) under mild reaction conditions. Most current convertible isonitriles fulfill several of these requirements, but none can fulfill all of them. Therefore there is an ongoing need for readily accessible and easily convertible isonitrile reagents.

2,4,4-Trimethoxy-butylamine, recently developed by Fukuyama et. al.,[6] can be used as a precursor for cleavable amides **1** (Scheme 1). These intermediates appear to also combine all the requisites for the concept of convertible isonitriles discussed above. The amides **1** can be easily converted into *N*-acylpyrroles under mild conditions. These compounds provide a large range of transformation possibilities and can be converted into other functionalities. Despite their high reactivity toward nucleophiles, they exhibit a pronounced stability during isolation and storage.[7] Herein we report the synthesis and application of the 4-isocyanoperm-ethyl-butane-1,1,3-triol (**2**, abbreviated **IPB**) as a new convertible isonitrile for IMCRs.

IPB **2** was prepared in 15 g amounts from 2,4,4-trimethoxy-butylamine in a two-step procedure and 95% overall yield, available from bulky tetramethoxypropane.[8] The reagent is stable and it can be stored at −18 °C for weeks without decomposition. However, IPB **2** turned out to be very reactive in U-4CRs, including such with functionalized building blocks (Table 1). All products have a

* Corresponding author. Tel.: +49 (345) 5582 1301; fax: +49 (345) 5582 1309.
E-mail address: wessjohann@ipb-halle.de (L.A. Wessjohann).

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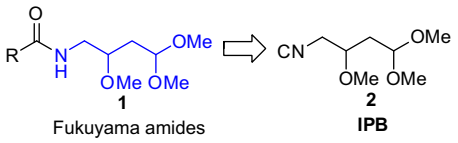
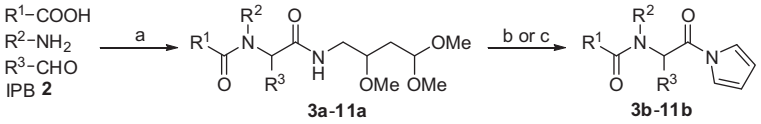


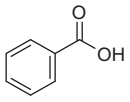
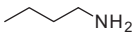
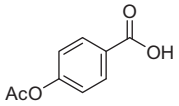
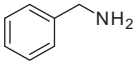
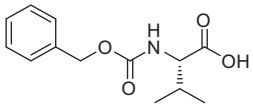
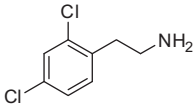
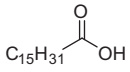
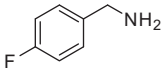
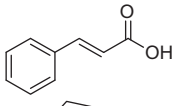
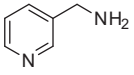
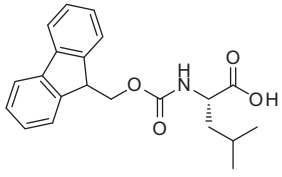
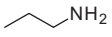
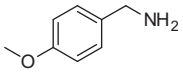
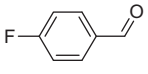
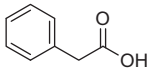
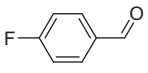
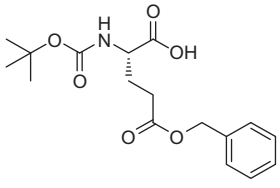
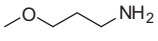
Scheme 1. IPB **2** as a precursor of Fukuyama amides **1**.

good solubility in standard organic solvents used. The U-4CRs as well as the conversion into the *N*-acylpyrroles work excellently for most of the tested substrates.[9,10] The two-step procedure tolerates the presence of many protective groups like Fmoc, Cbz, Boc, and benzyl esters (entries 3, 6, and 9). A pyridyl moiety in the Ugi-components was also compatible with the employed conditions (entry 5). The U-4CR involving 4-acetoxy benzoic acid gave the deacetylated product in 73% yield (entry 2).

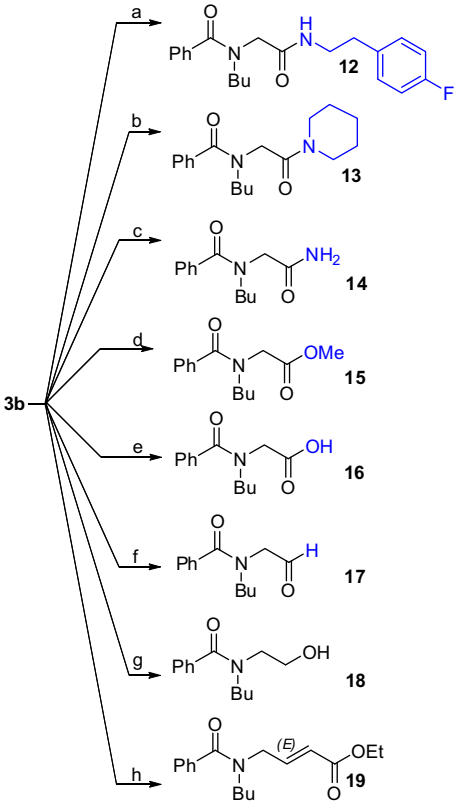
To our disappointment, some of the substrates tested furnished lower yields in the conversion step when the original Fukuyama conditions were applied, probably due to partial thermal decomposition of the starting materials. This prompted us to investigate milder conversion conditions. In this endeavor, it was discovered that the *N*-acylpyrroles readily form in the presence of 5% trifluoroacetic acid (TFA) in dichloromethane at room temperature within 60 min.[3] This procedure resulted in the desired *N*-acylpyrroles in

Table 1
Reactivity study of IPB (**2**) in Ugi-4CRS and conversion of the products **3a**–**11a** to *N*-acylpyrroles **3b**–**11b**



Entry	Product	Acid	Amine	Aldehyde	Isolated yields (%)	
					a: U-4CR	**b**: *N*-acylpyrrole[d]
1	**3a**,**b**				84	98 [b] (90)[c]
2	**4a**,**b**				73	88 (92)
3	**5a**,**b**				48	65 (70)
4	**6a**,**b**				90	48 (n.d.)[e]
5	**7a**,**b**				91[f]	89 (n.d.)[e]
6	**8a**,**b**				75	66 (70)
7	**9a**,**b**				98	55 (50)
8	**10a**,**b**				48	69 (75)
9	**11a**,**b**				61	66 (n.d.)

[a] Reaction conditions: carboxylic acid (1.0 mmol), amine (1.0 mmol), aldehyde (1.7 mmol), and IPB (**2**, 1.0 mmol), MeOH, rt, 18 h.
[b] camphorsulfonic acid (CSA, 10 mol %), quinoline (10 mol %), toluene, reflux, 30 min.
[c] 5% TFA, CH_2Cl_2, rt, 1 h.
[d] yields in parenthesis correspond to the *N*-acylpyrrole formation using 5% TFA (method c).
[e] TLC analysis revealed considerable side product formation.
[f] Reflux for 3 h.



Scheme 2. Reactions and conditions: (a) *p*-$FC_6H_4CH_2CH_2NH_2$, MeOH, reflux, 8 h, 64%. (b) piperidine, toluene, reflux, 12 h, 77%. (c) NH_4OH, MeOH, reflux, 8 h, 64%. (d) MeONa, MeOH, reflux, 8 h, 98%. (e) LiOH, THF/H_2O, rt, 12 h, 92%. (f) DBU (10 mol %), THF, rt, yield n.d. (g) $NaBH_4$, MeOH, rt, 3 h, then DBU (10 mol %), $NaBH_4$, THF/MeOH, rt, 16 h, 70%. (h) $NaBH_4$, MeOH, rt, 3 h, then DBU (10 mol %), $(EtO)_2POCHCO_2Et$, MeCN, rt, 18 h, 51%.

comparable or slightly better yields for most IPB-MCR products and, most important, it facilitated work-up and purification for compounds **3b**–**11b** (Table 1). Overall, both methods have their merits, with Fukuyama's being less acidic and the TFA-version allowing lower temperatures and easier work-up.

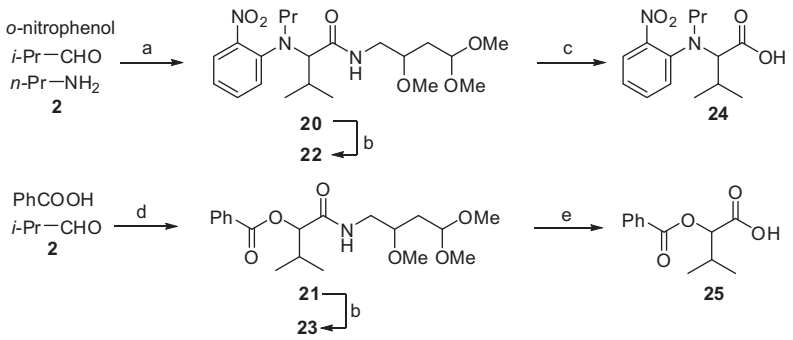
Finally the conversion of the IMCR-originated *N*-acylpyrroles **3b**–**11b** with varied nucleophiles into other organic functionalities had to be tested (Scheme 2). *N*-Acylpyrrole **3b** was chosen as the model compound for the conversion protocols. Reaction of **3b** with 4-fluorophenethylamine or piperidine afforded the respective secondary and tertiary amides (**12** and **13**) in good yields. Treatment of **3b** with NH_4OH in refluxing methanol afforded the desired primary amide **14** in 64% yield. The same process employing sodium methoxide as the nucleophile afforded the respective methyl ester **15** in quantitative yield.[11] The formation of **14** and **15** is particularly noteworthy because secondary amides generated from some other convertible isonitriles can be transformed into primary amides or methyl esters under harsh acidic conditions only.[4b,c,j,k] Saponification of **3b** to the corresponding carboxylic acid **16** was accomplished in the presence of lithium hydroxide at room temperature in 92% yield, i.e. in the overall reaction cascade IPB serves as a neutral formate carbanion equivalent, adding the –COOH group to imine (U-4CR).

Additionally, the suitability of the pyrrolic carbinol chemistry for more complex transformations was investigated, based on the *N*-acylpyrrole **3b**.[12] In a sequential procedure, **3b** was reduced with sodium borohydride, followed by the addition of a catalytic amount of DBU to afford aldehyde **17**.[13] Although it was possible to verify the formation of **17** by TLC and ESI-MS analysis, we failed to isolate it in pure form, probably due to its reactivity.

In view of this result, **17** was generated and reacted further in situ in order to obtain advanced derivatives. Thus, reaction of **3b** with an excess of sodium borohydride gave the corresponding primary alcohol **18** in 70% yield. In another experiment, **3b** was converted into **17** and trapped by a Horner-Wadsworth-Emmons (HWE) olefination.[14] This procedure afforded the desired alkene **19** in 51% yield. Compounds like **19** are valuable intermediates and have been employed in the preparation of 3-aza–bicyclo[3.1.0]hexane ring systems,[15] constrained amino acid analogs,[16] papain inhibitors,[17] and in the total synthesis of (±)-isocynodine and (±)-isocyanometrine.[18] This clearly underlines the synthetic utility of the Ugi-4CR/HWE-olefination combination.

The reactivity of **2** in other IMCRs was investigated too. The Ugi-Smiles reaction of IPB, 2-nitrophenol, isobutyraldehyde, and propylamine afforded product **20** in excellent yield (97%, Scheme 3). A Passerini reaction involving benzoic acid and isobutyraldehyde, proceeded well with reagent **2** and resulted in the desired product **21** in 81% yield. Intermediates **20** and **21** were converted into the respective *N*-acylpyrroles **22**–**23** in good yields using 10 mol % CSA and 10 mol % quinoline in refluxing toluene. Treatment of **22** in the presence of potassium hydroxide gives the corresponding carboxylic acid **24** in 46% yield. A benchmark challenge is the saponification of the *N*-acylpyrrole intermediate **23**, because the Passerini product carries an internal ester, which often is more hydrolysis sensitive than the amides resulting from Ugi reactions. A mild procedure previously employed in the hydrolysis of *N*-acylindoles (DMAP in $^tBuOH/H_2O$) works well for the substrate **23** and affords the desired carboxylic acid **25** in 60% yield.[4a,i]

In conclusion, a new convertible isonitrile IPB (**2**) has been developed which allows mild functional group interconversions via an activated carboxylic amide intermediate. The reagent can be prepared in multigram scale from readily available and



Scheme 3. Reactions and conditions: (a) MeOH, rt, 18 h., 97%. (b) CSA (10 mol %), quinoline (10 mol %), toluene, reflux 30 min 70% for **22**, 70% for **23**. (c) KOH, MeOH/THF/H_2O, M.W. 110 °C., 30 min 46%. (d) CH_2Cl_2, rt, 24 h, 81%. (e) DMAP, $^tBuOH/H_2O$, 100 °C, 2 h, 60%.

affordable starting materials in a short sequence. It has great stability in handling and storage, and shows good to excellent reactivity in different IMCRs. The activation/conversion conditions are compatible with numerous functionalities, and therefore can be applied to many highly functionalized molecules. The generated *N*-acylpyrrole intermediates present a good balance between stability and reactivity, and can be transformed into other carbonyl functions in good yields. Sequential procedures involving the formation of a carbaldehyde intermediate made the conversion of **3b** into a primary alcohol and olefin possible in reasonable yields. The IMCR reagent **2** also displays good reactivity in Ugi-Smiles and Passerini reactions. The compounds generated by these latter IMCRs were successfully converted into the respective *N*-acylpyrroles and subsequently into the corresponding carboxylic acids **24** and **25** in good yield and chemoselectivity. Thus several of the constraints found in some of the earlier convertible isonitriles, with limited stability, reactivity, or limited convertibility do not apply here.[4]

Based upon the results exposed above, we propose IPB (**2**) as a very readily accessible, universal convertible isonitrile for use in IMCRs and other isonitrile based reactions.

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R.A.W.N.F. and S.S. contributed equally to this work. The authors thank Dr. Jürgen Schmidt and Dr. Andrea Porzel for HRMS and NMR support. R.A.W.N.F. is grateful to CNPq (Brazil) for a Ph.D. fellowship. This work was supported by funds from the state of Saxony-Anhalt (LSA, WZW-Projekt Lipopeptide).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.064.

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8. For details see Supplementary data.
9. *General procedure for Ugi-4CR*: To a stirred solution of a suitable amine (1.0 mmol) in MeOH (10.0 mL) aldehyde (1.7 mmol) is added and the contents are stirred for 2 h. Then the carboxylic acid (1.0 mmol) and IPB (**2**, 0.17 g, 1.0 mmol) are added and stirring is continued for 18 h. The solvent is removed under reduced pressure and the crude material purified by silica gel column chromatography to afford the desired product.
*Example compound: N-Butyl-N-(2-oxo-2-(2,4,4-trimethoxybutylamino)ethyl) benzamide (**3a**):* Purified by silica gel column chromatography (methanol/dichloromethane 3:97). Yield: 84%. R_f = 0.44 (hexane/ethyl acetate 5:5).1H-NMR (400 MHz, $CDCl_3$) δ = 0.77 and 0.94 (t, J = 7.2 Hz, 3H), 1.13 (t, J = 7.2 Hz, 2H), 1.54 (m, 2H), 1.73 (m, 1H), 1.80 (m, 1H), 3.31–3.51 (m, 14H), 4.10 (m, 2H), 4.51 (dd, J = 5.2 Hz, 5.2 Hz,1H), 6.95 (bs, 1H), 7.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.4, 13.4, 19.5, 19.7, 30.3, 30.4, 35.0, 41.3, 50.0, 50.7, 52.9, 56.9, 75.9, 101.7, 126.5, 128.4, 129.7, 135.4, 135.4, 169.4, 172.7. HRMS (ESI+) m/z calcd for $C_{20}H_{32}N_2O_5$ $(M+Na)^+$ 403.2209, found 403.2203.
10. *General procedure for the conversion of Ugi products **3a-11a** into N-acylpyrroles **3b–11b**: Method A (CSA/quinoline/heat):* To a solution of a suitable amide like **3a**–**13a** (0.5 mmol) in toluene (10 mL), 10-camphorsulfonic acid (10 mol %) and quinoline (10 mol%) are added. After 1 min at room temperature the stirred mixture is refluxed for 30 min. The contents are cooled, transferred to a separatory funnel and washed with 1 M aqueous HCl (2 × 30 mL). The acidic aqueous phase is further extracted with ethyl acetate (1 × 20 mL). The organic layers are combined, washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The residual material is purified by silica gel column chromatography to give the desired product.
Method B (TFA/rt): A suitable amide like **3a**–**13a** (0.5 mmol) is dissolved in 5% (v/v) TFA in CH_2Cl_2 (10 mL). The contents are stirred for 1 h at room temperature before evaporating the solvent under reduced pressure. The residual material is directly purified by silica gel column chromatography to give the desired product.
*Example compound: N-Butyl-N-(2-oxo-2-(1H-pyrrol-1-yl)ethyl) benzamide (**3b**)*: Purified by silica gel column chromatography (ethyl acetate/hexanes 3:7). Yield method **A**: 98%. Yield method **B**: 90%. R_f 0.38 (hexane/ethyl acetate 5:5).^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.79 and 0.96 (t, J = 7.2 Hz, 3H), 1.15 and 1.38 (m, J = 7.2 Hz, 2H), 1.53 and 1.64 (q, J = 7.2 Hz, 2H), 3.35 and 3.58 (t, J = 7.2 Hz, 2H), 4.15 and 4.79 (s, 2H), 6.33 and 7.15 (m, 2H), 7.37–7.48 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.5, 19.6, 30.4, 46.9, 49.9, 113.6, 118.8, 126.7, 128.4, 129.7, 135.6, 165.6, 172.5. HRMS (ESI+) m/z calcd for $C_{17}H_{20}N_2NaO_2$ $(M+Na)^+$ 307.1422, found 307.1416.
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