Supported TBD-Assisted Solution Phase Diversification of Formyl-Aza-Heterocycles Through Alkylation-Knoevenagel One Pot Sequences

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Abstract: An efficient solution-phase parallel procedure to perform the structural diversification of some formyl-nitrogen heterocycles (A) using the reusable TBD supported base is described. The library synthesis is based in a consecutive Alkylation-Knoevenagel functionalisation that uses alkyl halides (B), Michael acceptors (C) and activated methylene compounds (D) as diversity elements.

Keywords: Aza-Michael, Knoevenagel, polymer supported superbases, solution phase synthesis.

High efficiency based on environmentally friendly concepts is strongly required for the synthetic organic chemistry in the twenty first century. The efficiency involves not only a short reaction process and higher yields in each step, but also lower energy costs and reactions with less waste (high atom economy), as well as cheap and easily available starting materials and catalysts for the reaction sequence, possible recyclability and lower or absence of toxicity [1]. Aiming to satisfy these requirements, solution phase library generation has been fuelled by the development of successful concepts such as solid-supported reagents, catalysts and scavengers combining the advantages of both solid phase organic synthesis (for instance, inmobilization of toxic reagents) and solution phase chemistry (mainly the relative ease separating of spent reagents from the products by simple filtration and monitoring the progress of the reactions by LC-MS, TLC or standard NMR techniques) [2]. The research area of polymer-supported reagents and especially supported acid, bases and catalysts (Fig. **1**) has grown rapidly in the last years, providing a new frontier in the rapid production of a large number of chemical libraries of structurally diverse molecules, and particularly with the use of automation or parallel flow systems in multi-step sequences [3]. Among them, the supported superbases family has emerged as interesting tools for solution-phase synthesis and high-throughput chemistry [4].

The synthetic study of polymer-supported superbase reagents has grown from the pioneering work of the Tomoi´s laboratory [5]. It was showed that N-alkylation of DBU upon treatment with chloromethyl or bromoalkyl polystyrene resins was highly reliable. The synthesis of this type of reagents is normally based on this strategy [6], and some of these polymer supported superbase reagents are now commercially available. Among them, 1,5,7- triazabicyclo [4.4.0]dec-5-ene (TBD) is the prototype of a group of guanidine bases which have a multitude of applications in organic synthesis [7]. The silica gel–TBD (**1**) or polystyrene–TBD (**2**) are to date the most employed examples. A phosphacene derivate base with a similar basicity profile, the supported version of the Schwezinger base, PS–BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine) [6a, 8] (**3**; Fig. **1**) has also been successfully used as a strong base for parallel synthesis in combination with other polymeric reagents [9]. Other useful reagents such as the less basic supported tetramethylguanidine (**4**) and carbonate on polystyrene (**5**) have been successfully employed for diverse transformations as well [10].

In the context of our ongoing efforts toward the development of new efficient and clean methodologies for the rapid generation of diverse heterocyclic libraries by using supported reagents [11], we became interested in developing a simple and straightforward synthetic route to obtain disubstituted alkylidene-azaheterocycles such as indoles, quinolones, pyridazinones and imidazoles, usually considered as privileged structures in drug discovery [12], containing an exocyclic α,β-unsaturated framework (Figs. **2**, **3**). Derivatisation of these heterocyclic pharmacophores represents a convenient approach to generate chemical diversity during lead identification and optimisation. The resulting target molecules are important analogous of lead structures in drug discovery such as the inhibitor of catechol-O-methyltransferase (COMT), entacapone (**7**) [13], the dynamin protein inhibitor (**8**) [14], the antiplatelet pyridazinone (**9**) [15] or the antiproliferative acylthiourea (**10**) [16] as well as the thyrphostins (**11**, **12**) [17], a family of synthetic protein tyrosine kinase inhibitors that selectively inhibit the autophosphorylation receptor and are used to study the receptor function (Fig. **2**).

The general structure of the target molecules is shown in the retrosynthetic scheme (Fig. **3**). Two possible pathways were designed to access the pretended library. The final products **ABC** would require an initial N-alkylation

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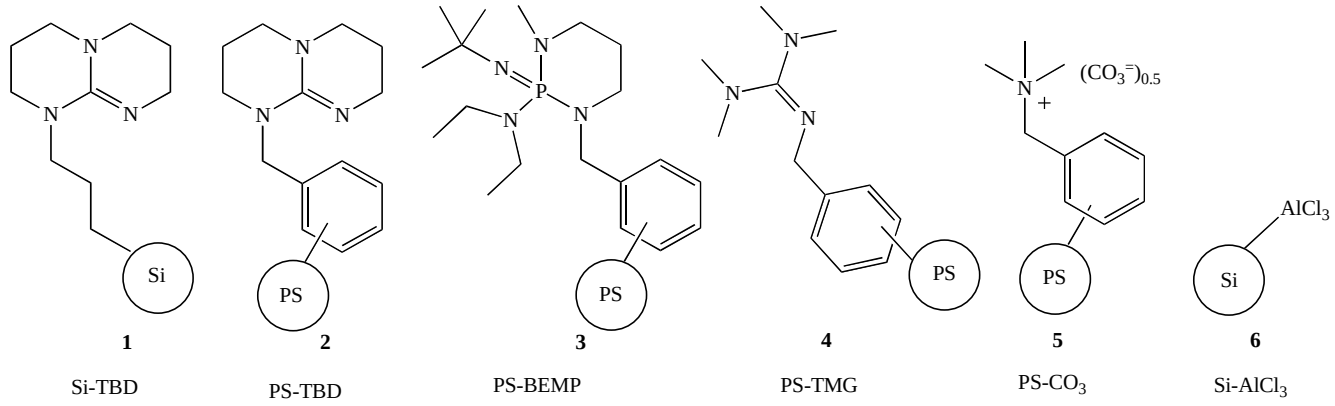


Fig. (1). Supported reagents employed in this work.

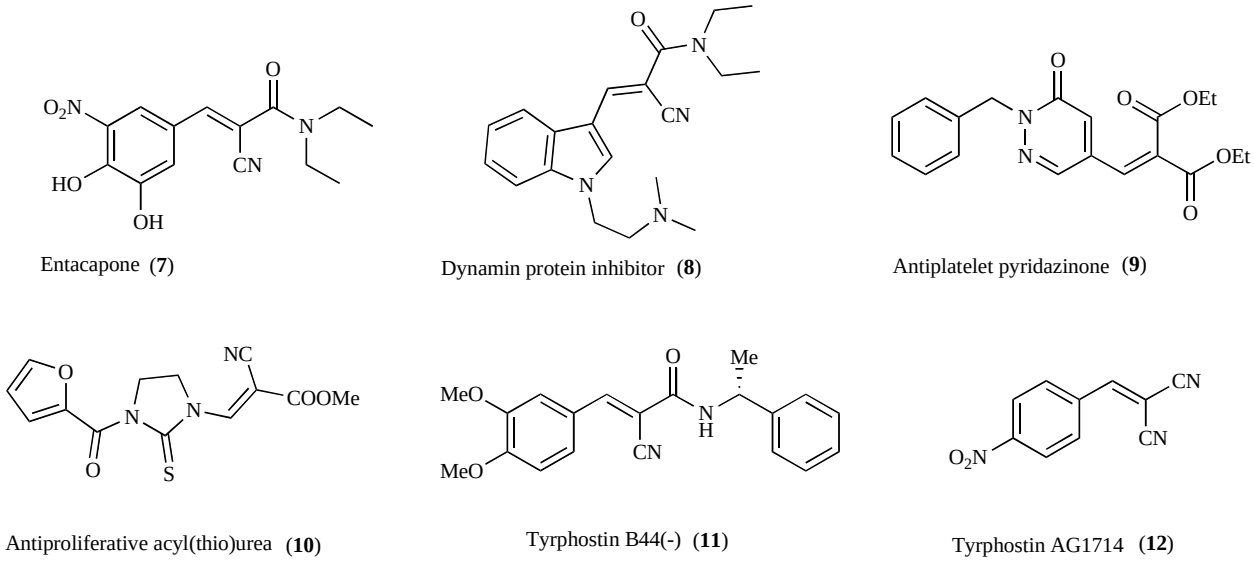


Fig. (2). Prominent lead structures containing Knoevenagel-type fragments.

(pathway A) or Knoevenagel condensation (pathways B) starting from the formyl-azaheterocycles **A** to give the intermediates **AB** or **AC**. The formyl aza-heterocycles **A1**, **A2**, **A3** and **A4** (Fig. **3**) were selected as convenient starting materials considering the reactivity of the formyl group and the acidic NH of these synthons to generate a library of N-alkylated-Knoevenagel compounds. These scaffolds are commercially available (**A2**, **A4**) or easily prepared (**A1**, **A3**) [18].

An optimal combinatorial approach for a rapid library generation would require a common effective, versatile and reusable catalyst for both processes without intermediates isolation. Taking into a account the key role of an efficient base in the success of the double transformation (alkylation+Knoevenagel) we first turned our attention to the usefulness of the described methodologies for both reactions in these heterocycles. It has been reported the use of conventional bases (e.g. K_2CO_3, Et_3N, TBD, MTBD, DBU or BEMP) to perform the alkylation or the Michael addition to quinolones [19], pyridazinones [20] and indoles or imidazoles [21], while Knoevenagel condensation often requires the use of specific reagents ($AlCl_3$, piperidine, Ac_2O) [20, 21] depending on the reactivity of each scaffold. Therefore, our preliminary efforts were aimed to find a compatible base to achieve the one-pot procedure to access the target structures following the pathway A (alkylation-Knoevenagel), designing as a proof of concept, a reaction model (see supplementary material) between the scaffolds **A1-3** and alkyl halides or α,β-unsaturated esters as alkylating agents and methyl cyanoacetate as an activated methylene compound. DBU, K_2CO_3, TEA were chosen for these screening, considering the basicity profile required for both transformations. Unfortunately, these experiments showed low transformation rates and a different behaviour depending on the studied scaffold and sequence used, affording only traces of the desired compounds in the best cases (0-5%) and complex mixtures of by-products. Among them, DBU often successfully drived the alkylation step but failed in the subsequent Knoevenagel step in all the starting scaffolds.

A sight of poor results obtained using conventional bases, the use of supported superbases was envisioned as an improved alternative that could avoid the use of high temperatures, long reaction times and tedious workup of intermediates. Although the catalytic activity of the supported reagents (showed in Fig. **1**) in key transformations of organic chemistry such as Knoevenagel condensation or alkylations with alkyl halides or Michael acceptors has been

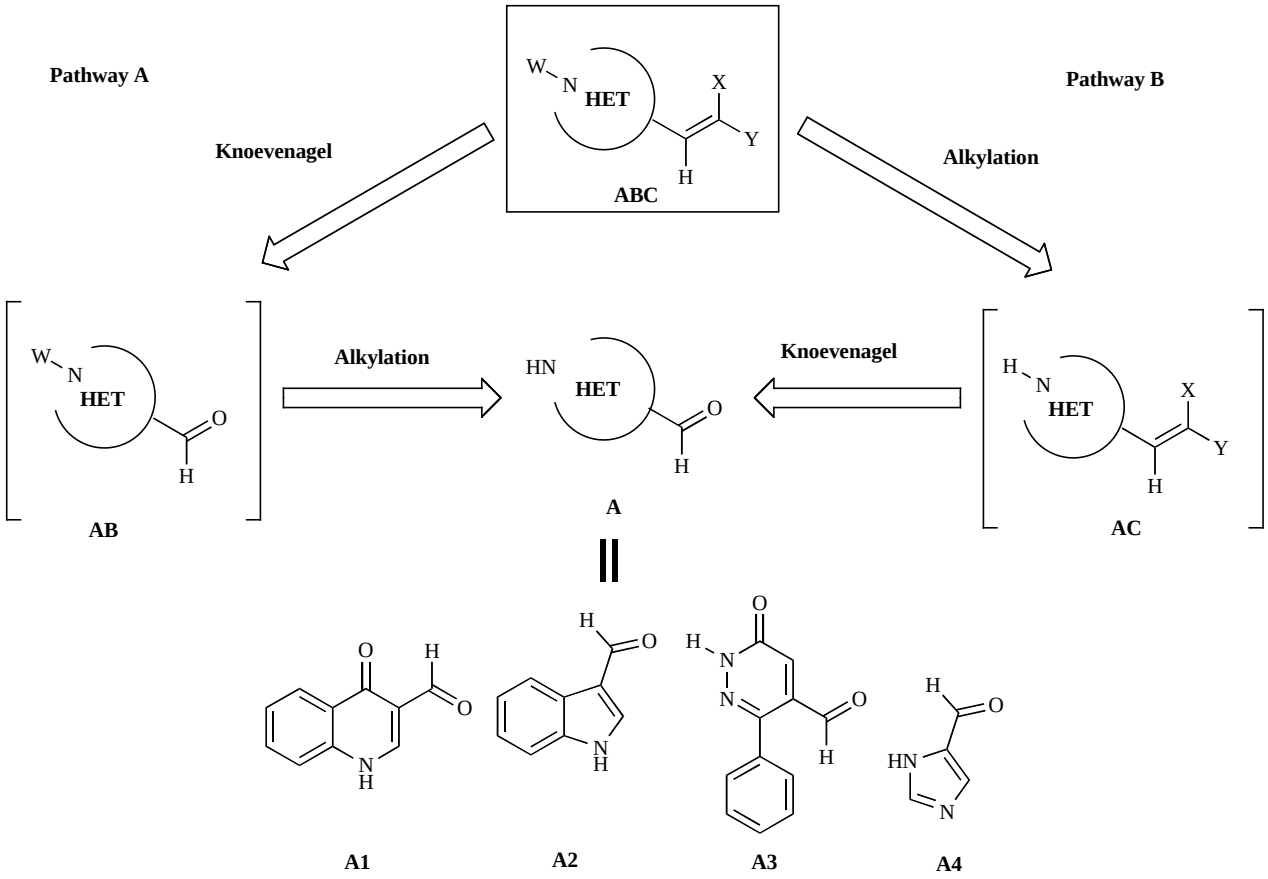


Fig. (3). General structure of the targeted libraries, retrosynthetic scheme and structure of the starting scaffolds **A**.

reported [6, 7, 21, 22], the study of its behaviour and reusability in one pot consecutive double functionalisations in an effective manner is scarce. Therefore, the first stage of the study involved a comprehensive screening process to firstly choose the most efficient pathway (**A** or **B**) to follow up and secondly to identify mild and selective alkylation conditions by employing different alkyl halides or Michael acceptors, which could be optimized for each scaffold and, most importantly, would be compatible with the experimental conditions of the Knoevenagel [22] reaction. Pathway A showed to be the best option since Knoevenagel reaction proceeds faster from N-blocked adducts and consequently the further optimisations were performed using this strategy.

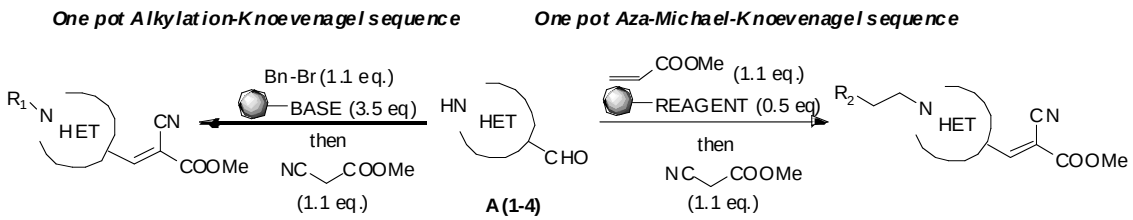
In order to define the scope and efficiency of these methodologies, we have selected again two reaction models (Table **1**) using benzyl bromide and methyl acrylate as alkylating reagents and methyl cyanoacetate as activated methylene compound and screened a variety of reaction conditions adaptable to the different scaffolds **A1-4** employing the supported bases **1-5**, chosen by its basicity profile or effectiveness to catalyze the one pot reaction. As an alternative to these reagents and considering its reported application in Aza-Michael [23] and Knoevenagel reactions [15] of its supported version, the silica-aluminium chloride (**6**) was also tested as versatile and effective catalyst for the Aza-Michael-Knoevenagel sequences.

The solubility of the scaffolds in several solvents (THF, toluene, DMF, MeCN) was first examined, being this issue a key factor in the success of the one pot sequences. The best results were obtained using THF for quinolone **A1** and pyridazinone **A3**, toluene for indole **A2** and DMF for imidazole **A4** (entries 4, 14, 15, 16, 19, 20 and 27). MeCN was efficient for the first step of alkylation but, as a general rule, longer reaction times were required for the complete conversion of the intermediates during the Knoevenagel transformation (entry 5). Toluene was optimal only when indole was employed as scaffold. This protocol was monitored by thin layer chromatography or EI–MS.

The effect of the nature of the supported reagent on the behaviour was carefully examined. (**1**) and (**2**) showed to be the most effective and versatile reagents taking into account the scaffold variability. Inversely, during the optimisation process we found that the reactions using stronger PS–BEMP (**3**) were slightly faster during the alkylation step (1.5 equiv of base, r.t., 10–20 min, with almost quantitative yields) than PS–TBD (**2**) or Si–TBD (**1**) (which require 2.5 equiv of supported base and increased reaction times). However, while the alkylation process proceeded almost quantitatively by using either (**1**), (**2**) or (**3**), the Knoevenagel condensation employing PS–BEMP (**3**) showed to be problematic [longer reaction times (48–72 h) and presence of by-products, (Table **1**, entries 6, 7, 13 and 21)].

Such behaviour was observed during consecutive reactions, as in the case of scaffolds **A1**, **A2** and **A4**. Other supported bases such as PS-TMG (**4**) or PS-carbonate (**5**) didn´t improve the results obtained using the polymeric cyclic guanidines (**1**) or (**2**). Inversely, although silica-

Table 1. Optimisation Process Through the Two Model Reactions Designed

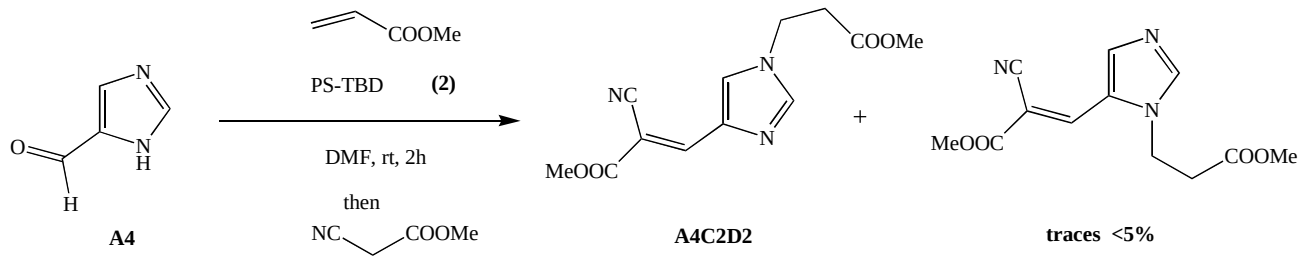


Entry	Scaffold	Supp. Regnt	Alk. Reagent	Solvent	Temp (ºC) (1st-2nd Step)	Yield (%)
1	**A1**	Si-TBD (1)	$BrCH_2Ph$	THF	40	72
2	**A1**	PS-TBD (1)	$BrCH_2Ph$	THF	40	70
3	**A1**	Si-TBD (2)	$H_2C{=}CH_2COOMe$	THF	40	60
4	**A1**	PS-TBD (2)	$H_2C{=}CH_2COOMe$	THF	40	66
5	**A1**	PS-TBD (2)	$H_2C{=}CH_2COOMe$	MeCN	40	40[a]
6	**A1**	PS-BEMP (3)	$BrCH_2Ph$	THF	40	20[b,d]
7	**A1**	PS-BEMP (3)	$H_2C{=}CH_2COOMe$	THF	40	34[b,d]
8	**A1**	PS-TMG (4)	$BrCH_2Ph$	THF	40	25[a]
9	**A1**	PS-TMG (4)	$H_2C{=}CH_2COOMe$	THF	40	45
10	**A1**	PS-CO_3 (5)	$BrCH_2Ph$	Toluene	40	14[a,c]
11	**A2**	PS-CO_3 (5)	$H_2C{=}CH_2COOMe$	Toluene	rt-60	30
12	**A2**	Si-$AlCl_3$ (6)	$H_2C{=}CH_2COOMe$	Toluene	rt-60	0[a]
13	**A2**	PS-BEMP (3)	$H_2C{=}CH_2COOMe$	Toluene	40	30[b,d]
14	**A2**	Si-TBD (1)	$BrCH_2Ph$	Toluene	rt-60	65
15	**A2**	PS-TBD (1)	$BrCH_2Ph$	Toluene	rt-60	67
16	**A2**	PS-TBD (1)	$H_2C{=}CH_2COOMe$	Toluene	rt-60	78
17	**A2**	PS-TMG (4)	$H_2C{=}CH_2COOMe$	Toluene	rt-60	44[c]
18	**A2**	PS-TMG (4)	$BrCH_2Ph$	Toluene	rt-60	34[a,c]
19	**A3**	PS-TBD (2)	$H_2C{=}CH_2COOMe$	THF	rt	50
20	**A3**	PS-TBD (1)	$BrCH_2Ph$	THF	rt	60
21	**A3**	PS-BEMP (3)	$H_2C{=}CH_2COOMe$	THF	rt	30 [b,d]
22	**A3**	PS-TMG (4)	$BrCH_2Ph$	THF	rt	48[a,c]
23	**A3**	PS-CO_3 (5)	$H_2C{=}CH_2COOMe$	DMF	rt	20
24	**A4**	PS-TBD (2)	$BrCH_2Ph$	DMF	rt	20[e]
25	**A4**	PS-CO_3 (4)	$H_2C{=}CH_2COOMe$	DMF	rt	40[a]
26	**A4**	Si-$AlCl_3$ (6)	$H_2C{=}CH_2COOMe$	DMF	70-rt	0[a]
27	**A4**	PS-TBD (2)	$H_2C{=}CH_2COOMe$	DMF	rt	72 [a]

a) Uncompleted Alkylation step. b) Uncompleted Knoevenagel step. c) 5 eq. of supported base used. d) presence of byproducts. e) a mixture of 1,4 and 3,4 regiosomers (ratio 1.5/1) was obtained.

aluminium chloride (**6**) could catalysed efficiently the Knoevenagel reaction from N-blocked heterocycles **AB**, this reagent was ineffective to drive successfully the first step (Aza-Michael) of the sequence starting from scaffolds **A**, affording uncompleted N-alkylation reactions (entries 12 and 26) and was consequently discarded.

Aiming to validate the claimed intrinsic advantages of functionalised silicas [24] (such as no swelling and solvent compatibility) over polystyrene resins for these transformations, we decided to study the differences between (**1**) and (**2**). During these experiments we didn´t find significant variations in reactivity between them using the optimal solvents (see Table **2**, entries 1, 2, 14 and 15) for each heterocycle. This observation can be attributed to the fact that (**2**) can swell efficiently in all the solvents used. Consequently, the less expensive polystyrene version of TBD was chosen for further assays.



Scheme 1. Aza-Michael-Knoevenagel sequences on imidazole **A4**.

A more intriguing challenge was the optimisation of the Aza-Michael-Knoevenagel sequence on imidazole **A4**: N-alkylation of asymmetrically substituted imidazoles usually leads to formation of 1, 4 and 3, 4 regioisomeric mixtures [25]. In the light of the poor results obtained by simple alkylation using alkyl halides during the optimisation process (entry 24), we turned to a different N-alkylation strategy based on Aza-Michael reaction between **A4** and α,β-unsaturated esters which has been shown to lead to highly regioselective alkylations [26]. The 1,4-substituted product is favoured by intramolecular hydrogen bonding as well as for steric reasons. Therefore, we screened a variety of supported reagents for the Aza-Michael-Knoevenagel sequence. Among them, PS-TBD (**2**) was again the most effective catalyst, being slightly faster and more efficient than PS-carbonate (**5**) in the Knoevenagel step (Entries 25 and 27).

Although two possible final regioisomers (Scheme 1) were expected and the formation of the corresponding 1-alkyl and 3-alkyl-imidazoles was detected by TLC in a (10/1) ratio when PS-TBD (**2**) was used at rt in DMF, surprisingly, after addition of the corresponding active methylene compound in the second step, we have obtained almost exclusively the 1-alkyl-4-alkylidene-imidazoles **ACD** after simply filtering the supported base and purification of the obtained solid. The unequivocal identity of the isomer was confirmed by NOE experiments (see supporting information) as the desired 1-alkyl-4-disubstituted-imidazole **A4C2D2**. These results can be explained considering the low rates of the Knoevenagel condensation in the second step from the 1-alkyl-5-formyl intermediate.

Encouraged by these successful results using PS-TBD (**2**), the library production was performed using this reagent as base in all sequences. Small subsets of alkyl halides **B1**–**B4** (benzyl bromide, methyl or ethyl iodides and ethyl bromoacetate), acrylates **C1**–**C5** and activated methylene compounds **D1**–**D4** (methyl, ethyl, isopropyl cyanoacetates and malononitrile) (Fig. **4**, Table **2**) were employed as building blocks to evaluate their functional group compatibility and potential utility as a source of diversity.

The results shown in the Table **2** indicate that PS-TBD (**2**) has an optimal range of basicity to carry out these syntheses in good yields under mild conditions, compared with other related items. In addition to the catalytic efficacy

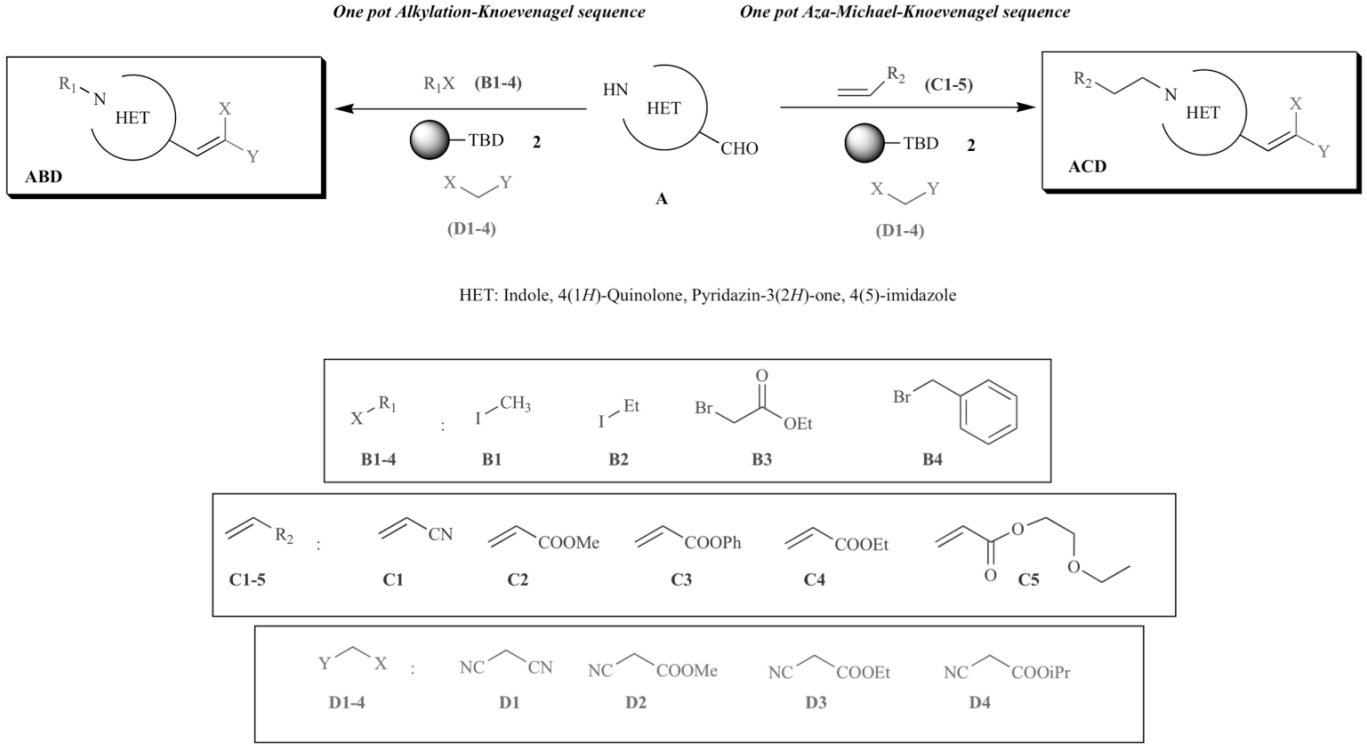
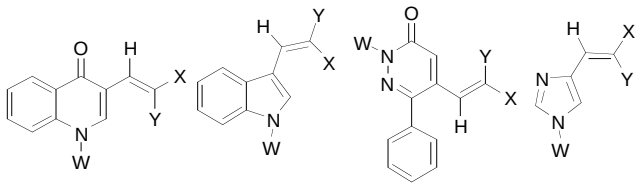


Fig. (4). Synthesis of densely substituted aza-heterocycles through one-pot consecutive functionalizations using PS-TBD (**2**).

Table 2. Synthesis of Disubstituted Heterocycles Using PS-TBD (2)



A1 **A2** **A3** **A4**

Compound	W	X/Y	Yield (%)	Compound	W	X/Y	Yield (%)
A1B1D2	CH_3	COOMe/CN	89[a]	**A2C4D4**	CH_2CH_2COOEt	COO^iPr/CN	68[d]
A1B3D1	CH_2-$COCH_2CH_3$	CN/CN	72[a]	**A2C3D2**	CH_2CH_2COOPh	COOMe/CN	75[d]
A1B2D3	CH_2CH_3	COOEt/CN	64[a]	**A3B1D2**	CH_3	COOMe/CN	69[e]
A1B4D3	CH_2Ph	COOEt/CN	70[a]	**A3B3D3**	CH_2-CO CH_2CH_3	COOEt/CN	65[e]
A1B4D4	CH_2Ph	COO^iPr/CN	63[a]	**A3B4D2**	CH_2Ph	COOMe/CN	72[e]
A1C2D3	CH_2CH_2COOMe	COOEt/CN	66[b]	**A3B2D1**	CH_2CH_3	CN/CN	70[e]
A1C4D2	CH_2CH_2COOEt	COOMe/CN	70[b]	**A3B1D4**	CH_3	COO^iPr/CN	57[e]
A1C3D3	CH_2CH_2COOPh	COOEt/CN	68[b]	**A3C1D3**	CH_2CH_2CN	COOEt/CN	52[f]
A1C3D1	CH_2CH_2COOPh	CN/CN	54[b]	**A3C2D1**	CH_2CH_2COOMe	CN/CN	65[f]
A1C1D2	CH_2CH_2CN	COOMe/CN	63[b]	**A3C4D2**	CH_2CH_2COOEt	COOMe/CN	62[f]
A2B3D2	CH_2-CO CH_2CH_3	COOMe/CN	65[c]	**A3C3D2**	CH_2CH_2COOPh	COOMe/CN	66[f]
A2B2D2	CH_2CH_3	COOMe/CN	74[c]	**A3C2D4**	CH_2CH_2COOMe	COO^iPr/CN	50[f]
A2C2D3	CH_2CH_2-$COOCH_3$	COOEt/CN	78[c]	**A4C2D2**	CH_2CH_2COOMe	COOMe/CN	72[g]
A2B1D1	CH_3	CN/CN	72[c]	**A4C2D1**	CH_2CH_2COOMe	CN/CN	74[g]
A2B4D3	CH_2Ph	COOEt/CN	67[c]	**A4C1D1**	CH_2CH_2CN	CN/CN	84[g]
A2B2D4	CH_2CH_3	COO^iPr/CN	63[c]	**A4C2D3**	CH_2CH_2COOMe	COOEt/CN	71[g]
A2C1D3	CH_2CH_2CN	COOEt/CN	70[d]	**A4C4D3**	CH_2CH_2COOEt	COOEt/CN	72[g]
A2C4D3	CH_2CH_2COOEt	COOEt/CN	78[d]	**A4C5D2**	$CH_2CH_2COO(CH_2)_2OEt$	COOMe/CN	65[g]

a) **A1** (0.60 mmol), R_1X (0.66 mmol), PS-TBD (1.5 mmol), THF, 40ºC, 1-3h., then activated methylene compound (0.66 mmol), 1-12h b) **A1** (0.60 mmol), Michael acceptor (0.66 mmol), PS-TBD (0.12 mmol), THF, 60ºC, 1-3h., then activated methylene compound (0.66 mmol), 50ºC, 1-12h c) **A2** (0.60 mmol), R_1X (0.66 mmol), PS-TBD (1.5 mmol), toluene, 40ºC, 1-3h., then activated methylene compound (0.66 mmol), 60ºC, 1-12h d) **A2** (0.60 mmol), Michael acceptor (0.66 mmol), PS-TBD (0.12 mmol), toluene, 60ºC, 1-3h., then activated methylene compound (0.66 mmol), 1-12h. e) **A3** (0.60 mmol), R_1X (0.66 mmol), PS-TBD (1.5 mmol), THF, 40ºC, 1-3h., then activated methylene compound (0.66 mmol), rt, 1-12h. f) **A3** (0.60 mmol), Michael acceptor (0.66 mmol), PS-TBD (0.12 mmol), THF, 40ºC, 2h., then activated methylene compound (0.66 mmol), rt, 1-12h. g) **A4** (0.60 mmol), Michael acceptor (0.66 mmol), PS-TBD (0.12 mmol), DMF, rt, 2h., then activated methylene compound (0.66 mmol), 1-12h. The stereochemistry of all compounds was determined through NMR experiments. Pyridazinone, quinolone and imidazole compounds have an *E* configuration and *Z* for indole derivatives. The *E* configuration was assigned unambiguously from the ^{1}H-coupled ^{13}C NMR spectrum (see supporting information) [27].

observed during the Alkylation-Knoevenagel reactions, a remarkable feature of the synthetic protocol documented here concerns the recyclability of TBD on polystyrene. Once the reaction had finished, the polymer-supported reagent was separated from the reaction mixture by filtration, submitted to a washing protocol (dioxane, CH_2Cl_2, diethyl ether) and then dried under vacuum for 12 hours. The recovered polymeric material was routinely reused (at least three times) during library production without significant loss of activity and with the average yield maintained within the series for substrates of similar reactivity (e.g. **A1B1D2**: 85%, **A1C2D3**: 64% and **A4C2D1**: 70%).

In conclusion, a simple solution-phase approach has been developed, easily adaptable to the parallel synthesis of libraries of indoles, quinolones, pyridazinones and imidazoles. Among the polymeric reagents screened, PS–TBD (**2**) showed to be an efficient and reusable supported superbase for the one-pot consecutive Alkylation–Knoevenagel and aza-Michael–Knoevenagel functionalisations, allowing to expand rapidly the molecular diversity of a variety of formyl-aza-heterocycles.

EXPERIMENTAL SECTION

Commercially available starting materials, reagents and solvents were purchased (Sigma-Aldrich) and used without further purification. When necessary, solvents were dried by standard techniques and distilled. The reactions were monitored by thin-layer chromatography (TLC) with 2.5 mm Merck silica gel GF 254 strips, and each one of the purified compounds showed a single spot; unless stated otherwise, UV light and/or iodine vapour were used for detection of compounds. Purification of crude compounds was carried out by preparative chromatography and/or then recrystallization. The one pot reactions were performed on a PLS (6×4) Organic Synthesiser from Advanced Chemtech.

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured using a Perkin-Elmer 1640 FTIR spectrophotometer with samples as potassium bromide pellets. The NMR spectra were recorded on Bruker AM300 and XM500 spectrometers. Chemical shifts are given as δ values against tetramethylsilane as internal standard and *J* values are given in Hz. Mass spectra were obtained on a Varian MAT-711 instrument. A complete structural characterization, including IR, NMR, mass spectrometry for the new compounds is provided. The starting material key aza-formyl-heterocycles are commercial (**A2** and **A4**) or were obtained (**A1** and **A3**) following a assisted two step sequence previously described by our group [16, 21]. A copy of the NMR, IR spectra of the **A1** precursor as well as the final compounds is provided in the supporting information.

General procedure for Alkylation-Knoevenagel sequence (Method A): A coated Kimble vial was charged with a mixture of the scaffold **A1**–**A4** (0.60 mmol) in the appropriate solvent [THF (3 mL) for **A1** or **A3**, toluene for **A2**, DMF for **A4**]. The supported organic base (1.5 mmol of PS–TBD **2**) and the alkyl halide (0.66 mmol) were added at the appropriate temperature (rt for **A4**, 40°C for **A1** and **A3**, r.t. for **A2**). The sample was vortexed for 30-60 min to give the corresponding N-blocked adduct. Addition of the activated methylene compound (1.1 equiv, stirring for 1–12 h) to the adduct at the appropriate temperature (40°C for **A1**, 60°C for **A2**, r.t. for **A3** and **A4**) in the corresponding solvent, led to the final product. The supported reagent was filtered by a fritted syringe in a Manifold Filtration System (Visiprep®) and the filtrate was evaporated in vacuum. The obtained solid or residue was purified by crystallization or preparative chromatography. The PS-TBD (**2**) was washed following the protocol: dioxane, CH_2Cl_2, diethyl ether and reused at least three times without important loss of activity.

(2*E*)-Ethyl-3-(1-benzyl-1,4-dihydro-4-oxoquinolin-3-yl)-2-cyanoacrylate (A1B4D3). Purification by preparative chromatography using AcOEt/hexane (1:4) mp: 218-219ºC (*iso*-PrOH); yield 70%. IR (KBr): ν_{max}/cm^{-1} 2233 (CN), 1709 (CO), 1665 (CO), 1599 (Aromatics). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 9.12 (s, 1H, CH), 8.88 (s, 1H, CH), 8.47 (d, *J*=8.2 Hz, 1H, Aromatic), 7.66-7.62 (m, 1H, Aromatics), 7.43-7.33 (m, 4H, Aromatics), 7.23-7.19 (m, 3H, Aromatics), 5.42 (s, 2H, CH_2), 4.34 (q, *J*= 7.2 Hz, 2H, CH_2), 1.35 (t, *J*=7.2 Hz, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 175.4, 162.7, 148.2, 145.7, 139.1, 133.6, 133.3, 129.4, 128.8, 128.0, 127.2, 126.3, 125.9, 117.1, 117.0, 113.6, 97.9, 62.2, 58.1, 14.2. MS (70 eV) *m*/*z* (%): 358 (M^+, 11), 285 (100), 91 (16). HRMS *m*/*z* calcd. for $C_{22}H_{18}N_2O_3$ (M+): 358.1317, found: 358.1320.

Ethyl 2-[3-(2,2-dicyanovinyl)-4-oxoquinolin-1(4*H*)-yl] acetate (A1B3D1). Purification by preparative chromatography using AcOEt/hexane (1:3) mp: 155-156ºC (*iso*-PrOH); yield 72%. IR (KBr): ν_{max}/cm^{-1} 2218 (CN), 1739 (CO), 1647 (CO), 1549 (Aromatics). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 8.83 (s, 1H, CH), 8.50 (dd, *J*=6.4 Hz, *J*=1.4, 1H, Aromatic), 8.42 (s, 1H, CH), 7.79-7.73 (m, 1H, Aromatic), 7.56-7.52 (m, 1H, Aromatic), 7.30-7.23 (m, 1H, Aromatic), 4.91 (s, 2H, CH_2), 4.30 (q, *J*= 7.1 Hz, 2H, CH_2), 1.30 (t, *J*= 7.1 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 174.5, 165.8, 152.9, 146.1, 139.0, 134.0, 128.3, 126.8, 126.7, 115.7, 114.0, 63.1, 55.2, 14.0. MS (70 eV) *m*/*z* (%): 307 (M^+, 100), 281 (11), 234 (54). HRMS *m*/*z* calcd. for $C_{17}H_{13}N_3O3$ (M+): 307.0957, found: 307.0967.

Ethyl (2*E*)-3-(1-ethyl-1,4-dihydro-4-oxoquinolin-3-yl)-2-cyanoacrylate (A1B2D3). Purification by preparative chromatography using AcOEt/hexane (1:2) mp: 176-177ºC (*iso*-PrOH); yield 64%. IR (KBr): ν_{max}/cm^{-1} 2214 (CN), 1711 (CO), 1632 (CO), 1550 (Aromatics), 1247 (O-R). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 9.07 (s, 1H, CH), 8.88 (s, 1H, CH), 8.51 (d, *J*=8.2 Hz, 1H, Aromatic), 7.79-7.73 (m, 1H, Aromatic), 7.54-7.46 (m, 2H, Aromatics), 4.34 (q, *J*=7.1 Hz, 2H, CH_2), 4.31 (q, *J*=7.3 Hz, 2H, CH_2), 1.60 (t, *J*= 7.3 Hz, 3H, CH_3), 1.37 (t, *J*= 7.1 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 175.2, 162.8, 148.3, 144.5, 138.6, 133.3, 128.2, 127.3, 125.8, 117.2, 116.1, 113.4, 97.2, 62.2, 49.4, 14.4, 14.2. MS (70 eV) *m*/*z* (%): 296 (M^+, 8), 251 (5), 223 (100), 105 (22). HRMS *m*/*z* calcd. for $C_{17}H_{16}N_2O_3$ (M+): 296.1161, found: 296.1168.

Isopropyl (2*E*)-3-(1-benzyl-1,4-dihydro-4-oxoquinolin-3-yl)-2-cyanoacrylate (A1B4D4). Purification by preparative chromatography using AcOEt/hexane (1:4) mp: 210-212ºC (*iso*-PrOH); yield 53%. IR (KBr): ν_{max}/cm^{-1} 2230 (CN), 1707 (CO), 1627 (CO), 1600 (Aromatics), 1092 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 9.15 (s, 1H, CH), 8.89 (s, 1H, CH), 8.47 (d, *J*=8.2 Hz, 1H, Aromatic), 7.65-7.48 (m, 1H, Aromatic), 7.45-7.32 (m, 5H, Aromatic), 7.25-7.22 (m, 2H, Aromatic), 5.44 (s, 2H, CH_2), 5.21-5.17 (m, 1H, CH), 1.35 (d, *J*=6.2 Hz, 6H, 2 x CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 175.7, 162.8, 148.3, 146.1, 139.1, 133.8, 133.7, 129.9, 129.2, 128.4, 127.6, 126.8, 126.3, 117.5, 114.1, 98.8, 97.5, 70.6, 58.5, 22.2. FAB (70 eV) *m*/*z* (%): 373 (M^+, 5), 307 (100), 289 (12). HRMS *m*/*z* calcd. for $C_{23}H_{20}N_2O_3$ (M+): 372.1474, found: 372.1474.

Methyl (2*E*)-3-(1-methyl-1,4-dihydro-4-oxoquinolin-3-yl)-2-cyanoacrylate (A1B1D2). Purification by preparative chromatography using AcOEt/hexane (1:3). mp: 236-238ºC (*iso*-PrOH); yield 77%. IR (KBr): ν_{max}/cm^{-1} 2216 (CN), 1710 (CO), 1626 (CO), 1550 (Aromatics), 1254 (O-R). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 9.04 (s, 1H, CH), 8.89 (s, 1H, CH), 8.51 (dd, *J*=6.5 *J*=1.4 Hz, 1H, Aromatic), 7.80-7.74 (m, 1H, Aromatic), 7.55-7.48 (m, 2H, Aromatics), 3.96 (s, 3H, CH_3), 3.90 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 175.2, 163.1, 148.8, 146.4, 139.8, 133.8, 128.4, 127.3, 126.5, 117.5, 116.6, 113.4, 96.9, 53.4, 42.6. MS (70 eV) *m*/*z* (%): 268 (M^+, 21), 237 (7), 210 (15), 209 (100). HRMS *m*/*z* calcd. for $C_{15}H_{12}N_2O_3$ (M+): 268.0848, found: 268.0848.

Ethyl (*Z*)-3-(1-ethyl-1*H*-indol-3-yl)-2-cyanoacrylate (A2B2D2). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 185-186ºC (*iso*-PrOH); yield 74%. IR (KBr): ν_{max}/cm^{-1} 2212 (CN), 1714 (CO), 1593 (Aromatics), 1120 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 8.58 (s, 1H, CH), 8.57 (s, 1H, CH), 7.83 (d, *J*= 8.5 Hz, 1H, Aromatic), 7.45-7.42 (m, 1H, Aromatic), 7.38-7.30 (m, 2H, Aromatics), 4.28 (q, *J*=7.2 Hz, 2H, CH_2), 3.91 (s, 3H, OCH_3), 1.56 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 164.9, 157.5, 146.5, 134.0, 133.7, 124.2, 123.0, 119.0, 118.9, 110.9, 110.4, 94.7, 53.1, 42.8, 15.5. MS (70 eV) *m*/*z* (%): 254 (M^+, 100), 239 (53), 223 (23), 179 (22), 140 (39). HRMS *m*/*z* calcd. for $C_{15}H_{14}N_2O_2$ (M+): 254.1055, found: 254.1058.

2-[(1-Methyl-1*H*-indol-3-yl)-methylene]malononitrile (A2B1D1). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 192-194ºC (*iso*-PrOH); yield 82%. IR (KBr): ν_{max}/cm^{-1} 2212 (CN), 1568 (Aromatics). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 8.42 (s, 1H, CH), 8.01 (s, 1H, CH), 7.73-7.70 (m, 1H, Aromatic), 7.45-7.34 (m, 3H, Aromatics), 3.94 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 150.3, 137.2, 135.4, 128.0, 124.9, 123.8, 118.5, 116.0, 115.8, 111.1, 110.7, 34.7. MS (70 eV) *m*/*z* (%): 207 (M^+, 100), 179 (15), 165 (18), 138 (12). HRMS *m*/*z* calcd. for $C_{13}H_9N_3$ (M+): 207.0796, found: 207.0799.

Ethyl (*Z*)-3-(1-benzyl-1*H*-indol-3-yl)-2-cyanoacrylate (A2B4D3). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 130-131ºC (*iso*-PrOH). Yield: 67%. IR (KBr): ν_{max}/cm^{-1} 2209 (CN), 1747 (CO), 1578 (Aromatics), 1094 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 8.61 (s, 1H, CH), 8.60 (s, 1H, CH), 7.86-7.83 (m, 1H, Aromatic), 7.37-7.27 (m, 6H, Aromatics), 7.18-7.15 (m, 2H, Aromatics), 5.41 (s, 2H, CH_2), 4.37 (q, *J*= 7.1 Hz, 2H, CH_2), 1.39 (t, *J*= 7.1 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 164.3, 146.2, 136.7, 135.6, 134.5, 129.5, 129.0, 128.7, 127.2, 124.4, 123.1, 119.0, 118.6, 111.5, 110.8, 94.8, 62.3, 51.8, 14.7. MS (70 eV) *m*/*z* (%): 330 (M^+, 75), 183 (1), 139 (2), 91(100). HRMS *m*/*z* calcd. for $C_{21}H_{18}N_2O_2$ (M+): 330.1368, found: 330.1374.

Methyl (*Z*)-3-[1-(2-ethoxycarbonylmethyl)-1*H*-indol-3-yl]-2-cyanoacrylate (A2B3D2). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 158-159ºC (*iso*-PrOH); Yield: 72%. IR (KBr): ν_{max}/cm^{-1} 2216 (CN), 1751 (CO), 1700 (CO), 1588 (Aromatics), 1099 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 8.58 (s, 1H, CH), 8.51 (s, 1H, CH), 7.85-7.82 (m, 1H, Aromatic), 7.39-7.30 (m, 3H, Aromatics), 4.94 (s, 2H, CH_2), 4.24 (q, *J*= 7.1 Hz, 2H, CH_2), 3.91 (s, 3H, OCH_3), 1.28 (t, *J*= 7.1 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 167.2, 164.5, 146.4, 136.9, 134.8, 128.5, 124.7, 123.3, 119.1, 118.4, 111.3, 110.5, 95.1, 62.7, 53.2, 49.0, 14.5. MS (70 eV) *m*/*z* (%): 312 (M^+, 48), 239 (100), 207 (11), 152 (18). HRMS *m*/*z* calcd. for $C_{17}H_{16}N_2O_4$ (M+): 312.1110, found: 312.1118.

Isopropyl (*Z*)-3-(1-ethyl-1*H*-indol-3-yl)-2-cyanoacrylate (A2B2D4). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 97-98ºC (*iso*-PrOH). Yield: 76%. IR (KBr): ν_{max}/cm^{-1} 2214 (CN), 1743 (CO), 1100 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 8.55 (s, 1H, CH), 8.54 (s, 1H, CH), 7.84-7.81 (m, 1H, Aromatic), 7.44-7.41 (m, 1H, Aromatic), 7.37-7.30 (m, 2H, Aromatics), 5.21-5.04 (m, 1H, CH), 4.28 (q, *J*= 7.3 Hz, 3H, -CH_2), 1.55 (t, *J*= 7.3 Hz, 2H, CH_3), 1.36 (d, *J*= 6.3 Hz, 3H, CH_3), 1.29 (d, *J*= 6.3 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 162.8, 146.1, 136.3, 133.4, 128.9, 124.1, 122.9, 118.9, 118.8, 110.9, 110.4, 94.5, 69.9, 42.7, 22.2, 21.9, 15.5. MS (70 eV) *m*/*z* (%): 282 (M^+, 57), 240 (100), 225 (67), 194 (21), 140 (54). HRMS *m*/*z* calcd. for $C_{17}H_{18}N_2O_2$ (M+): 282.1368, found: 282.1372.

Methyl (2*E*)-3-(1,6-dihydro-1-benzyl-6-oxo-3-phenyl-pyridazin-4-yl)-2-cyano acrylate (A3B4D2). Purification by preparative chromatography using AcOEt/hexane (1:3). mp: 201-202ºC (*iso*-PrOH). Yield: 72%. IR (KBr): ν_{max}/cm^{-1} 2230 (CN), 1739 (CO), 1662 (CO), 1583 (Aromatics). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 7.89 (s, 1H, CH), 7.52-7.45 (m, 6H, Aromatics + CH), 7.38-7.30 (m, 5H, Aromatics), 5.40 (s, 2H, CH_2), 3.91 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 160.9, 158.3, 149.6, 144.6, 135.5, 135.2, 133.7, 129.9, 129.8, 129.0, 128.9, 128.8, 128.6, 128.2, 112.2, 110.2, 55.7, 53.9. MS (70 eV) *m*/*z* (%): 371 (M^+, 100), 370 (33), 267 (19). HRMS *m*/*z* calcd. for $C_{22}H_{17}N_3O_3$ (M+): 371.1269, found: 371.1275.

Isopropyl (2*E*)-3-(1,6-dihydro-1-methyl-6-oxo-3-phenyl-pyridazin-4-yl)-2-cyanoacrylate (A3B1D4). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 156-158ºC (*iso*-PrOH). Yield: 57%. IR (KBr): ν_{max}/cm^{-1} 2354 (CN), 1721 (COO), 1701 (COO), 1664 (CO), 1585 (Aromatics), 1084 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 7.89 (s, 1H, CH), 7.52 (s, 1H, CH), 7.49-7.44 (m, 3H, Aromatics), 7.40-7.36 (m, 2H, Aromatics), 5.19-5.11 (m, 1H, CH), 3.89 (s, 3H, CH_3), 1.34 (d, *J*=6.2 Hz, 6H, 2 x CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 160.3, 159.3, 149.4, 145.0, 135.9, 134.1, 130.3, 129.4, 129.3, 129.1, 113.0, 111.6, 72.2, 41.0, 22.0. MS (70 eV) *m*/*z* (%): 323 (M^+, 14), 236 (100), 208 (31), 164 (65), 139 (26), 114 (27), 77 (32). HRMS *m*/*z* calcd. for $C_{18}H_{17}N_3O_3$ (M+): 323.1269, found: 323.1273.

2-[(1-Ethyl-1,6-dihydro-6-oxo-3-phenylpyridazin-4-yl)-methylidene]malononitrile (A3B2D1). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 228-230ºC; (*iso*-PrOH). yield 80%. IR (KBr): ν_{max}/cm^{-1} 2230 (CN), 1755 (CO), 1669 (CO), 1583 (Aromatics). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 7.54-7.52 (m, 4H, Aromatics + 1H, CH), 7.47 (s, 1H, CH), 7.42-7.34 (m, 2H, Aromatics), 4.31 (q, *J*= 7.1 Hz, 2H, CH_2), 1.45 (t, *J*= 7.1 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 158.8, 155.1, 144.6, 134.8, 134.2, 130.7, 129.9, 129.7, 129.1, 112.5, 111.2, 92.1, 48.2, 13.8. MS (70 eV) *m*/*z* (%): 276 (M^+, 18), 247 (18), 222 (17), 191 (31), 50 (100). HRMS *m*/*z* calcd. for $C_{16}H_{12}N_4O$ (M+): 276.1011, found: 276.1014.

Methyl (2*E*)-3-(1,6-dihydro-1-methyl-6-oxo-3-phenyl-pyridazin-4-yl)-2-cyanoacrylate (A3B1D2). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 220-221ºC (*iso*-PrOH). Yield: 79%. IR (KBr): ν_{max}/cm^{-1} 2229 (CN), 1727 (CO), 1659 (CO), 1580 (Aromatics), 1083 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 7.92 (s, 1H, -CH), 7.53-7.44 (m, 4H, Aromatics+ CH), 7.39-7.35 (m, 2H, Aromatics), 3.92 (s, 3H, CH_3), 3.89 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 160.9, 158.9, 149.6, 144.6, 135.4, 133.7, 129.9, 129.1, 129.0, 128.7, 112.9, 110.3, 53.9, 40.5. MS (70 eV) *m*/*z* (%): 295 (M^+, 100), 236 (100), 208 (35), 164 (30). HRMS *m*/*z* calcd. for $C_{16}H_{13}N_3O_3$ (M+): 295.0957, found: 295.0966.

Ethyl (2*E*)-3-[1,6-dihydro-1-(ethoxycarbonylmethyl)-6-oxo-3-phenylpyridazin-4-yl]-2-cyanoacrylate (A3B3D3). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 141-142ºC (*iso*-PrOH). Yield: 75%. IR (KBr): ν_{max}/cm^{-1} 2232 (CN), 1762 (CO), 1730 (CO), 1673 (CO), 1584 (Aromatics), 1093 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 7.89 (d, *J*=1.2 Hz, 1H, H_4), 7.55 (s, 1H, CH), 7.51-7.42 (m, 3H, Aromatics), 7.40-7.29 (m, 2H, Aromatics), 4.97 (s, 2H, CH_2), 4.37 (q, *J*=7.1 Hz, 2H, CH_2), 4.32 (q, *J*= 7.1 Hz, 2H, CH_2), 1.36 (t, *J*= 7.1 Hz, 3H, CH_3), 1.30 (t, *J*= 7.1 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 166.8, 160.3, 158.5, 149.0, 145.2, 136.0, 133.4, 130.0, 129.6, 128.9, 128.8, 112.9, 110.9, 63.4, 61.9, 53.5, 14.1, 13.9. MS (70 eV) *m*/*z* (%): 381 (M^+, 62), 308 (100),

262 (70), 234 (67), 164 (60). HRMS *m/z* calcd. for $C_{20}H_{19}N_3O_5$ (M+): 381.1325, found: 381.1328.

General procedure for Michael-Knoevenagel sequence (Method B): A coated Kimble vial was charged with a mixture of the scaffold **A1**–**A4** (0.60 mmol) in the appropriate solvent [THF (3 mL) for **A1** or **A3**, toluene for **A2**, DMF for **A4**]. The supported organic base (0.12 mmol of PS–TBD **2**) and the Michael acceptor (0.72 mmol) were added at the appropriate temperature (rt for **A4**, 60°C for scaffolds **A1**, **A2**, **A3**). The sample was vortexed for 30-60 min to give the corresponding N-blocked adduct. Addition of the activated methylene compound (1.1 equiv, stirring for 1–12 h) to the adduct at the appropriate temperature (40°C for **A1**, 60°C for **A2**, rt for **A3** and **A4**) in the corresponding solvent, led to the final product. The supported reagent was filtered by a fritted syringe in a Manifold Filtration System (Visiprep®) and the filtrate was evaporated in vacuum. The obtained solid or residue was purified by crystallization or preparative chromatography. The PS-TBD (**2**) was washed following the protocol: dioxane, CH_2Cl_2, diethyl ether and reused at least three times without important loss of activity.

Methyl (2*E*)-3-[1-(2-ethoxycarbonylethyl)-1,4-dihydro-4-oxoquinolin-3-yl]-2-cyanoacrylate (A1C4D2). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 186-187ºC (*iso*-PrOH). Yield: 70%. IR (KBr): ν_{max}/cm^{-1} 2220 (CN), 1717 (CO), 1624 (CO), 1584 (Aromatics), 1093 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 9.10 (s, 1H, CH), 8.81 (s, 1H, CH), 8.47 (d, *J*=8.2 Hz, 1H, Aromatic), 7.74-7.70 (m, 1H, Aromatic), 7.48-7.45 (m, 2H, Aromatics), 4.54 (t, *J*= 6.7 Hz, 2H, -CH_2), 4.15 (q, *J*= 7.2 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 2.91 (t, *J*= 6.7 Hz, 2H, CH_2), 1.20 (t, *J*=7.2 Hz, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 175.2, 169.6, 163.2, 148.4, 145.9, 138.3, 133.4, 128.3, 127.2, 125.9, 116.8, 115.8, 113.3, 97.2, 61.5, 53.0, 49.6, 33.0, 14.0. MS (70 eV) *m/z* (%): 354 (M^+, 16), 323 (4), 295 (100), 267 (16). HRMS *m/z* calcd. for $C_{19}H_{18}N_2O_5$ (M+): 354.1216, found: 354.1220.

Methyl (2*E*)-3-[1-(2-cyanoethyl)-1,4-dihydro-4-oxoquinolin-3-yl]-2-cyanoacrylate (A1C1D2) Purification by preparative chromatography using AcOEt/hexane (1:3). mp: 200-201ºC (*iso*-PrOH). Yield: 63%. IR (KBr): ν_{max}/cm^{-1} 2218 (CN), 1704 (CO), 1633 (CO), 1588 (Aromatics), 1091 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 9.01 (s, 1H, CH), 8.82 (s, 1H, CH), 8.51 (d, *J*=8.2 Hz, 1H, Aromatic), 7.80-7.76 (t, *J*=7.2 Hz, 1H, Aromatic), 7.54-7.41 (m, 2H, Aromatics), 4.56 (t, *J*= 6.8 Hz, 2H, CH_2). 3.89 (s, 3H, OCH_3), 3.00 (t, *J*= 6.8 Hz, 2H, CH_2). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 162.3, 148.0, 144.6, 138.0, 137.0, 133.9, 128.8, 126.3, 117.1, 115.0, 114.9, 106.2, 98.1, 77.1, 53.1, 49.1, 17.9. MS (70 eV) *m/z* (%): 307 (M^+, 5), 276 (5), 248 (100), 195 (8). HRMS *m/z* calcd. for $C_{17}H_{13}N_3O_3$ (M+): 307.0957, found: 307.0960.

Ethyl (2*E*)-3-[1-(2-methoxycarbonylethyl)-1,4-dihydro-4-oxoquinolin-3-yl]-2-cyanoacrylate (A1C2D3). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 173-174ºC (*iso*-PrOH). Yield 66%. IR (KBr): ν_{max}/cm^{-1} 2212 (CN), 1725 (COO), 1627 (CO), 1610 (CO), 1593 (Aromatics), 1092 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 9.11 (s, 1H, CH), 8.80 (s, 1H, CH), 8.48-8.46 (m, 1H, Aromatic), 7.75-7.70 (m, 1H, Aromatic), 7.49-7.42 (m, 2H, Aromatics), 4.55 (t, *J*= 6.7 Hz, 2H, CH_2). 4.33 (q, *J*= 7.1 Hz, 2H, CH_2), 3.70 (s, 3H, OCH_3), 2.94 (t, *J*= 6.7 Hz, 2H, CH_2), 1.35 (t, *J*= 7.1 Hz, 3H, -CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 175.2, 170.1, 162.7, 148.0, 145.8, 138.3, 133.4, 128.4, 127.1, 125.9, 116.8, 115.7, 113.4, 97.8, 62.2, 52.4, 49.6, 32.8, 14.2. MS (70 eV) *m/z* (%): 354 (M^+, 7), 310 (5), 281 (100). HRMS *m/z* calcd. for $C_{19}H_{18}N_2O_5$ (M+): 354.1216, found: 354.1220.

Ethyl (2*E*)-3-[1-(2-phenoxycarbonylethyl)-1,4-dihydro-4-oxoquinolin-3-yl]-2-cyanoacrylate (A1C3D3). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 195-196ºC (*iso*-PrOH). Yield: 68%. IR (KBr): ν_{max}/cm^{-1} 2219 (CN), 1752 (COO), 1719 (COO), 1632 (CO), 1586 (Aromatics), 1095 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 9.15 (s, 1H, CH), 8.83 (s, 1H, CH), 8.53 (dd, *J*=6.4, *J*=1.5Hz, 1H, Aromatic), 7.82-7.76 (m, 1H, Aromatic), 7.60-7.50 (m, 2H, Aromatics), 7.39-7.33 (m, 2H, Aromatics), 7.26-7.21 (m, 1H, Aromatic), 7.06-6.90 (m, 2H, Aromatics), 4.67 (t, *J*= 6.8 Hz, 2H, CH_2), 4.36 (q, *J*= 7.1 Hz, 2H, CH_2), 3.23 (t, *J*= 6.8 Hz, 2H, CH_2), 1.37 (t, *J*= 7.1 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 175.2, 168.9, 163.0, 150.3, 148.5, 146.1, 138.7, 134.0, 130.0, 128.9, 127.7, 126.7, 126.4, 121.6, 117.3, 116.1, 114.1, 98.7, 62.7, 49.8, 33.5, 14.64. MS (70 eV) *m/z* (%): 416 (M^+, 2), 344 (23), 343 (100), 281 (6). HRMS *m/z* calcd. for $C_{24}H_{20}N_2O_5$ (M+): 416.1372, found: 416.1375.

Phenyl 2-[3-(2,2-dicyanovinyl)-quinolin-1(4*H*)-yl]acetate (A1C3D1). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 185-187ºC (*iso*-PrOH). Yield 54%. IR (KBr): ν_{max}/cm^{-1} 2221 (CN), 1752 (COO), 1643 (CO), 1585 (Aromatics), 1158 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 9.09 (s, 1H, CH), 8.40 (s, 1H, CH), 8.53 (d, *J*=7.1 Hz, 1H, Aromatic), 7.83-7.80 (m, 1H, Aromatic), 7.60-7.54 (m, 2H, Aromatics), 7.41-7.36 (m, 2H, Aromatics), 7.28-7.03 (m, 1H, Aromatic), 7.05 (d *J*=7.7 Hz, 2H, Aromatics), 4.67 (t, *J*= 6.8 Hz, 2H, CH_2), 3.23 (t, *J*= 6.8 Hz, 2H, CH_2). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 168.9, 162.1, 153.4, 150.4, 147.0, 144.5, 138.1, 134.4, 130.0, 129.1, 127.5, 127.0, 126.9, 121.5, 116.3, 114.1, 50.1, 33.3. MS (70 eV) *m/z* (%): 369 (M^+, 8), 276 (11), 234 (52), 94 (38), 55 (100). HRMS *m/z* calcd. for $C_{22}H_{15}N_3O_3$ (M+): 369.1113, found: 369.1119.

Ethyl (*Z*)-3-[1-(2-cyanoethyl)-1*H*-indol-3-yl]-2-cyanoacrylate (A2C1D3). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 153-154ºC (*iso*-PrOH). Yield 80%. IR (KBr): ν_{max}/cm^{-1} 2215 (CN), 1721 (CO), 1589 (Aromatics), 1039 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 8.55 (s, 1H, CH), 8.54 (s, 1H, CH), 7.86 (dd, *J*=5.1, *J*=1.6 Hz, 1H, Aromatic), 7.45-7.33 (m, 3H, Aromatics), 4.57 (t, *J*= 6.9 Hz, 2H, CH_2), 4.37 (q, *J*= 7.1 Hz, 2H, CH_2), 2.94 (t, *J*= 6.9 Hz, 2H, CH_2), 1.35 (t, *J*= 7.1 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 164, 145.8, 138.0, 135.9, 133.0, 128.0, 124.9, 123.5, 118.0, 116.5, 111.5, 110.2, 96.3, 62.5, 43.3, 19.4, 14.7. MS (70 eV) *m/z* (%): 293 (M^+, 100), 253 (64), 225 (26), 179 (9). HRMS *m/z* calcd. for $C_{17}H_{15}N_3O_2$ (M+): 293.1164, found: 293.1170.

Ethyl (*Z*)-3-{1-[2-(methoxycarbonylethyl)]-1*H*-indol-3-yl}-2-cyanoacrylate (A2C2D3). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 85-87ºC (*iso*-PrOH). Yield: 78%. IR (KBr): ν_{max}/cm^{-1} 2215 (CN), 1732 (CO), 1586 (Aromatics), 1095 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 8.54 (s, 1H, CH), 8.53 (s,

1H, CH), 7.83-7.80 (m, 1H, Aromatic), 7.44-7.29 (m, 3H, Aromatics), 4.55 (t, *J*= 6.9 Hz, 2H, CH_2). 4.34 (q, *J*= 7.0 Hz, 2H, CH_2), 3.70 (s, 3H, CH_3), 2.94 (t, *J*= 6.9 Hz, 2H, CH_2), 1.38 (t, *J*= 7.0 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 171.0, 164.2, 146.1, 136.2, 134.1, 128.8, 124.4, 123.2, 119.1, 118.5, 110.8, 110.7, 94.9, 62.3, 52.6, 43.2, 34.7, 14.7. MS (70 eV) *m*/*z* (%): 326 (M^+, 100), 312 (36), 253 (32), 239 (24). HRMS *m*/*z* calcd. for $C_{18}H_{18}N_2O_4$ (M+): 326.1267, found: 326.1270.

Ethyl (*Z*)-3-{1-[2-(ethoxycarbonylethyl)]-1*H*-indol-3-yl}-2-cyanoacrylate (A2C4D3). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 78-80ºC (*iso*-PrOH) Yield: 78%. IR (KBr): ν_{max}/cm^{-1} 2226 (CN), 1731 (CO), 1587 (Aromatics), 1092 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 8.54 (s, 1H, -CH), 8.53 (s, 1H, -CH), 7.80 (d, *J*= 6.8 Hz, 1H, Aromatic), 7.45-7.42 (m, 1H, Aromatic), 7.37-7.28 (m, 2H, Aromatics), 4.54 (t, *J*= 6.8 Hz, 2H, CH_2). 4.33 (q, *J*= 7.1 Hz, 2H, CH_2), 4.15 (q, *J*= 7.1 Hz, 2H, CH_2), 2.89 (t, *J*= 6.8 Hz, 2H, CH_2), 1.38 (t, *J*= 7.1 Hz, 3H, CH_3), 1.21 (t, *J*= 7.1 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 170.6, 164.2, 146.1, 139.7, 136.3, 134.1, 128.8, 124.4, 123.1, 119.0, 118.5, 110.8, 94.8, 62.3, 61.7, 43.3, 34.9, 14.7, 14.4. MS (70 eV) *m*/*z* (%): 340 (M^+, 100), 253 (31), 225 (35), 179 (27), 140 (24). HRMS *m*/*z* calcd. for $C_{19}H_{20}N_2O_4$ (M+): 340.1423, found: 340.1425.

Methyl (*Z*)-3-{1-[2-(phenoxycarbonylethyl)]-1*H*-indol-3-yl}-2-cyanoacrylate (A2C3D2). Purification by preparative chromatography using AcOEt/hexane (1:4). M.P: 106-107ºC (*iso*-PrOH). Yield: 75%. IR (KBr): ν_{max}/cm^{-1} 2214 (CN), 1757 (CO), 1711 (CO), 1580 (Aromatics), 1094 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 8.61 (s, 1H, CH), 8.59 (s, 1H, CH), 7.86 (d, *J*= 8.4 Hz, 1H, Aromatic), 7.51 (d, *J*= 8.4 Hz, 1H, Aromatic), 7.41-7.36 (m, 4H, Aromatics), 7.33-7.22 (m, 1H, Aromatic), 7.09 (d, *J*= 7.8 Hz, 1H, Aromatic). 7.00 (d, *J*= 7.8 Hz, 1H, Aromatic), 4.67 (t, *J*= 6.8 Hz, 2H, CH_2), 3.91 (s, 3H, CH_3), 3.18 (t, *J*= 6.8 Hz, 2H, CH_2). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 170.2, 168.7, 146.3, 136.5, 134.0, 129.9, 129.9, 128.0, 126.6, 126.4, 124.6, 123.2, 121.8, 121.7, 119.2, 110.8, 94.6, 43.2, 35.0, 32.2. MS (70 eV) *m*/*z* (%): 374 (M^+, 28), 239 (100), 179 (23), 94 (37). HRMS *m*/*z* calcd. for $C_{22}H_{18}N_2O_4$ (M+): 374.1267, found: 374.1266.

Isopropyl (*Z*)-3-{1-[2-(ethoxycarbonylethyl)]-1*H*-indol-3-yl}-2-cyanoacrylate (A2C4D4). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 101-102ºC (*iso*-PrOH). Yield: 68%. IR (KBr): ν_{max}/cm^{-1} 2211 (CN), 1711 (CO), 1641 (CO), 1097 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 8.56 (s, 1H, -CH), 8.55 (s, 1H, -CH), 7.83 (d, *J*= 7.3 Hz, 1H, Aromatic), 7.45-7.41 (m, 1H, Aromatic), 7.39-7.30 (m, 3H, Aromatics), 5.29-5.15 (m, 1H, CH), 4.56 (t, *J*= 6.8 Hz, 2H, CH_2), 4.16 (q, *J*= 7.1 Hz, 2H, CH_2), 2.90 (t, *J*= 6.8 Hz, 2H, CH_2), 1.37 (d, *J*= 6.2 Hz, 6H, 2 x CH_3), 1.22 (t, *J*= 7.1 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 170.1, 164.0, 145.9, 136.1, 134.0, 128.5, 124.4, 123.0, 119.1, 118.8, 110.7, 109.3, 95.3, 70.1, 61.7, 43.3, 35.0, 22.2, 14.5. MS (70 eV) *m*/*z* (%): 354 (M^+, 56), 340 (30), 312 (56), 225 (100), 179 (66), 140 (70). HRMS *m*/*z* calcd. for $C_{20}H_{22}N_2O_4$ (M+): 354.1579, found: 354.1583.

Isopropyl (2*E*)-3-{1-[2-(methoxycarbonylethyl)]-1,6-dihydro-6-oxo-3-phenylpyridazin-4-yl}-2-cyanoacrylate (A3C2D4). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 113-114ºC (*iso*-PrOH). Yield: 50%. IR (KBr): ν_{max}/cm^{-1} 2210 (CN), 1733 (COO), 1700 (COO), 1656 (CO), 1589 (Aromatics), 1100 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 7.89 (s, 1H, CH), 7.50 (s, 1H, CH), 7.48-7.43 (m, 3H, Aromatics), 7.37-7.34 (m, 2H, Aromatics), 5.29-5.11 (m, 1H, CH), 4.55 (t, *J*=7.1 Hz, 2H, CH_2), 3.67 (s, 3H, OCH_3), 2.91 (t, *J*= 7.1 Hz, 2H, CH_2), 1.34 (d, *J*=6.2 Hz, 6H, 2 x CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 171.9, 160.0, 158.0, 149.4, 145.0, 135.2, 133.2, 130.3, 129.7, 129.3, 129.1, 113.5, 111.8, 72.2, 52.3, 48.0, 32.8, 22.0. MS (70 eV) *m*/*z* (%): 395 (M^+, 1), 295 (18), 253 (25), 222 (47), 164 (42), 59 (100). HRMS *m*/*z* calcd. for $C_{21}H_{21}N_3O_5$ (M+): 395.1481, found: 395.1487.

Ethyl (2*E*)-3-[1-(2-cyanoetil)-1,6-dihydro-6-oxo-3-phenylpyridazin-4-yl]-2-cyanoacrylate (A3C1D3). Purification by preparative chromatography using AcOEt/hexane (1:4) mp: 173-174ºC (*iso*-PrOH). Yield: 52%. IR (KBr): ν_{max}/cm^{-1} 2235 (CN), 1739 (CO), 1669 (CO), 1584 (Aromatics), 1094 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 7.90 (s, 1H, CH), 7.54 (s, 1H, CH), 7.51-7.47 (m, 3H, Aromatics), 7.45-7.38 (m, 2H, Aromatics), 4.53 (t, *J*= 6.7 Hz, 2H, CH_2), 4.38 (q, *J*=7.1 Hz, 2H, CH_2), 2.98 (t, *J*= 6.7 Hz, 2H, CH_2), 1.38 (t, *J*= 7.1 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 160.2, 158.3, 148.9, 136.1, 133.2, 130.2, 129.6, 129.0, 128.9, 128.5, 116.7, 112.9, 111.2, 63.5, 47.7, 16.5, 13.9. MS (70 eV) *m*/*z* (%): 348 (M^+, 68), 319 (29), 275 (32), 266 (65), 222 (100), 164 (19). HRMS *m*/*z* calcd. for $C_{19}H_{16}N_4O_3$ (M+): 348.1222, found: 348.1229.

Methyl 3-[4-(2,2-dicyanovinyl)-1,6-dihydro-6-oxo-3-phenylpyridazin-4-yl]propanoate (A3C2D1). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 127-128ºC (*iso*-PrOH). Yield: 65%. IR (KBr): ν_{max}/cm^{-1} 2235 (CN), 1736 (COO), 1670 (CO), 1588 (Aromatics), 1092 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 7.58-7.50 (m, 5H, Aromatics), 7.47 (s, 1H, CH), 7.34 (s, 1H, CH), 4.38 (t, *J*=6.9 Hz, 2H, CH_2), 3.67 (s, 3H, OCH_3), 2.90 (t, *J*= 6.9 Hz, 2H, CH_2). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 171.5, 158.2, 154.9, 144.5, 134.4, 134.0, 130.8, 129.9, 129.7, 129.1, 113.2, 111.1, 91.9, 52.3, 48.2, 32.7. MS (70 eV) *m*/*z* (%): 334 (M^+, 22), 303 (16), 275 (26), 247 (50), 234 (100), 222 (25), 191 (23). HRMS *m*/*z* calcd. for $C_{18}H_{14}N_4O_3$ (M+): 334.1065, found: 334.1068.

Methyl (2*E*)-3-{1-[2-(ethoxycarbonylethyl)]-1,6-dihydro-6-oxo-3-phenylpyridazin-4-yl}-2-cyanoacrylate (A3C4D2). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 151-152ºC (*iso*-PrOH). Yield: 62%. IR (KBr): ν_{max}/cm^{-1} 2135 (CN), 1736 (COO), 1703 (COO), 1665 (CO), 1588 (Aromatics), 1093 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 7.91 (s, 1H, CH), 7.49-7.44 (m, 4H, 3H Aromatics+ 1H CH), 7.37-7.33 (m, 2H, Aromatics), 4.54 (t, *J*= 7.1 Hz, 2H, CH_2), 4.13 (q, *J*= 7.1 Hz, 2H, CH_2), 3.91 (s, 3H, OCH_3), 2.88 (t, *J*= 7.1 Hz, 2H, CH_2), 1.20 (t, *J*= 7.1 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 171.2, 161.3, 158.8, 150.0, 145.0, 135.7, 134.0, 130.0, 129.8, 129.3, 129.1, 113.3, 110.8, 61.2, 54.3, 48.1, 33.0, 14.5. MS (70 eV) *m*/*z* (%): 381 (M^+, 11), 336 (12), 282 (17), 267 (100), 222 (46), 164 (19). HRMS *m*/*z* calcd. for $C_{20}H_{19}N_3O_5$ (M+): 381.1324, found: 381.1325.

Methyl (2*E*)-3-{1,6-dihydro-6-oxo-1-[2-(phenoxycarbonylethyl)]-3-phenylpyridazin-4-yl}-2-cyanoacrylate (A3C3D2). Purification by preparative chromatography using

AcOEt/hexane (1:4). mp: 113-114ºC (*iso*-PrOH). Yield: 66%. IR (KBr): ν_{max}/cm^{-1} 2134 (CN), 1743 (COO), 1707 (COO), 1662 (CO), 1581 (Aromatics), 1108 (C-O-C). ^{1}H-NMR ($CDCl_3$ 300 MHz), δ (ppm): 7.92 (s, 1H, CH), 7.53 (s, 1H, CH), 7.48-7.43 (m, 3H, Aromatics), 7.37-7.16 (m, 5H, Aromatics), 6.96 (d, *J*=6.7 Hz, 2H, Aromatics), 4.68 (t, *J*=6.7 Hz, 2H, CH_2), 3.92 (s, 3H, CH_3), 3.14 (t, *J*= 6.7 Hz, 2H, -CH_2). ^{13}C-NMR ($CDCl_3$ 75 MHz), δ (ppm): 169.8, 162.2, 158.9, 150.9, 149.8, 145.3, 135.8, 134.0, 130.4, 129.9, 129.7, 129.4, 129.2, 126.3, 121.8, 113.3, 110.9, 54.35, 48.05, 33.29. HRMS *m/z* calcd. for $C_{24}H_{19}N_3O_5$ (M+): 429.1324, found: 429.1325.

Methyl (*E*)-3-{1-[2-(methoxycarbonyl)ethyl]-1*H*-imidazol-4-yl}-2-cyanoacrylate (A4C2D2). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 163.2-165.3ºC. (*iso*-PrOH). Yield: 72%. IR (KBr): ν_{max}/cm^{-1} 2220 (CN), 1735 (COO), 1715 (COO), 1608 (CO). ^{1}H-RMN ($CDCl_3$, 300 MHz), δ (ppm): 8.07 (s, 1H, C=CH), 7.87 (s, 1H, H_5), 7.52 (s, 1H, H_3), 4.17 (t, *J*=6.2 Hz, 2H, CH_2), 3.71 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 2.66 (t *J*=6.2 Hz, 2H, CH_2). ^{13}C-RMN ($CDCl_3$, 75.5 MHz), δ (ppm): 170.3, 163.1, 148.4, 139.2, 135.9, 126.0, 116.1, 98.6, 52.9, 52.2, 42.9, 35.1. MS (70 eV) *m/z* (%): 263 (M^+, 87), 232 (61), 204 (100). HRMS *m/z* calcd. for $C_{12}H_{13}N_3O_4$(M+): 263.0906, found: 263.0910.

Methyl 3-[4-(2,2-dicyanovinyl)-1*H*-imidazol-1-yl)propanoate (A4C2D1). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 141.2-143.4ºC (*iso*-PrOH). Yield: 74%. IR (KBr): ν_{max}/cm^{-1} 2218 (CN), 1718 (COO), 1611 (CO). ^{1}H-RMN ($CDCl_3$, 300 MHz), δ (ppm): 7.75 (s, 1H, C=CH), 7.55 (s, 2H, H_5 + H_3), 4.18 (t,, *J*=6.1 Hz, 2H, CH_2), 3.54 (s, 3H, OCH_3), 2.66 (t, *J*=6.1 Hz, 2H, CH_2). ^{13}C-RMN ($CDCl_3$, 75.5 MHz), δ (ppm): 170.3, 151.9, 139.8, 135.5, 127.2, 113.9, 113.7, 63.8, 52.3, 43.0, 35.0. MS (70 eV) *m/z* (%): 230 (M^+, 58), 171 (100), 157 (100). HRMS *m/z* calcd. for $C_{11}H_{10}N_4O_2$ (M+): 230.0804, found: 230.0814.

2-[(1-(2-Cyanoethyl)-1H-imidazol-4-yl)methylene]malononitrile (A4C1D1). Purification by recrystalisation. mp: 194.1-196.3ºC (*iso*-PrOH). Yield: 84%. IR (KBr): ν_{max}/cm^{-1} 2205 (CN), 1605 (CO). ^{1}H-RMN (DMSO-d_6, 300 MHz), δ (ppm): 8.25 (s, 1H, C=CH), 8.09 (s, 1H, H_5), 8.06 (s, 1H, H_3), 4.38 (t, *J*=6.3 Hz, 2H, CH_2), 3.10 (t, *J*=6.3 Hz, 2H, CH_2). ^{13}C-RMN (DMSO-d_6, 75.5 MHz), δ (ppm): 151.9, 141.4, 135.2, 131.0, 118.3, 115.5, 113.8, 74.8, 42.5, 19.3. MS (70 eV) *m/z* (%): 197 (M^+, 97), 157 (100), 130 (40). HRMS *m/z* calcd. for $C_{10}H_7N_5$ (M+): 197.0701, found: 197.0708.

Ethyl (*E*)-3-{1-[2-(ethoxycarbonyl)ethyl]-1*H*-imidazol-4-yl}-2-cyanoacrylate (A4C4D3). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 115.4-117.2ºC (*iso*-PrOH). Yield: 72%. IR (KBr): ν_{max}/cm^{-1} 2224 (CN), 1726 (COO), 1708 (COO), 1605 (CO). ^{1}H-RMN ($CDCl_3$, 300 MHz), δ (ppm): 8.25 (s, 1H, C=CH), 8.06 (s, 1H, H_5), 7.69 (s, 1H, H_3), 4.39-4.30 (m, 4H, 2xCH_2), 4.17 (q, *J*=7.1 Hz, 2H, CH_2), 2.83 (t, *J*=6.2 Hz, 2H, CH_2), 1.37 (t, *J*=7.1 Hz, 3H, OCH_3), 1.25 (t, *J*=7.1 Hz, 3H, OCH_3). ^{13}C-RMN ($CDCl_3$, 75.5 MHz), δ (ppm): 169.9, 162.6, 148.2, 139.2, 135.9, 125.9,116.1, 99.0, 62.1, 61.3, 42.9, 35.4, 14.0, 13.9. MS (70 eV) *m/z* (%): 291 (M^+, 58), 246 (63), 218 (100), 146 (67). HRMS *m/z* calcd. for $C_{14}H_{17}N_3O_4$ (M+): 291.1219, found: 291.1224.

Ethyl (*E*)-3-{1-[2-(methoxycarbonyl)ethyl]-1*H*-imidazol-4-yl}-2-cyanoacrylate (A4C2D3). Purification by preparative chromatography using AcOEt/hexane (1:4). mp: 136.1-138.3ºC (*iso*-PrOH). Yield: 71%. IR (KBr): ν_{max}/cm^{-1} 2221 (CN), 1735 (COO), 1713 (COO), 1609 (CO). ^{1}H-RMN ($CDCl_3$, 300 MHz), δ (ppm): 8.30 (s, 1H, C=CH), 8.10 (s, 1H, H_5), 7.74 (s, 1H, H_3), 4.41 (t, *J*=7.1 Hz, 2H, CH_2), 4.39 (t, *J*=6.2 Hz, 2H, CH_2), 4.35 (s, 3H, OCH_3), 2.87 (t, *J*=6.2 Hz, 2H, CH_2), 1.42 (t, *J*=7.2 Hz, 3H, OCH_3). ^{13}C-RMN ($CDCl_3$, 75.5 MHz), δ (ppm): 170.3, 162.5, 148.1, 139.1, 135.9, 125.9, 116.2, 99.1, 62.1, 52.2, 42.9, 35.1, 14.0. MS (70 eV) *m/z* (%): 277 (M^+, 91), 232 (80), 205 (100), 146 (87). HRMS *m/z* calcd. for $C_{13}H_{15}N_3O_4$ (M+): 277.1063, found: 277.1063.

Methyl (*E*)-3-{1-[2-(2-ethoxyethoxy)carbonyl]ethyl-1*H*-imidazol-4-yl}-2-cyanoacrylate (A4C5D2). Purification by recrystalisation. Yield: 65%. mp: 98.3-99.8 ºC (*iso*-PrOH). IR (KBr): ν_{max}/cm^{-1} 2134 (CN), 1743 (COO), 1707 (COO), 1662 (CO), 1581 (Aromatics), 1108 (C-O-C). ^{1}H-RMN ($CDCl_3$, 300 MHz), δ (ppm): 8.25 (s, 1H, C=CH), 8.05 (s, 1H, H_5), 7.71 (s, 1H, H_3), 4.35 (t, *J*=6.3 Hz, 2H, CH_2), 4.27 (t, *J*=4.7 Hz, 2H, CH_2), 3.90 (s, 3H, OCH_3), 3.61 (t, *J*=4.7 Hz, 2H, CH_2), 3.51 (q, *J*=7.0 Hz, 2H, CH_2), 2.88 (t, *J*=6.3 Hz, 2H, CH_2), 1.21 (t, *J*=7.0 Hz, 2H, CH_3). ^{13}C-RMN ($CDCl_3$, 75.5 MHz), δ (ppm): 169.9, 163.1, 148.2, 139.4, 135.7, 126.1, 116.1, 98.4, 67.8, 66.4, 64.3, 52.9, 42.8, 35.3, 14.8. MS-CI (70 eV) *m/z* (%): 325 (6), 324 (40), 323 (57), 322 (100), 321 (10). HRMS *m/z* calcd. for $C_{15}H_{19}N_3O_5$ (M+): 321.3285, found: 321.3290.

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SUPPLEMENTARY MATERIAL

Supplementary material (copies of all the NMR, C13, IR and mass spectra for disubstituted heterocycles ABD and ACD) is available online at publisher's website.

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diazabicyclo[5.4.0]undec-7-ene (DBU, pKa≈23.9), the Schwesinger.s phosphazene base, that is, 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP, pKa≈27.6). See reference [1], page 187.

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